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### Baseline MRI Predictors of Cognitive Processing Speed in Participants with Secondary Progressive Multiple Sclerosis from the Phase 3 Expand Study

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#### Abstract Text:

#### Background:

Siponimod showed beneficial effects on magnetic resonance imaging (MRI) lesion activity, total brain and gray matter (GM) atrophy, MTR measures and cognitive processing speed in secondary progressive multiple sclerosis (SPMS) participants from the EXPAND study.

#### Objectives:

To explore the predictive value of a variety of MRI measures of brain tissue damage on time-to-6-month confirmed  $\geq 4$ -points cognitive worsening/improvement on Symbol Digit Modalities Test (SDMT;  $6mCW_{SDMT}/6mCI_{SDMT}$ ) in siponimod-treated SPMS EXPAND study participants over short- (Core) and long-term (Core+Extension) periods (total up-to-5 years).

#### Methods:

Siponimod-treated participants (MRI cohort [N=1099]; MTR cohort [n=402]) were stratified into quartiles of Baseline total normalized brain volume (NBV), cortical GM (cGM) and thalamic volume, T1-hypointense lesion volume (T1HLV), T2-lesion volume (T2LV), median normalized MTR of normal appearing brain tissue (nMTR-NABT), normal-appearing white matter (NAWM) and cGM, and by absence/presence of gadolinium-enhancing (Gd+) T1 lesions.  $6mCW_{SDMT}/6mCI_{SDMT}$  and absolute SDMT change from Baseline were analyzed by Cox-regression analysis with respective outcome as Baseline covariate comparing worst (WQ) vs best quartile (BQ).

#### Results:

Over both short- and longer-terms, thalamic and cGM volume were the strongest MRI predictors of  $6mCW$  for participants in the worst vs best quartile ( $HR_{WQ/BQ}$  range: 1.46–2.30,  $p < 0.05$  for both); participants in WQ of nMTR (cGM, NAWM and NABT), T1HLV, T2LV and thalamic volume were significantly less likely to experience  $6mCI$  ( $HR_{WQ/BQ}$  range: 0.24–0.52,  $p < 0.0120$  for all). All parameters except Gd+ T1 lesions at Baseline were significantly associated with absolute SDMT change, which showed strongest association for thalamic volume followed by T1HLV, T2LV and nMTR-NABT ( $\Delta$  range $_{WQ/BQ}$ : 4.19–6.15; all  $p \leq 0.0005$  except nMTR-NABT  $p = 0.0107$ ).

#### Conclusions:

Baseline GM volume (especially thalamic volume), and MTR-reflected myelination were associated with clinically meaningful worsening and improvement in cognitive processing speed in siponimod-treated SPMS participants, suggesting relevance as prognostic MRI measures of decline in cognitive processing speed both in short and longer-terms.

**Title:**

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**Preferred Presentation Format:**

Poster

**Category:**

Disease-modifying therapy

**Would you give CMSC and International Journal of MS Care the first preference to any article that is submitted for publication based on this abstract presentation?:**

Yes

**Category:** Disease-modifying therapy

**Keywords:**

Disease-modifying treatments in MS and Imaging and MS

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