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

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Oral presentation

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Background

- Composite endpoints (CEPs) have the potential to capture disease progression more comprehensively as they account for functions that are not, or not optimally, captured by a single endpoint alone[1]
- With CEPs, increment of the number of events is expected to increase power/statistical efficiency
- The phase 3 EXPAND study in patients with SPMS[2] evaluated the efficacy of siponimod on confirmed disability progression (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, resulted in higher sensitivity to detect treatment effects in SPMS[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

9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; 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.

Objective

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

CEP, Composite endpoints; SPMS, secondary progressive multiple sclerosis

Methods

This post hoc analysis included data from patients with SPMS from the Phase 3 EXPAND core study:

Overall population	Subgroup of patients with active disease[a]	Subgroup of patients with non-active disease[b]
Siponimod: N=1099 Placebo: N=546	Siponimod: N=516 Placebo: N=263	Siponimod: N=557 Placebo: N=270

Statistical analysis:

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

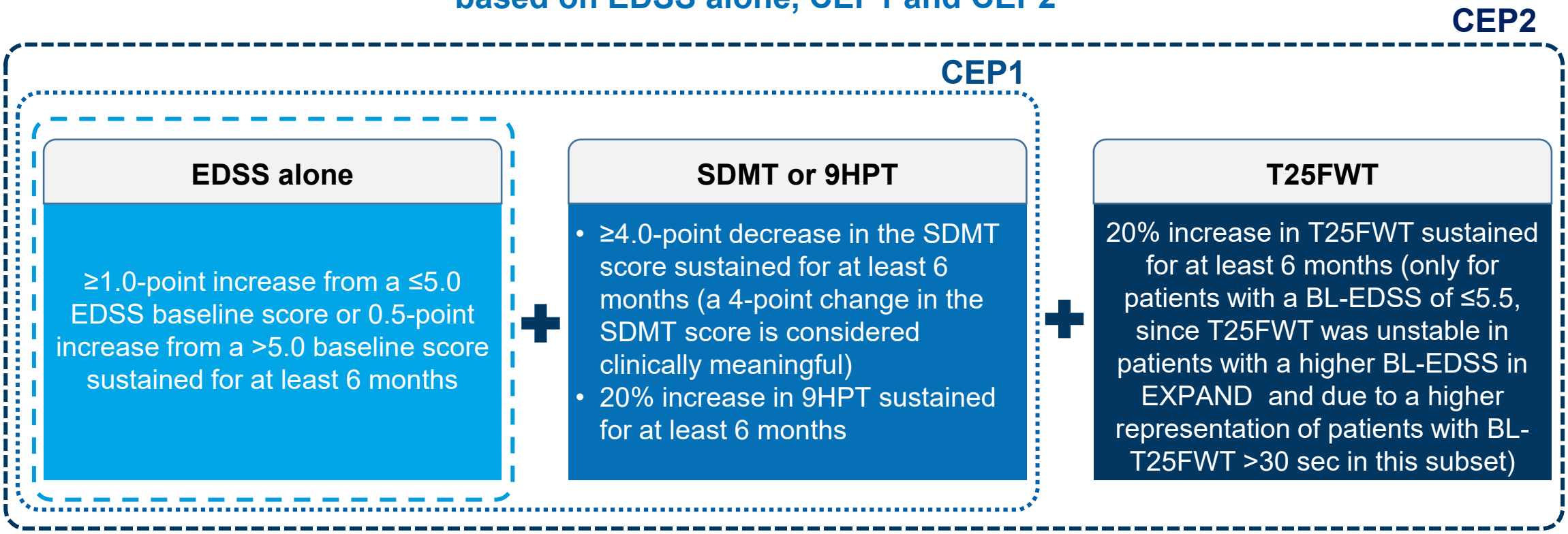
[a]Defined as the presence of at least one relapse in the 2 years before screening and/or ≥1 Gd+ T1 lesion at baseline.
[b]Defined as no relapse in the 2 years prior to screening and no Gd+ T1 lesion at baseline.

CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SPMS, secondary progressive multiple sclerosis

Methods

Investigated endpoints

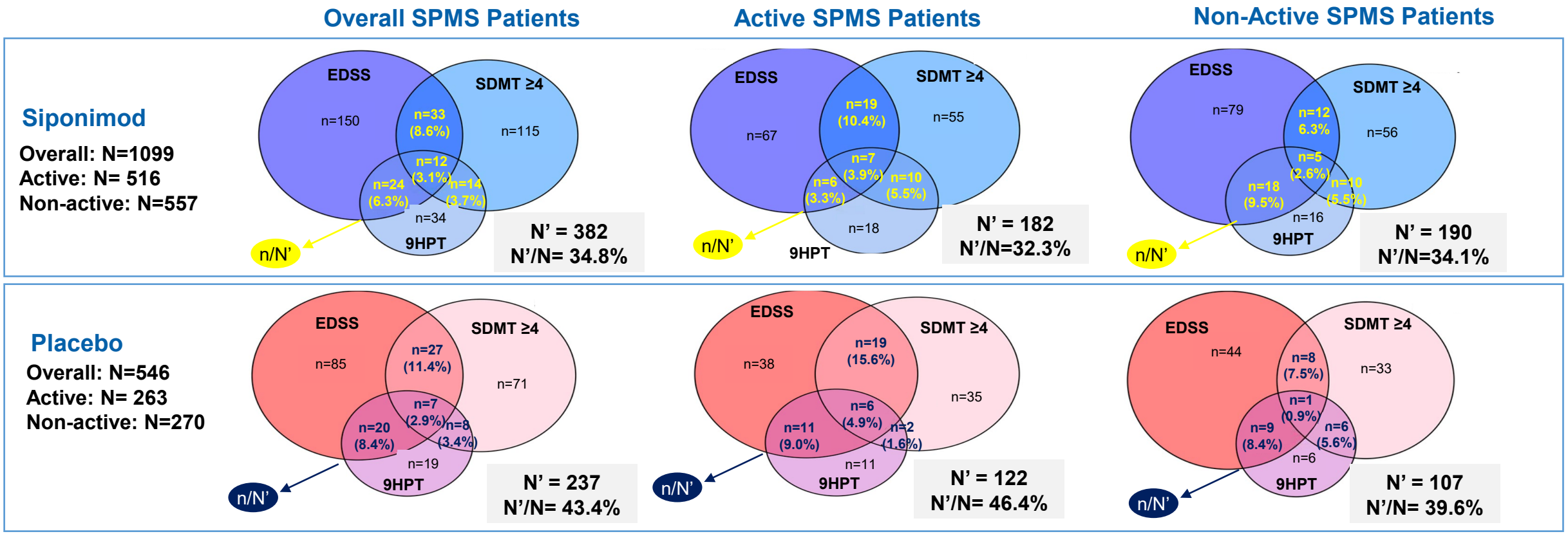
Compared treatment effect on reducing time-to-6-month confirmed disease progression based on EDSS alone, CEP1 and CEP2



+, and/or; 9HPT, 9-Hole Peg Test; BL, baseline; 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.

Results

Contribution of each individual component by CEP1 in overall, active SPMS and non-active SPMS patients



