A Functional Composite Endpoint to Characterize Disease Progression in Patients with Active or Non-active Secondary Progressive Multiple Sclerosis

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Introduction

- Composite endpoints (CEPs) have the potential to capture disease progression more comprehensively as they account for functions not, or not optimally, captured by a single endpoint alone[1]
- The phase 3 EXPAND study in patients with SPMS[2] evaluated the efficacy of siponimod on CDP as measured by the primary outcome (EDSS), cognitive processing speed (by SDMT) and several other outcomes, including upper limb function (9HPT) and ambulation (T25FWT)[2,3]
- A previous analysis combining SDMT and EDSS, captured to a great part distinct populations who might benefit from treatment[4]
- In the current analysis, 9HPT and T25FWT are included with SDMT and EDSS in the construction of novel CEP to determine treatment effects on the functional domains of high clinical relevance in SPMS

Objective

- To characterize disease progression using novel CEPs relevant to SPMS and evaluate their performance in active and non-active SPMS patients

Methods

- This post hoc analysis included patients with SPMS from the phase 3 EXPAND core study:
  - **Overall population**
    (Siponimod [N=1099], placebo [N=546])
  - **Subgroup of patients with active disease[a]**
    (Siponimod [N=516], placebo [N=263])
  - **Subgroup of patients with non-active disease[b]**
    (Siponimod [N=557], placebo [N=270])

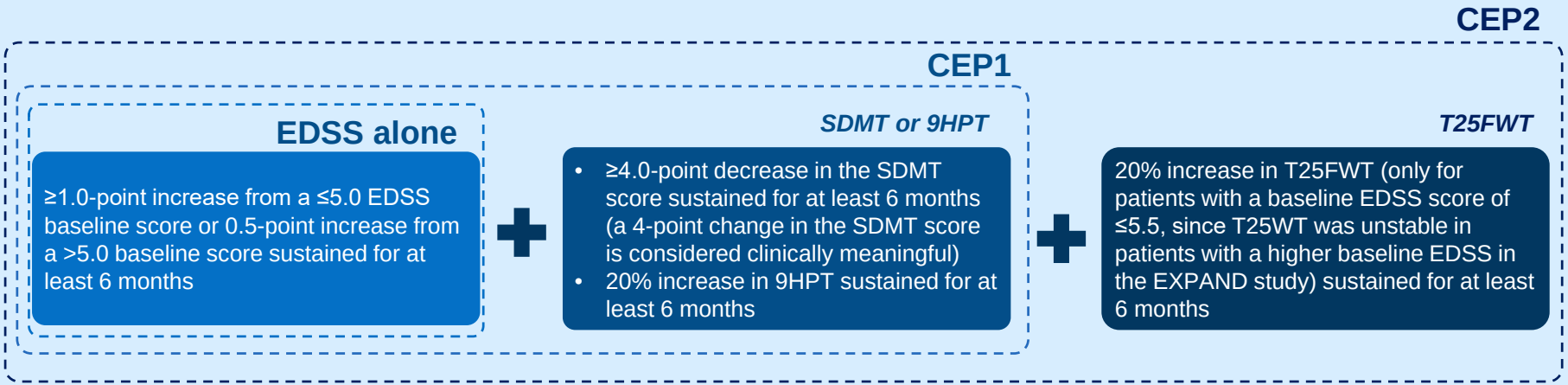
[a]Defined as the presence of at least one relapse in the 2 years before screening and/or ≥1 Gd+ T1 lesion at baseline; [b]Defined as no relapse in the 2 years prior to screening and no Gd+ T1 lesion at baseline.
9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test.

1. Cohen J, et al. *Lancet Neurol.* 2012;11:467–476; 2. Kappos L, et al. *Lancet.* 2018;391(10127):1263–1273; 3. Benedict HBR, et al. *Neurology.* 2018;90:S44.004; 4.Kappos L, et al. Presented at AAN 2019. S12.006.

