Baseline MRI Predictors of Cognitive Processing Speed in Participants with Secondary Progressive Multiple Sclerosis from the Phase 3 EXPAND study

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Introduction

- In the core part of the phase 3 EXPAND study, siponimod compared with placebo, significantly reduced the risk of disability progression, worsening in CPS, and MRI measures of disease activity in patients with secondary progressive multiple sclerosis[1,2]
- Several studies suggest that gray matter volume loss, which reflects neurodegeneration, is detectable from the earliest stage of MS,[3,4] and is associated with long-term disability accumulation and cognitive decline[5-7]

Objective

- To explore the prognostic value of different MRI measures reflecting inflammatory and/or neurodegenerative processes on time-to-6-month confirmed clinically meaningful (≥4 points) worsening/improvement on SDMT ($6mCW_{SDMT}$/$6mCI_{SDMT}$) and absolute change in SDMT from baseline in patients randomized and treated with siponimod

Methods

- This exploratory analysis used data from the core and extension[a] parts of the phase 3 EXPAND study
- Patients randomized to siponimod[b] (MRI cohort [n=1099]; MTR cohort [n=402]) were stratified in to quartiles per baseline MRI parameters and the prognostic value was assessed by comparing “worst” versus “best” quartile or “presence versus absence” of the parameters as below:

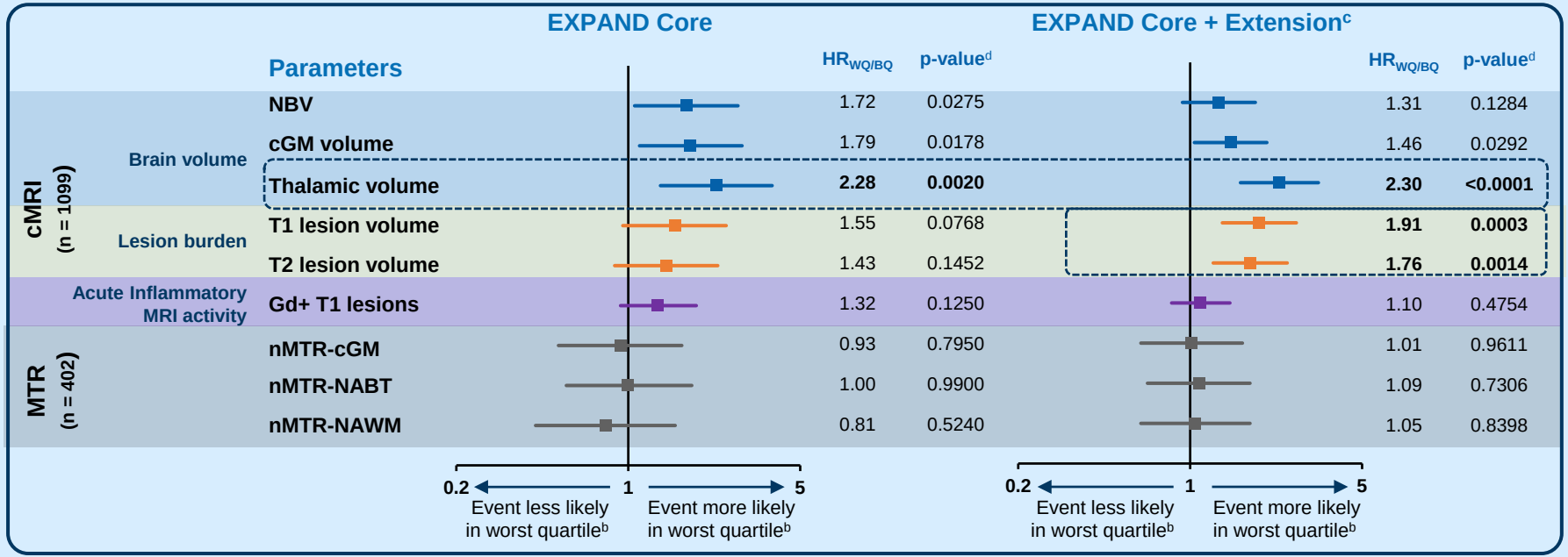
Brain volume *(Q1 [worst]/Q4 [best])* • *Normalized brain volume (NBV)* • *Cortical gray matter (cGM) volume* • *Thalamic volume*	**Lesion burden** *(Q4 [worst]/Q1 [best])* • *T1-hypointense lesion volume* • *T2 lesion volume*
Median normalized MTR *(Q1 [worst]/Q4 [best])* • *nMTR-cGM* • *nMTR-NAWM* • *nMTR-NABT*	**Acute inflammatory MRI activity** *(presence versus absence)* • *Gd+ T1 lesions*

