Siponimod Slows Physical Disability Progression and Decline in Cognitive Processing Speed in SPMS Patients with Active Disease: A Post Hoc Analysis of the EXPAND Study

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Background

- In the core part of the Phase 3 EXPAND study, siponimod significantly reduced the relative risk of 3-month CDP by 21% and 6-month CDP by 26% compared with placebo and showed clinically meaningful benefits in cognitive processing speed\textsuperscript{1,2}
- Furthermore, in SPMS patients with active disease\textsuperscript{a}, siponimod significantly reduced clinical and MRI outcomes versus placebo\textsuperscript{3}:
  - 3-month CDP by 31% and 6-month CDP by 37%
  - Annualised relapse rate by 46%
  - Risk of cumulative number of T1 Gd+ lesions by 85%
  - Number of new/enlarging T2 lesions by 80%

\textbf{Objective:} To assess the efficacy of siponimod on disability progression and cognitive processing speed in SPMS patients with active disease

\textsuperscript{a}Defined as the presence of relapses in the 2 years before screening and/or \textgeq 1 T1 Gd+ lesion at baseline. CDP, confirmed disability progression; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis
This post-hoc analysis included SPMS patients with active disease\(^a\) and subgroups of patients with active disease, defined based on previous DMT use at baseline.

Patient groups highlighted in blue box are included in the analysis:

- \(a\) defined as patients with relapses in the 2 years before screening and/or ≥1 Gd+ T1 lesion at baseline;
- \(b\) patients those who received and stopped IFN/MS-DMT prior to first dose of study treatment.

DMT, disease-modifying therapy; Gd+, gadolinium-enhancing; IFN, interferon; SPMS, secondary progressive multiple sclerosis.
**Study Outcomes and Statistical Analysis**

<table>
<thead>
<tr>
<th>Outcomes/patients</th>
<th>Statistical method</th>
</tr>
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<tbody>
<tr>
<td><strong>In all SPMS patients with active disease</strong></td>
<td></td>
</tr>
<tr>
<td>• Time to 3mCDP and 6mCDP</td>
<td>• Using a Cox proportional hazards model with treatment, country/region, baseline EDSS and SPMS group (with/without superimposed relapses, baseline definition) as covariates</td>
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</table>
| • Sustained\(^a\) worsening/improvement in cognitive processing speed  
  *(clinically meaningful change ≥4 points on the SDMT score)* | • Using a Cox proportional hazards model with treatment, country, baseline EDSS, baseline SDMT-Oral score and SPMS group (with/without superimposed relapses, baseline definition) as covariates |
| **In subgroups of patients with active disease** | |
| • Time to 6mCDP | • Cox proportional hazards model with treatment and baseline EDSS as covariates |

\(^a\)sustained on all available assessments after the assessment of a negative/positive response  
CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis
## Baseline Demographics and Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All SPMS patients with active disease</th>
<th>Overall EXPAND population (N=1645)</th>
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<tbody>
<tr>
<td></td>
<td>Siponimod n=516</td>
<td>Placebo n=263</td>
</tr>
<tr>
<td>Age, years</td>
<td>46.2±8.1</td>
<td>47.2±8.5</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>331 (64.1)</td>
<td>166 (63.1)</td>
</tr>
<tr>
<td>Duration of MS since first symptom, years</td>
<td>15.6±7.9</td>
<td>15.5±8.2</td>
</tr>
<tr>
<td>Time since conversion to SPMS, years</td>
<td>3.2±3.3</td>
<td>3.1±3.2</td>
</tr>
<tr>
<td>EDSS, median (range)</td>
<td>6.0 (2.0–7.0)</td>
<td>6.0 (2.5–6.5)</td>
</tr>
<tr>
<td>SDMT</td>
<td>38.1±14.0</td>
<td>38.6±13.2</td>
</tr>
<tr>
<td>Patients with relapses in the previous 2 years before screening, n (%)</td>
<td>388 (75.2)</td>
<td>202 (76.8)</td>
</tr>
<tr>
<td>Proportion of patients with Gd+ T1 lesions, n (%)</td>
<td>236 (46.7)</td>
<td>114 (44.2)</td>
</tr>
<tr>
<td>T2 lesion volume, cm³, median (range)</td>
<td>12.0 (0.0–116.6)</td>
<td>12.7 (0.0–103.6)</td>
</tr>
<tr>
<td>Normalised brain volume, cm³, median (range)</td>
<td>1417.7 (1171–1723)</td>
<td>1417.8 (1228–1679)</td>
</tr>
</tbody>
</table>

SPMS patients with active disease had more relapses and more MRI activities, as expected, compared with the overall EXPAND population. Otherwise the patient characteristics were similar.

Data are presented as mean (SD), unless stated otherwise; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis.
Effect of Siponimod on Time to 3mCDP and 6mCDP

All SPMS patients with active disease

Siponimod significantly reduced the risk of 3mCDP by 31% and 6mCDP by 37% versus placebo in all active patients.

CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis.
### Effect of Siponimod on 6mCDP

**Subgroups of patients with active disease based on previous DMT use at baseline**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Siponimod n/N</th>
<th>Placebo n/N</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DMT</td>
<td>80/394</td>
<td>59/203</td>
<td>0.67 (0.48; 0.94)</td>
<td>0.0203</td>
<td>33%</td>
</tr>
<tr>
<td>Interferon at anytime</td>
<td>65/306</td>
<td>46/154</td>
<td>0.68 (0.47; 1.00)</td>
<td>0.0496</td>
<td>32%</td>
</tr>
<tr>
<td>Interferon as recent DMT</td>
<td>36/205</td>
<td>33/104</td>
<td>0.52 (0.32; 0.83)</td>
<td>0.0063</td>
<td>48%</td>
</tr>
</tbody>
</table>

Siponimod significantly reduced the risk of 6mCDP in all subgroups of patients regardless of previous treatment and this was consistent in all SPMS patients with active disease.

CDP, confirmed disability progression; CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis.
Effect of Siponimod on Cognitive Processing Speed

All SPMS patients with active disease

Siponimod reduced the risk of sustained worsening in cognitive processing speed by 28% and improved the chance of sustained improvement by 51% versus placebo.

aSustained on all available assessments after the assessment of a negative/positive response; Only patients with non-missing covariates are included in the model; CI, confidence interval; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis
Conclusions

• Siponimod significantly and delayed disability progression versus placebo in SPMS patients with active disease,
  – Reduced the relative risk of 3-month CDP (31%)
  – Reduced the relative risk of 6-month CDP (37%)
  – Relative risk reduction of 6-month CDP was consistent across subgroups of patients with active disease based on previous DMT use (32%-48%)

• Siponimod showed significant benefits in cognitive processing speed versus placebo in SPMS patients with active disease
  – Reduced the risk of sustained worsening (by 28%)
  – Improved the chance of sustained improvement (by 51%)

CDP, confirmed disability progression; DMT, disease-modifying therapy; SPMS, secondary progressive multiple sclerosis