Sustained reduction of disability and cognitive decline with long-term siponimod treatment in patients with active SPMS: EXPAND data up to 5 years

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Disclosures

Gavin Giovannoni is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck KGaA, Sanofi Genzyme, and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians' summit and several medical education meetings. He is also the Co-Chief Editor of Multiple Sclerosis and Related Disorders (Elsevier).
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Background and objective

- In the EXPAND Core study, the largest randomized Phase 3 trial in SPMS patients, siponimod significantly reduced the risk of disability progression, and meaningful worsening in cognitive processing speed (≥4-point decline in the SDMT score) versus placebo[1,2]
- In the subgroup of patients with active SPMS[a], the benefits of siponimod versus placebo were more pronounced. In the Core study, siponimod reduced the relative risk of[3]
  - Disability progression by 31% (3mCDP) and 37% (6mCDP)[3]
  - Meaningful worsening in cognitive processing speed based on SDMT by 27%[3]
- The treatment benefits of siponimod for the overall EXPAND population were sustained with long-term treatment for up to 5 years with a delay of approximately 50% for time to disability progression and meaningful worsening in cognitive processing speed[4]

Objective	**To assess the long-term efficacy and safety of siponimod in patients with active SPMS in the core and extension parts of the EXPAND study**

[a]presence of relapses in the 2 years prior to screening and/or ≥1 T1 gadolinium-enhancing lesion at baseline.
3mCDP/6mCDP, 3-/6-month confirmed disability progression; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis.
1. Kappos L, et al. *Lancet.* 2018;391:1263–1273; 2. Benedict RHB, et al. Presented at *AAN* 2018, S44.004; 3. Gold R, et al. Presented at *ECTRIMS* 2019, P750; 4. Kappos L, et al. Presented at *AAN* 2020, S40.003.

Methods

- This is a post-hoc subgroup analysis[a] (ITT population) of the Core and Extension parts of the Phase 3 EXPAND study
- The subgroup included patients with active SPMS who had received ≥1 dose of randomized treatment during the Core part and who were followed in the Extension part
  - **Placebo-siponimod group**: Patients randomized to receive placebo in the Core period and who switched to open-label siponimod in the Extension period
  - **Continuous siponimod group**: Patients randomized to receive siponimod in the Core period and continued siponimod in the Extension part

Endpoints

- Time to 6-month confirmed disability progression (6mCDP) based on the EDSS score
- Time to 6-month confirmed cognitive worsening (CPS; 6mCCW) based on the SDMT score
  - Meaningful worsening of CPS defined as ≥4-point decline in the SDMT score
- ARR

