Long-Term Efficacy and Safety of Siponimod in Active SPMS and Overall SPMS Populations: EXPAND Study Data Up to 5 Years

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Introduction

- The EXPAND study was conducted in a broad SPMS population (median EDSS=6.0); however, given approval was granted in relapsing MS and active SPMS groups in the Unites States[1], the response of the active SPMS subgroup is of clinical interest
- In the EXPAND Core study, siponimod significantly reduced the risk of disability progression, meaningful worsening in cognitive processing speed (≥4-point decline in the SDMT score), and the risk of relapses versus placebo[2,3]
- Long-term evaluation is important in the treatment of chronic disease progression in MS

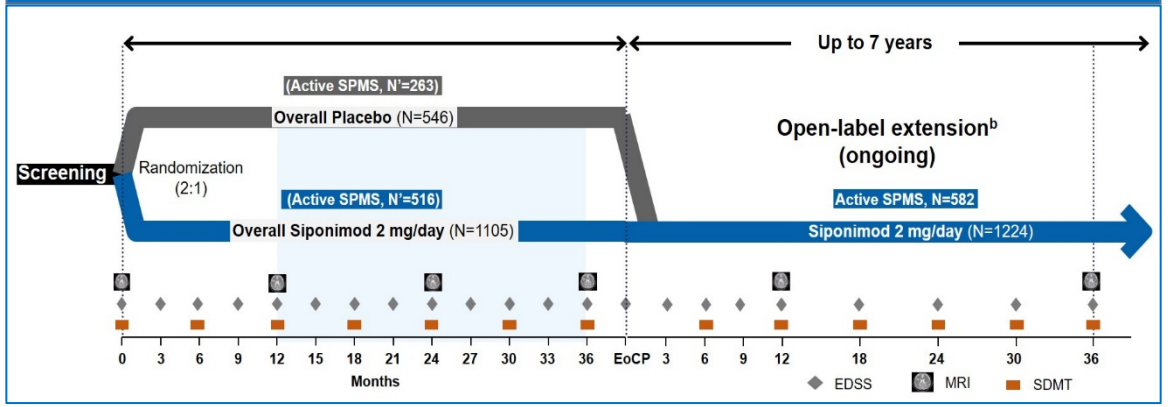
Objective

- To assess the long-term efficacy and safety of siponimod in the active SPMS subgroup and overall SPMS population from the Core and Extension parts of EXPAND

Methods

- This analysis included Core and 36-month extension data from all study participants who received ≥1 dose of siponimod 2 mg or placebo
- **Overall population:** Of the 1651 patients randomized in the EXPAND Core part, 1224 (74%) entered the Extension part (878 [72%] ongoing)
  - Study duration (Core+Extension): Median (range), 53.1 months (0.2–75.1); mean, 45.1 months; total 6088 PYs

Study design (EXPAND Core+Extension)[a]