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

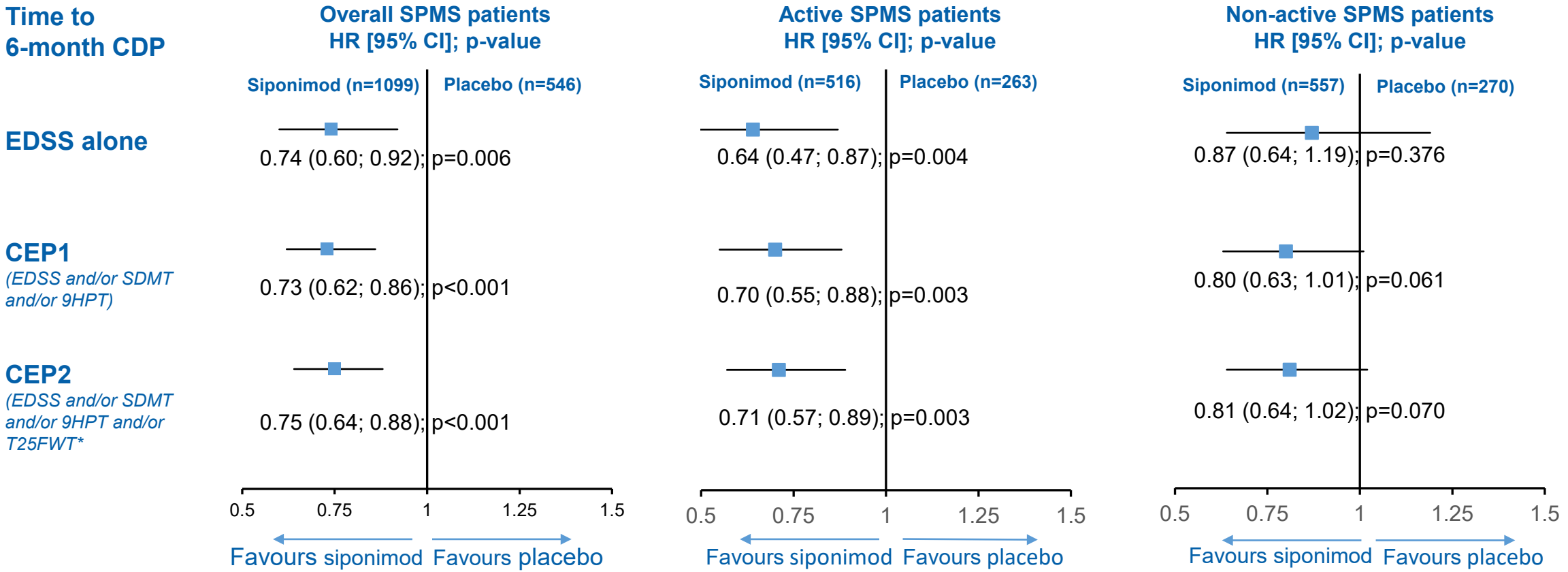
- The three endpoints, EDSS, SDMT and 9HPT, appear to capture distinct aspects of 6-month CDP with only minor overlap
- More overlap of the endpoints (i.e. more dimensions of disease progression) was observed in the placebo-treated active SPMS patients

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 effect as measured by risk reduction of disability progression with EDSS alone, CEP1 and CEP2