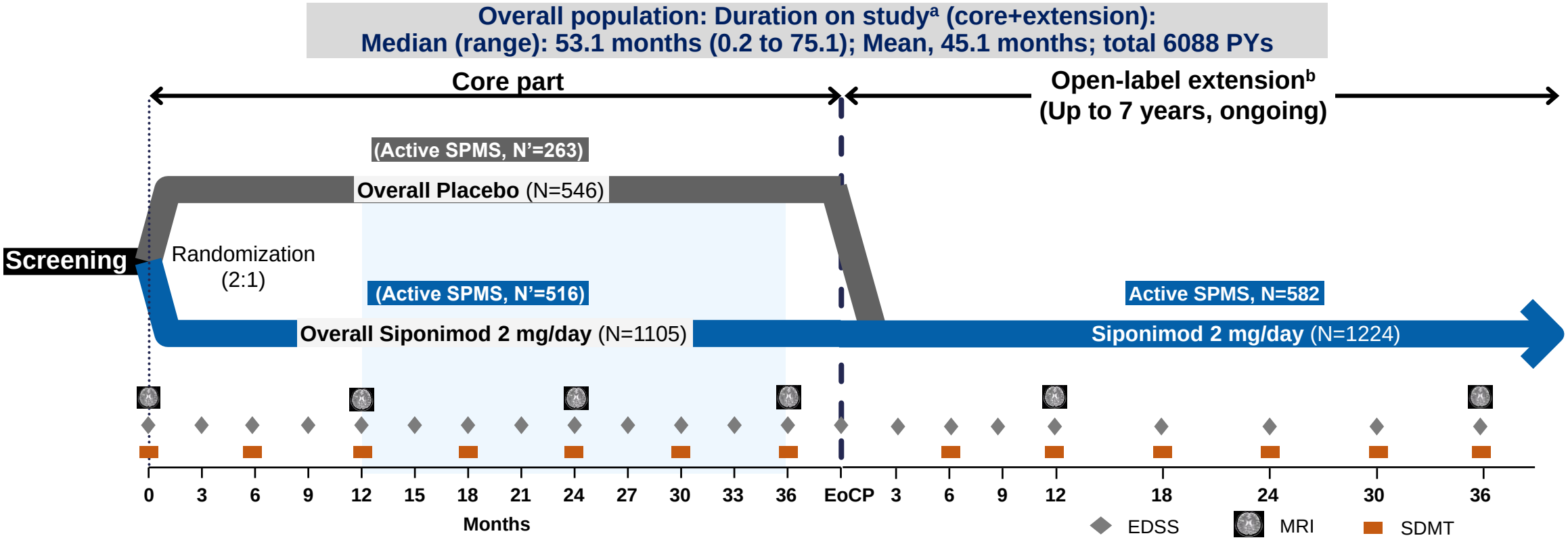
Statistical analyses

- Time to 6mCDP and time to 6mCCW were analyzed using a Cox proportional hazards model with treatment, baseline EDSS score and SPMS group as covariates using combined EDSS data from the Core and Extension parts
- The ARR was estimated by a negative binomial regression model adjusted for the appropriate covariates

*36 month extension; data cut-off [6 April 2019]; total study duration ≤5 years
6mCDP, 6-month confirmed disability progression; 6mCCW, 6-month confirmed cognitive worsening in the 4-point SDMT; ARR, annualized relapse rate; CPS, cognitive processing speed; EDSS, Expanded Disability Status Scale; ITT, intent-to –treat; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

EXPAND study design (Core and Extension[a])

Overall study population and patients with active disease



- Of the 1651 patients randomized in the EXPAND Core period, 1224 entered the Extension
- Of 779 active SPMS patients from the EXPAND Core period (continuous siponimod: N'=516; Placebo-siponimod: N'=263), 582 entered the Extension
  - Study duration (Core and Extension): median [range]: 53.8 [0.2; 74.5] months; mean, 45.8 months; total 2930 PYs

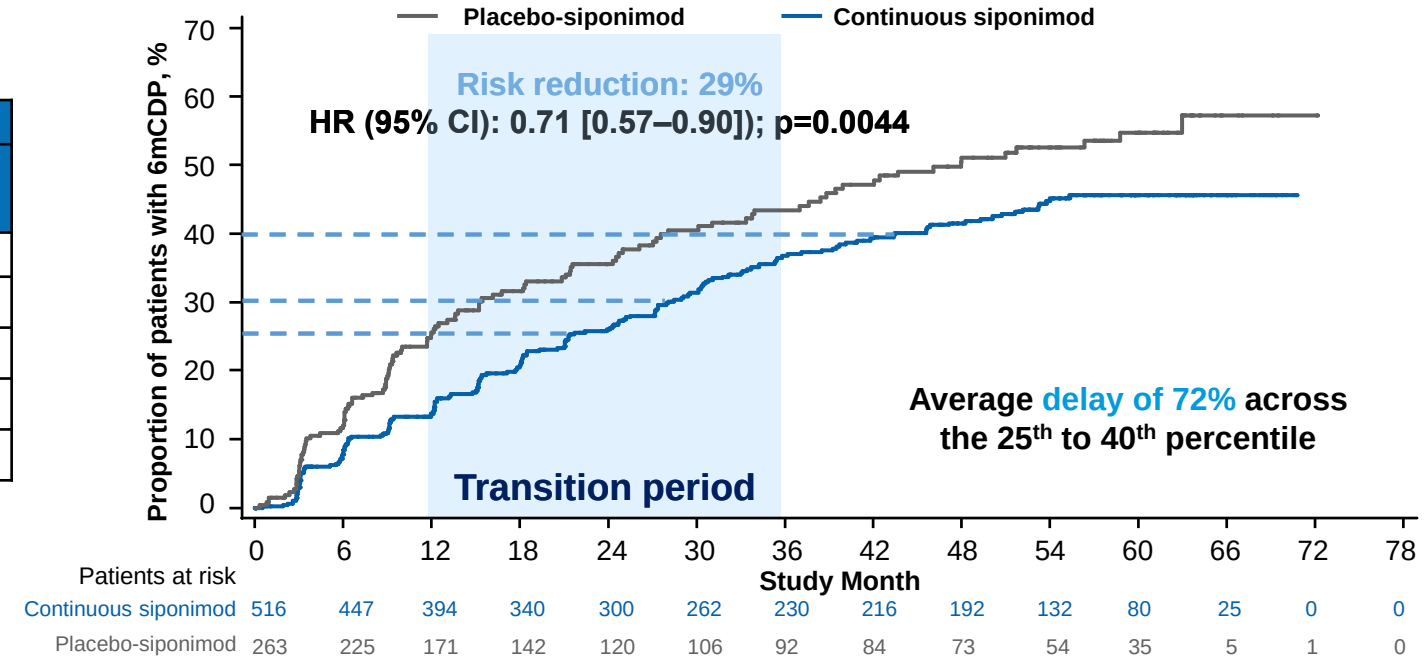
[a]Extension data cut-off: 06 April 2019 (Month 36 visit of extension]; total study duration ≤5 years (core+extension); [b]Open-label starts when patient has an "event"
EDSS, Expanded Disability Status Scale; EoCP, end of core part; PYs, patient years; MRI, magneric resonance imaging; N, total number of patients (safety set); N', total number of patients (full analysis set); SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS

Effect of siponimod on 6-month confirmed disability progression in active SPMS

Time to 6mCDP in active SPMS patients

Time-to-6mCDP percentiles in active SPMS patients

Percentile	Duration in months		
	Placebo-siponimod	Continuous siponimod	Delay
25th	12.0	21.3	78%
30th	15.2	28.1	84%
40th	28.1	43.5	55%
Median	48.0	n.r.	
		Average delay	**72%**



- **In active SPMS patients, risk of 6mCDP was reduced by 29% and time-to-6mCDP was prolonged by ~70% in the continuous siponimod versus placebo-siponimod groups**
- **In non-active SPMS patients, risk of 6mCDP was numerically reduced by 12.5% and time-to-6mCDP was prolonged by ~30%; for the placebo-siponimod group, the time to progression was longer vs active SPMS patients (40th percentile: 41.3 vs 28.1 months)**

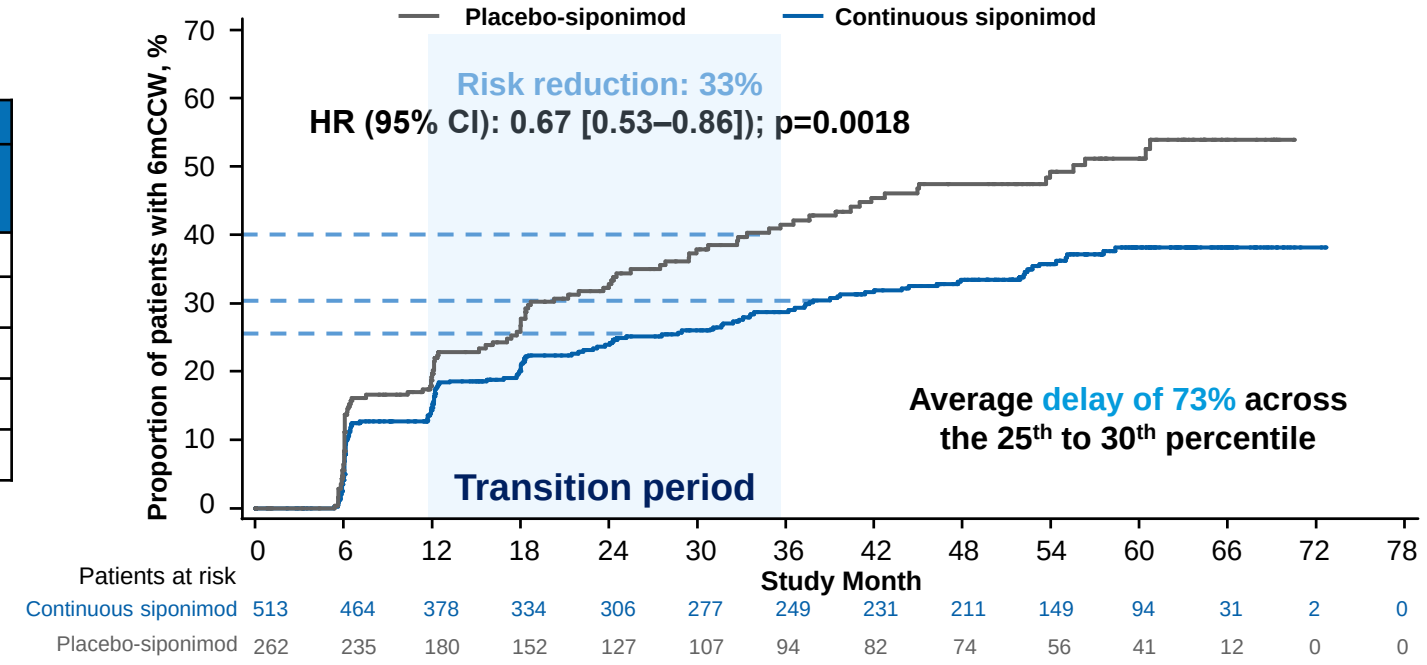
6mCDP, 6-month confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; n.r., not reached; SPMS, secondary progressive multiple sclerosis