[a]Extension data cut-off: 06-Apr-2019 (Month 36 visit of extension); total study duration (core + extension): ≤5 years (median 54.1 months); median duration of core part was 21 months; [b]To avoid confounding effect due to variable exposure during the core part and patients switching from placebo to siponimod in the extension part. $6mCW_{SDMT}$/CI_{SDMT}, 6-month confirmed worsening/improvement on SDMT; CPS, cognitive processing speed; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; SDMT, Symbol Digit Modalities Test; Q, quartile.

1. Kappos L, et al. *Lancet.* 2018;391:1263–1273; 2. Benedict RHB, et al. *Neurology* 2021;96(3): e377-e386; 3. Arnold DL. et al. Presented at *ECTRIMS* 2019, P1057; 4. Larochelle C. et al. *Trends Neurosci.* 2016;39:325–339; 5. Eshaghi A, et al. *Ann Neurol.* 2018;83:210–222; 6. Rocca MA, et al. *Radiology.* 2010;257:463–469; 7. Schoonheim MM, et al. *Neurology.* 2015;84:776–783.

Results

Time-to-6-month confirmed WORSENING (≥ 4 points) on SDMT (6mCW$_{SDMT}$)[a] :Hazard ratio (Worst vs. Best quartile)[b]

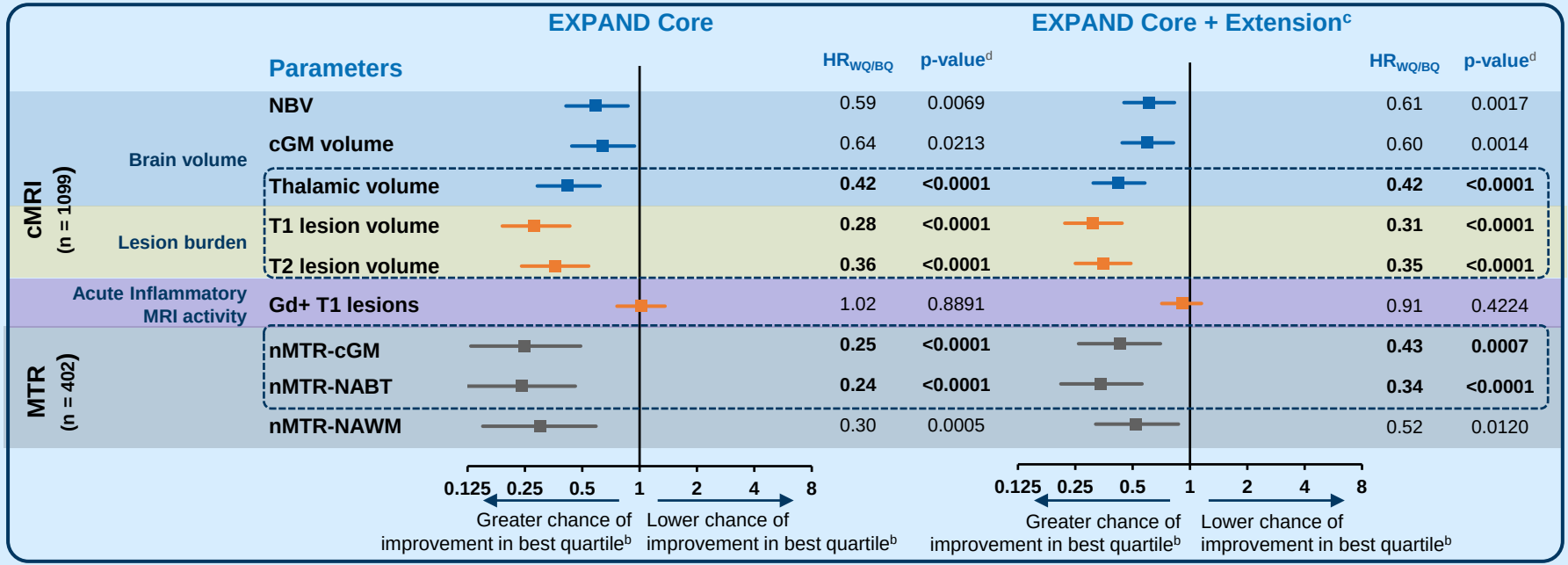


- Thalamic volume followed by cGM volume, and NBV showed strong prognostic value for SDMT worsening in the shorter term, while only thalamic and cGM volume remained significant in the longer term; T1 and T2 LV became significantly prognostic in the longer term
- MTR and Gd+ T1 lesions were not prognostic of clinically meaningful SDMT worsening

[a]Cox regression analysis adjusted for SDMT at baseline; [b]For acute inflammatory activity, the HR was based on presence versus absence of Gd+ T1 lesions; [c]Extension data cut-off: 06-Apr-2019 (Month 36 visit of extension]; total study duration (core + extension): ≤5 years (median 54.1 months); median duration of core part was 21 months; [d]p-values provided are nominal. No multiplicity adjustment were made, therefore, statistical interpretation should be made with caution. cGM, cortical gray matter; Gd+, gadolinium-enhancing; HR$_{WQ/BQ}$, hazard ratio (worst vs. best quartile); cMRI, conventional magnetic resonance imaging; n, number of patients; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; NBV, normalized brain volume; SDMT, Symbol digit modalities test

Results

Time-to-6-month confirmed IMPROVEMENT (≥ 4 points) on SDMT ($6mCI_{SDMT}$)[a] :Hazard ratio (Worst vs. Best quartile)[b]