Methods

Investigated endpoints

- Compared treatment effect on reducing **time-to-6-month confirmed disease progression** based on EDSS alone, CEP1 and CEP2



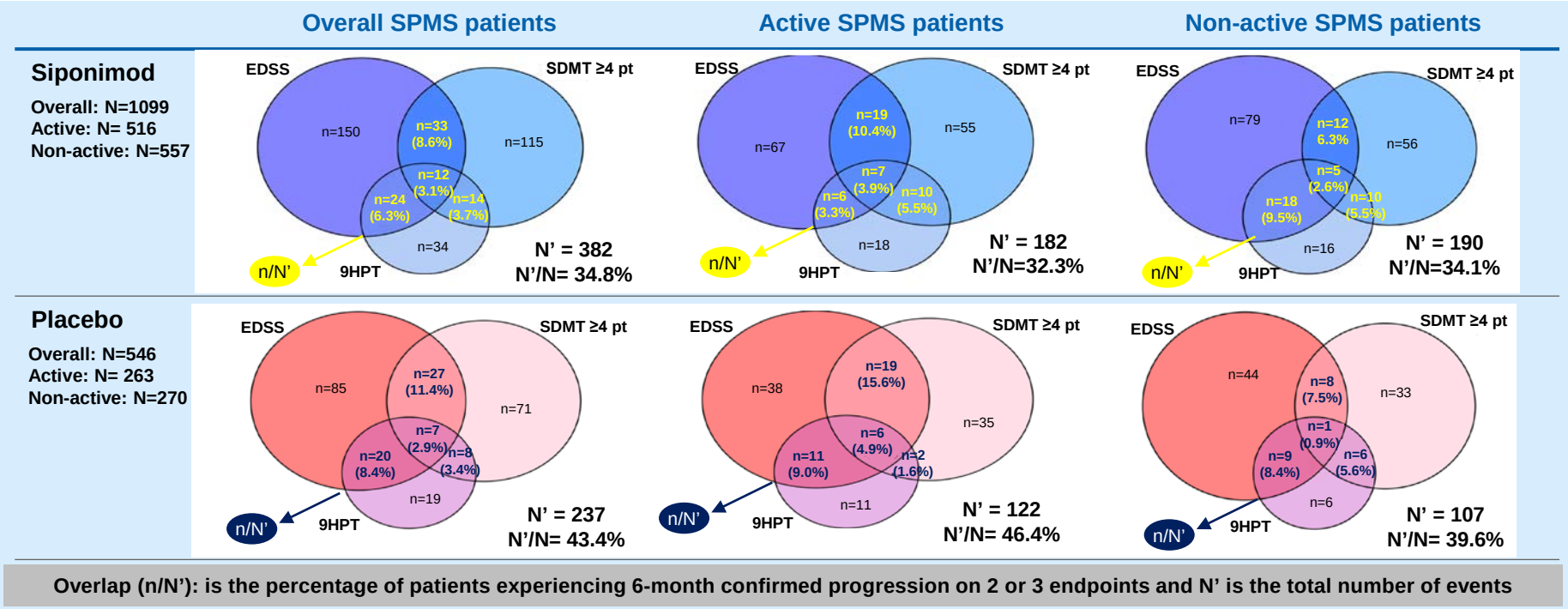
Statistical analysis

- Time-to-6-month confirmed disease progression was analyzed using the Cox proportional hazards model with treatment, country/region, baseline EDSS score, and SPMS subgroups (with/without superimposed relapses, baseline definition) as covariates
- Risk reduction was derived as (1 - hazard ratio) * 100

+, and/or; 9HPT, 9-Hole Peg Test; CEP, composite endpoint; EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test

Results

Contribution of each individual component to the total number of events captured by CEP1