Effect of siponimod on clinically meaningful worsening in cognitive processing speed in active SPMS

Time to 6mCCW in active SPMS patients

Time-to-6mCCW percentiles in active SPMS patients

Percentile	Duration in months		
	Placebo-siponimod	Continuous siponimod	Delay
25th	17.4	25.2	45%
30th	18.7	37.6	100%
40th	33.4	n.r.	
Median	55.5	n.r.	
		Average delay	**73%**

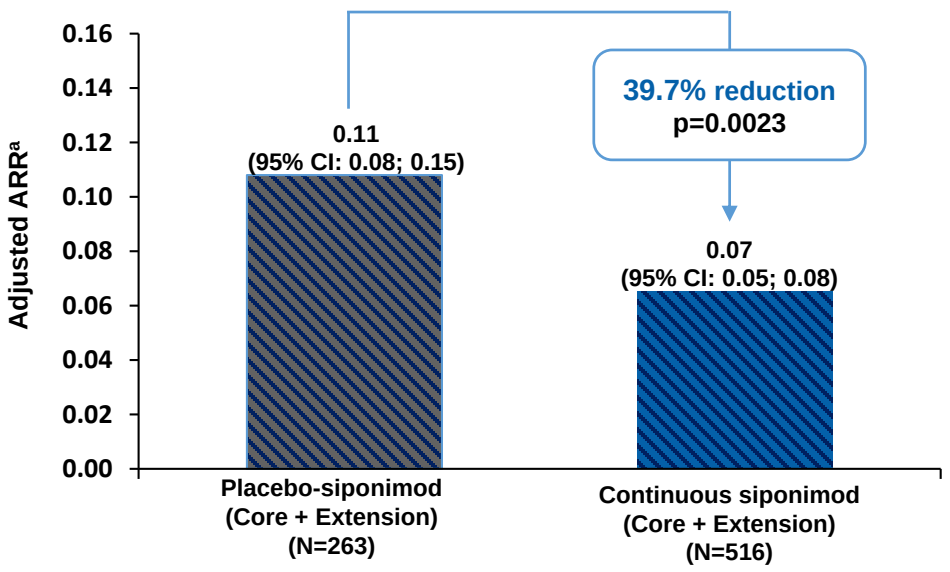


- **In active SPMS patients, risk of 6mCCW was reduced by 33%, and time to 6mCCW was delayed by ~70% in the continuous siponimod versus placebo-siponimod groups**
- **In non-active SPMS patients, risk of 6mCCW was numerically reduced by 12.3% and time-to-6mCCW was prolonged by ~24%; in the placebo-siponimod group, the time to progression was longer versus active SPMS (40th percentile: 48.5 vs 33.4 months)**