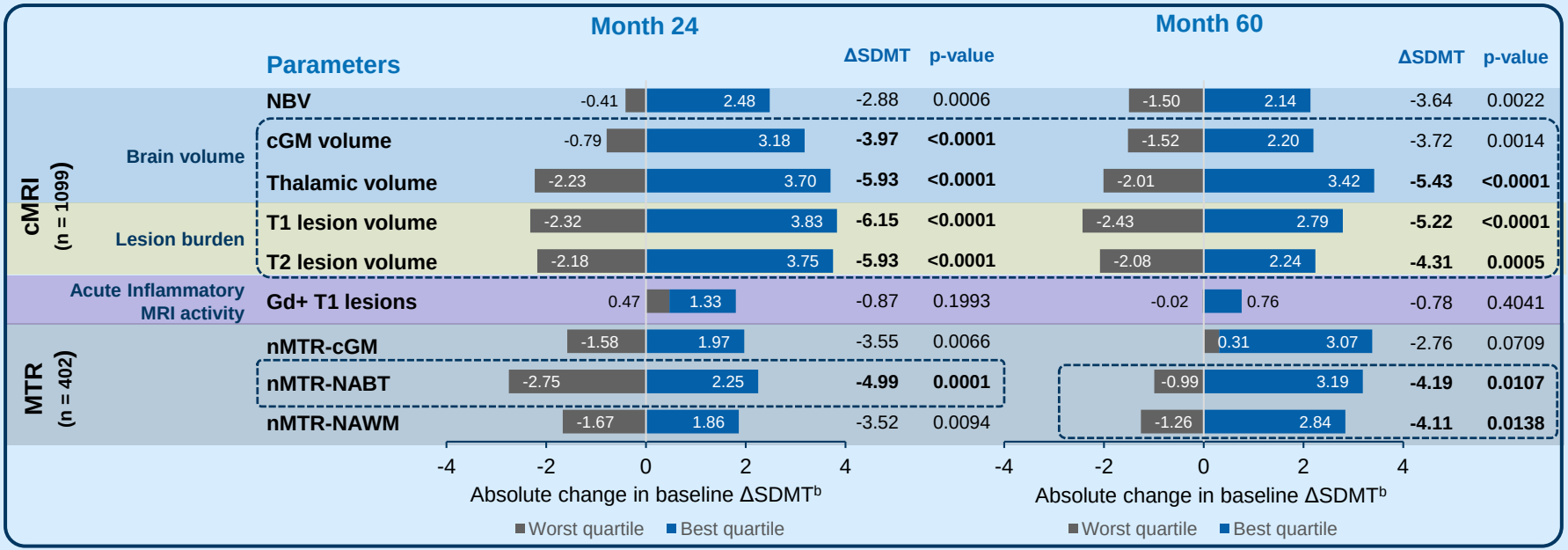


- All MRI parameters except Gd+ T1 lesions were associated with SDMT improvement in both the shorter and longer term (i.e. patients in best quartile were more likely to improve)

[a]Cox regression analysis adjusted for SDMT at baseline; [b]For acute inflammatory activity, the HR was based on presence versus absence of Gd+ T1 lesions; [c] Extension data cut-off: 06-Apr-2019 (Month 36 visit of extension]; total study duration (core + extension): ≤5 years (median 54.1 months); median duration of core part was 21 months; [d]p-values provided are nominal. No multiplicity adjustment were made, therefore, statistical interpretation should be made with caution. cGM, cortical gray matter; Gd+, gadolinium-enhancing; $HR_{WQ/BQ}$, hazard ratio (worst vs. best quartile); cMRI, conventional magnetic resonance imaging; n, number of patients; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; NBV, normalized brain volume; SDMT, Symbol digit modalities test

Results

Absolute change in SDMT from baseline (Worst vs. Best quartile)[a]



- All MRI parameters except for Gd+ T1 lesions were significantly associated with absolute changes on SDMT; for some parameters, the differences between worst versus best quartile exceeded the cut-off for clinically meaningful change (≥4 points)
- The most pronounced differences between worst versus best quartiles for both short and longer term were observed for thalamic volume and T1/T2 lesion volumes

[a]Analyzed using mixed model repeated measures model with visit as categorical factor; [b]For acute inflammatory activity, the values were based on presence versus absence of Gd+ T1 lesions.
cGM, cortical gray matter; Gd+, gadolinium-enhancing; cMRI, conventional magnetic resonance imaging; n, number of patients; nMTR, normalized magnetization transfer ratio; NABT, normal appearing brain tissue; NAWM, normal appearing white matter; NBV, normalized brain volume; ΔSDMT, change in Symbol digit modalities test

Conclusions

- In patients with SPMS treated with siponimod, baseline thalamic volume followed by cortical gray matter volume demonstrated the most consistent prognostic value for clinically meaningful changes in cognitive processing speed as measured by SDMT during both shorter term and longer term follow-up
- Baseline MTR, a marker of myelin density, was associated with confirmed clinically meaningful improvement on SDMT
- High baseline T2 and T1 lesion volumes were associated with worse SDMT in longer term follow-up and low baseline T2 and T1 were prognostic of better SDMT outcomes at both shorter and longer term follow-up
- Gadolinium-enhancing lesions were not prognostic for any SDMT outcomes
- MRI markers of neurodegeneration and tissue integrity were prognostic for worsening and improvement of cognitive processing speed as measured by SDMT

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The final responsibility for the content lies with the authors.

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