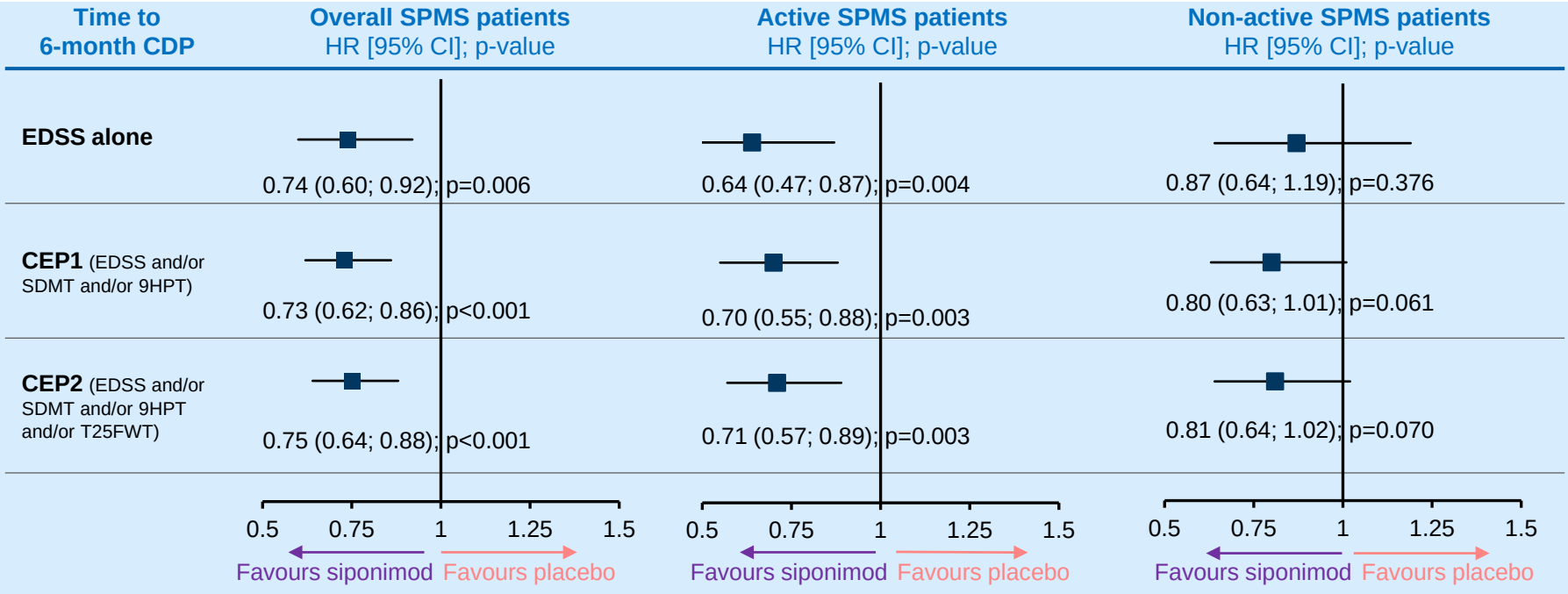
Overlap (n/N'): is the percentage of patients experiencing 6-month confirmed progression on 2 or 3 endpoints and N' is the total number of events

- The three endpoints, EDSS, SDMT and 9HPT, appear to capture distinct aspects of 6-month CDP with only minor overlap
- More overlap of the endpoints (i.e. more dimensions of the disease progression) was observed in the placebo-treated active SPMS patients
- EDSS is still expected to drive the performance of CEP1

The figures are indicative rather than actual representation of the data. 9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; CEP, composite endpoint; EDSS, Expanded Disability Status Scale; pt, points; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test

Results – Treatment effects

Effect of treatment on time-to-6-month confirmed disability progression based on EDSS alone, CEP1 and CEP2



- Siponimod treatment was associated with significant reductions in the risk of 6-month CDP compared to placebo in the overall and active SPMS populations (risk reduction range: 25%–37%)
- In non-active SPMS patients, the trend favoring siponimod treatment was more pronounced with the composite endpoints
- Addition of T25FWT in CEP2 did not further reduce the width of CIs (i.e. T25FWT didn't increase the precision of the HR estimate)

p-value. CEP1, 6-month CDP events based on EDSS and/or SDMT and/or 9-HPT; CEP2, 6-month CDP events based on EDSS and/or SDMT and/or 9HPT and/or T25FWT. CDP, confirmed disability progression; CEP, composite endpoints; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis

Conclusions

- Adding SDMT and 9HPT to the EDSS assessment (CEP1) allowed detection of treatment effects on a broader spectrum of symptoms in patients with SPMS compared with EDSS alone, in both patients with active and non-active disease
- Addition of T25FWT did not further increase the test sensitivity
- Siponimod treatment effect with the two composite endpoints was consistent with that observed with the EDSS a single endpoint e.g. statistically significant risk reductions in the overall EXPAND population and in patients with active disease
- However, a more pronounced trend was observed in non-active SPMS applying CEP1 and CEP2, indicating that the composite endpoints which cover different functional domains capture treatment effects more comprehensively
- Using such composite endpoints might help reducing sample sizes in future studies in SPMS