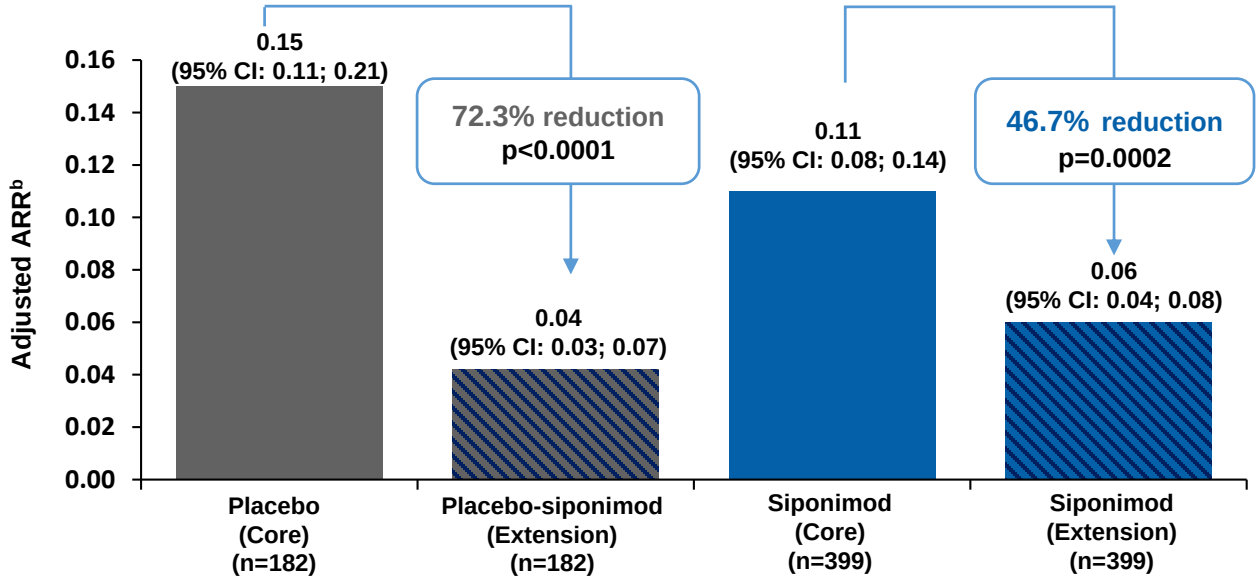
6mCCW, 6-month confirmed cognitive worsening; CI, confidence interval; HR, hazard ratio; n.r., not reached; SPMS, secondary progressive multiple sclerosis

Effect of siponimod on annualized relapse rate in active SPMS

Between-group comparison (continuous siponimod vs placebo-siponimod group)



Within-group comparison (Within placebo and siponimod groups)



- **In active SPMS patients, ARR was significantly reduced in the continuous siponimod versus the placebo-siponimod group**
- **In patients with non-active SPMS, the reduction in ARR in the continuous siponimod versus the placebo-siponimod group was also significant (0.03 vs 0.08; p<0.0001)**

[a]Obtained from fitting a negative binomial regression model adjusted for core part treatment group, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and baseline number of T1 Gd-enhancing lesions categories; [b]Poisson regression model adjusted for treatment period (core and extension period) and baseline EDSS
ARR, annualized relapse rate; CI, confidence interval; SPMS, secondary progressive multiple sclerosis

Conclusions

- Siponimod treatment effects on disability, cognitive processing speed, and relapse outcomes in patients with active SPMS are sustained for up to 5 years
  - Siponimod treatment was associated with a significant delay of approximately 70% in time to disability progression, and likewise a significant delay to experience a meaningful worsening in cognitive processing speed
  - Siponimod treatment was associated with significant reduction (~40%) in ARR in the continuous siponimod versus the placebo-siponimod group
- The superior effects observed with continuous siponimod (vs the placebo-siponimod group) together with the long-term safety profile of siponimod which was consistent with the core study (data not shown) highlight the benefit of earlier treatment initiation, and support the value of siponimod for the treatment of active SPMS

ARR, annualized relapse rate; SPMS, secondary progressive multiple sclerosis

Thank you