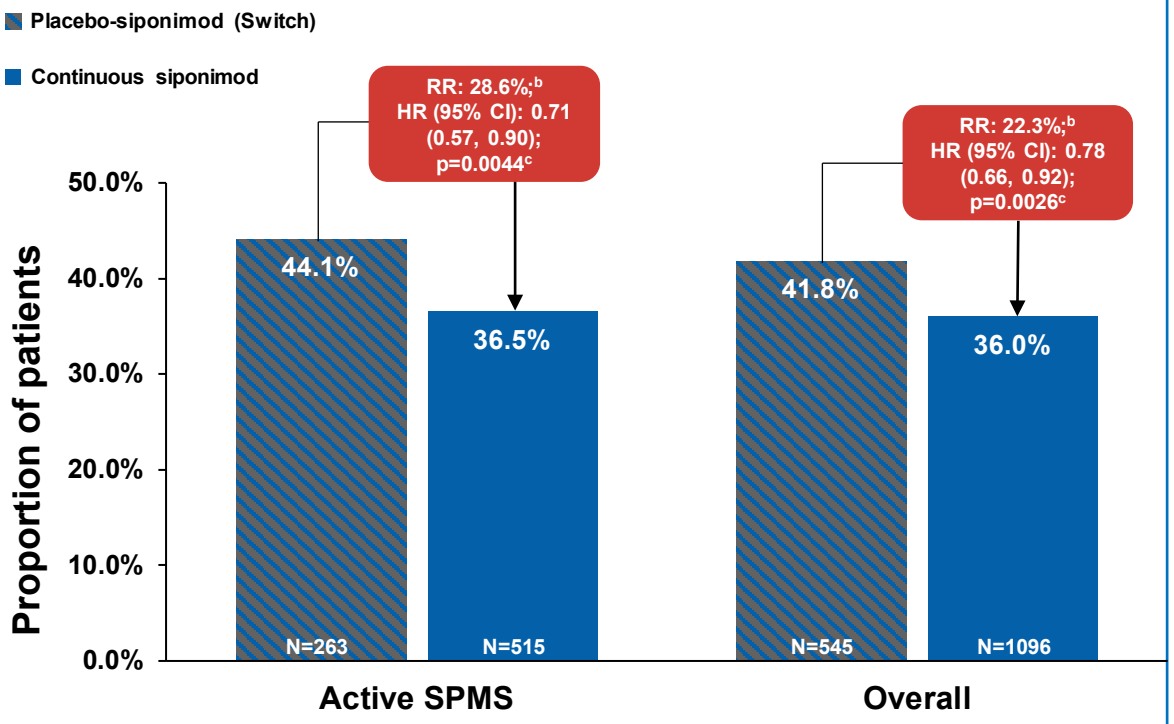
- **Active SPMS population:** Of 779 active SPMS patients from the EXPAND Core part (continuous siponimod: N'=516; placebo-siponimod: N'=263), 582 entered the Extension part
  - Study duration (Core+Extension parts): Median (range), 53.8 months (0.2–74.5); mean, 45.8 months; total 2930 PYs
- Time-to-6mCDP (by EDSS), time-to-6mCCW, and ARR
  - **Continuous†** (siponimod in Core+Extension) group
  - **Switch‡** (placebo in Core part and siponimod in Extension part) group
- Safety (Core and Core+Extension): AEs and SAEs

6mCCW, 6-month confirmed clinically meaningful worsening of ≥4 points from baseline in SDMT Oral score; AE, adverse event; ARR, annualized relapse rate; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; EoCP, end of Core part; MRI, magnetic resonance imaging; MS, multiple sclerosis; N, total number of patients (safety set); N', total number of patients (full analysis set); PY, patient-year; SAE, serious adverse event; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS.
*Active SPMS is defined as the presence of relapses 2 years before screening and/or ≥1 T1 gadolinium-enhancing lesion at baseline; †Continuous siponimod group: Patients randomized to receive siponimod in the Core period and continued siponimod in the Extension part. ‡Placebo-siponimod group: Patients randomized to receive placebo in the Core part and who switched to siponimod in the Extension part. **[a]Extension data Cut-off April 6, 2019; total study duration of ≤5 years (Month 36 visit to extension);** [b]Open-label starts when patient has an "event".

1. MAYZENT. Prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021; 2. Kappos L, et al. *Lancet*. 2018;391(10127):1263–1273; 3. Benedict RHB, et al. *Neurology*. 2021;96(3):e376–e386. doi:10.1212/WNL.0000000000011275

Long-Term Siponimod Treatment (Up to 5 years) Significantly Reduced the Risk of 6-mCDP in the Overall and Active SPMS Populations

Proportion of patients with 6mCDP[a]



Time-to-6mCDP (K-M estimates)

Percentile of population	Active SPMS			Overall		
	Switch (months)	Continuous (months)	Delay (%)	Switch (months)	Continuous (months)	Delay (%)
25th	12.0	21.3	78	13.6	21.0	54
30th	15.2	28.1	85	18.4	29.8	62
40th	28.1	43.5	55	33.9	44.9	32
50th	48.0	n.r.	-	51.7	n.r.	-
	Average delay (%)		72	Average delay (%)		49