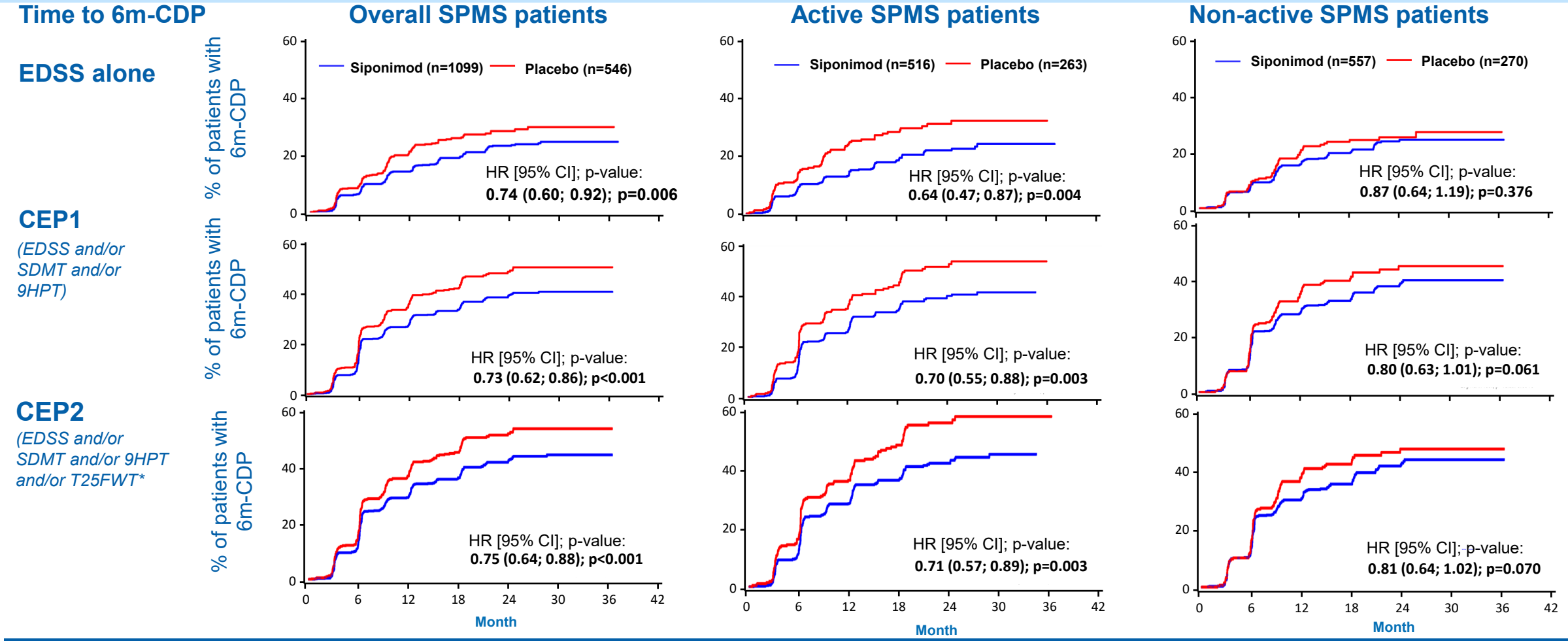


- Siponimod was associated with significant risk reductions (range: 25%–37%) versus placebo in the overall and active SPMS populations
- In non-active SPMS patients, the trend favoring siponimod treatment was more pronounced with the composite endpoints
- The CEPs yield smaller confidence interval and thus greater power to assess treatment difference
- 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)

*(*EDSS and/or SDMT and/or 9HPT and/or T25FWT, if BL-EDSS <=5.5) or (EDSS and/or SDMT and/or 9HP, if BL-EDSS >5.5)* 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. BL, baseline; CDP, confirmed disability progression; CEP, composite endpoints; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test

Results

Percentage of patients with CDP based on EDSS alone, CEP1 and CEP2 – Kaplan Meier (KM) estimates



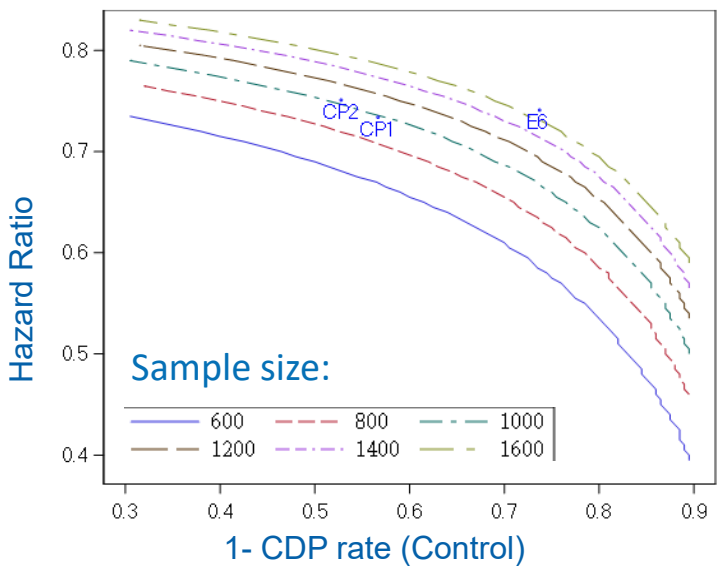
With EDSS alone, the percentage (KM estimates) of placebo patients with CDP at month 18 was 26% (Overall), 28.5% (active) and 24.7% (non-active); with CEP1, percentage with CDP events was incremented to 43% (overall), 45% (active) and 41% (non-active)

*(*EDSS and/or SDMT and/or 9HPT and/or T25FWT, if BL-EDSS <=5.5) or (EDSS and/or SDMT and/or 9HP, if BL-EDSS >5.5)* p-value. CEP1, 6-month CDP events based on EDSS and/or SDMT and/or 9-HPT ; 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; BL, baseline; CEP, composite endpoints; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio SPMS, secondary progressive multiple sclerosis