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9HPT, 9-Hole Peg Test; CEP, composite endpoint; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk Test

Poster Presented at the American Academy of Neurology (AAN) 2021, April 17-22, 2021

Results – Treatment effects

Back-up slide

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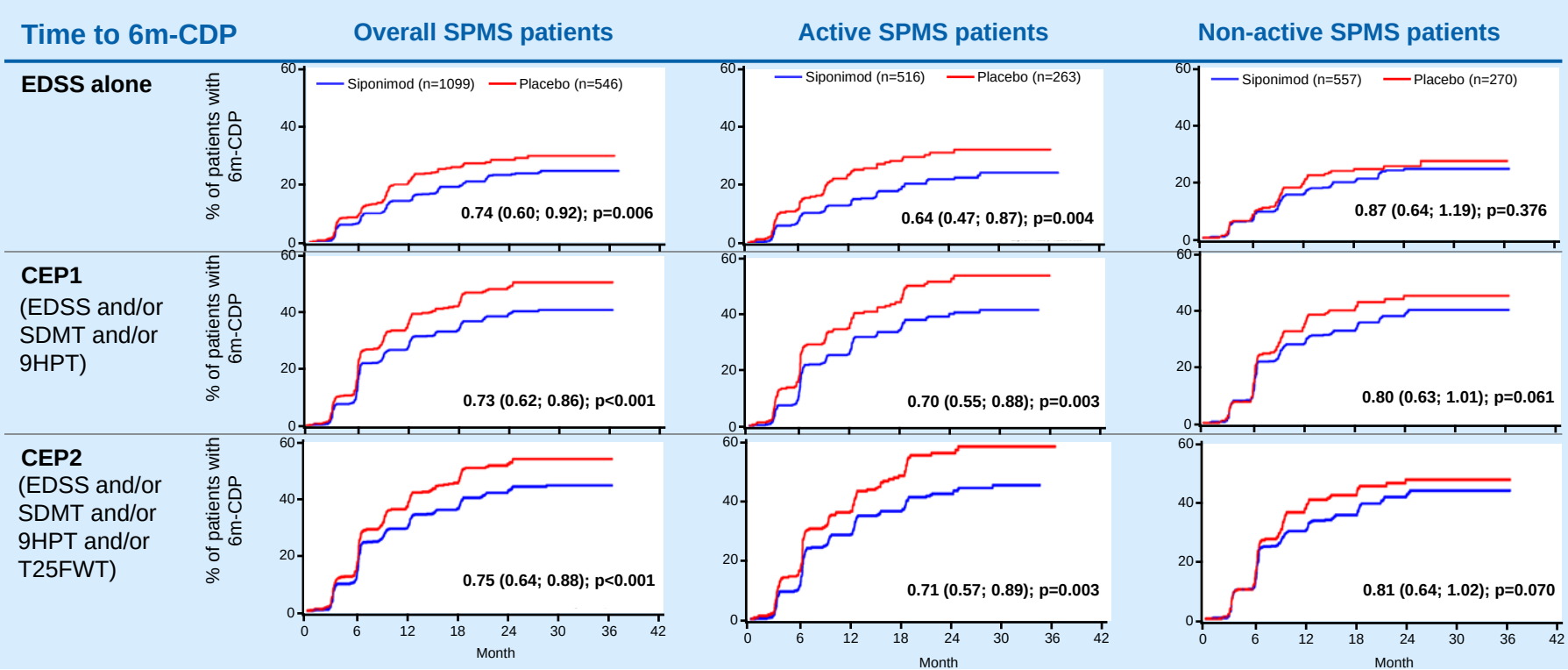
Effect of treatment on time-to-6-month confirmed disability progression based on EDSS alone, CEP1 and CEP2



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Numbers in the figure represent HR [95% CI]; p-value. CEP1, 6-month CDP events based on EDSS and/or SDMT and/or 9-HPT; CEP2, 6-month CDP events based on EDSS and/or SDMT and/or 9HPT and/or T25FWT
6m-CDP, 6 month confirmed disability progression; CEP, composite endpoints; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio SPMS, secondary progressive multiple sclerosis