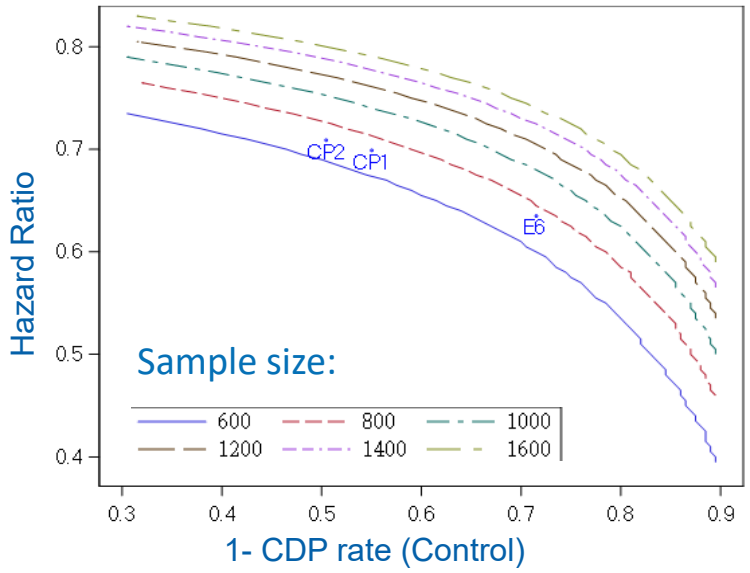
Results

Sample size and power calculation

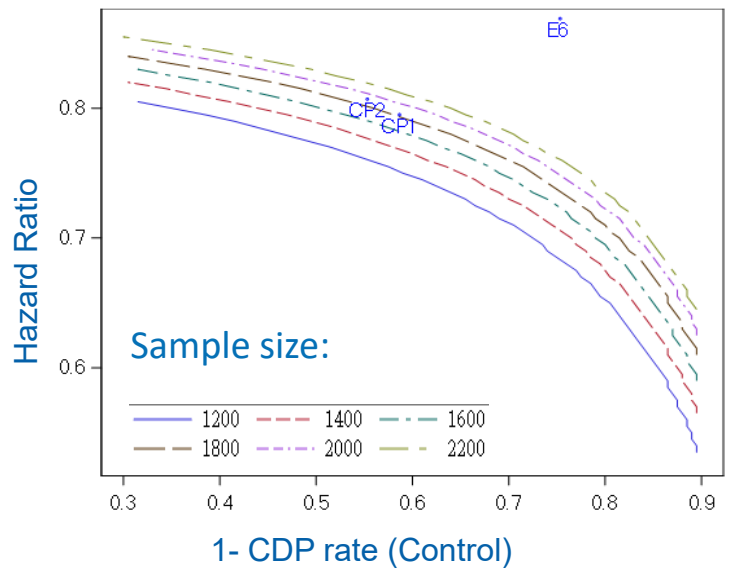
Overall SPMS Patients



Active SPMS Patients



Non-Active SPMS Patients



Singleton: E6: 6-Month CDP based on EDSS
Composite endpoint (CEP): CEP1: *EDSS and/or SDMT and/or 9HPT* ;
CEP2: (*EDSS and/or SDMT and/or 9HPT and/or T25FWT, if BL-EDSS <=5.5) or (EDSS and/or SDMT and/or 9HP, if BL-EDSS >5.5)*

Method: The Schoenfeld's [Collet, 2003] formulae was used to calculate number of events over a range of values for the Hazard ratio and CDP rates in ther placebo arm.
Assumptions : Superiority of active treatment vs placebo; two-sided test at the 5% significance level; 80% power; 1:1 allocation ratio; fixed follow-up of 24 months (i.e. Onset of CDP within 18 months); To account for permature withdrawal, a safety margin of 15% was added to this number.

- CEPs could be advantagiously used to reducte sample size by >600 subjects in future trials
- It may not be advantageous to expand the single EDSS endpoint in active disease
- A study in SPMS patients without active disease may not be feasible if based on the single EDSS endpoint instead of a composite

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; 9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; CEP, composite endpoints; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk test

Conclusions

- Adding SDMT and 9HPT to the EDSS assessment (CEP1) allowed detection of treatment effects on a broader spectrum of functions in patients with SPMS compared with EDSS alone, in both patients with active and non-active disease
- Addition of T25FWT did not further increase test sensitivity
- Siponimod treatment effect with the two composite endpoints was consistent with that observed with the anchor EDSS endpoint, i.e. 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 composite endpoints could help to reduce the sample sizes by more than 600 patients in future studies in full SPMS. In non-active SPMS, sample size could be reduced (as compared to EDSS alone) to a feasible range

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

Thank you