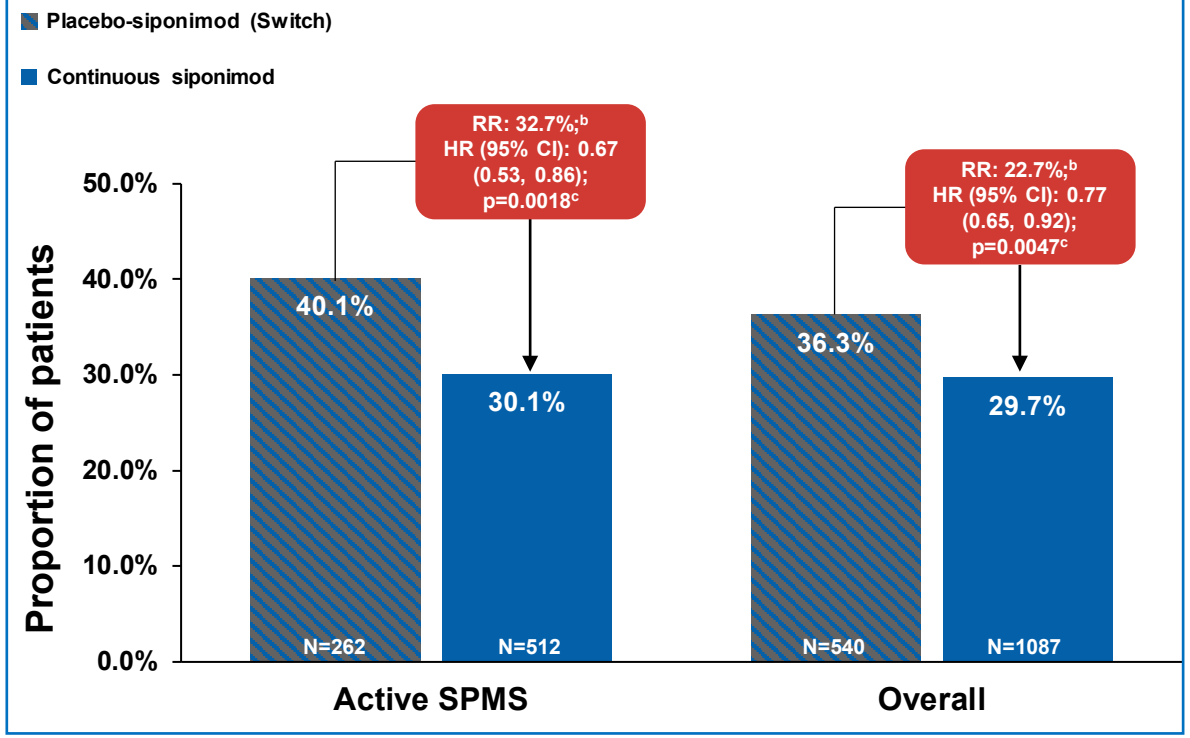
- In both the overall and active SPMS populations, siponimod treatment delayed the time to reach 6mCDP
  - Only in the switch group did 50% of the populations meet 6mCDP

6mCDP, 6-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; N, number of subjects included in the analysis (i.e. with non-missing covariates); K-M, Kaplan-Meier; n.r, not reached; RR, risk reduction; SPMS, secondary progressive multiple sclerosis.

[a]Using a Cox proportional hazards model with treatment, baseline EDSS and SPMS group (with/without superimposed relapses, baseline definition) as covariate on combined EDSS data from Core and Extention parts. [b]Risk reduction is derived as (1−HR)×100. [c]Indicates statistical significance (2-sided) at the 0.05 level.

Long-Term Siponimod Treatment (Up to 5 years) Significantly Reduced the Time to Worsening in Cognitive Processing Speed in the Overall and Active SPMS Populations

Proportion of patients with 6mCCW[a]



Time-to-6mCCW (K-M estimates)

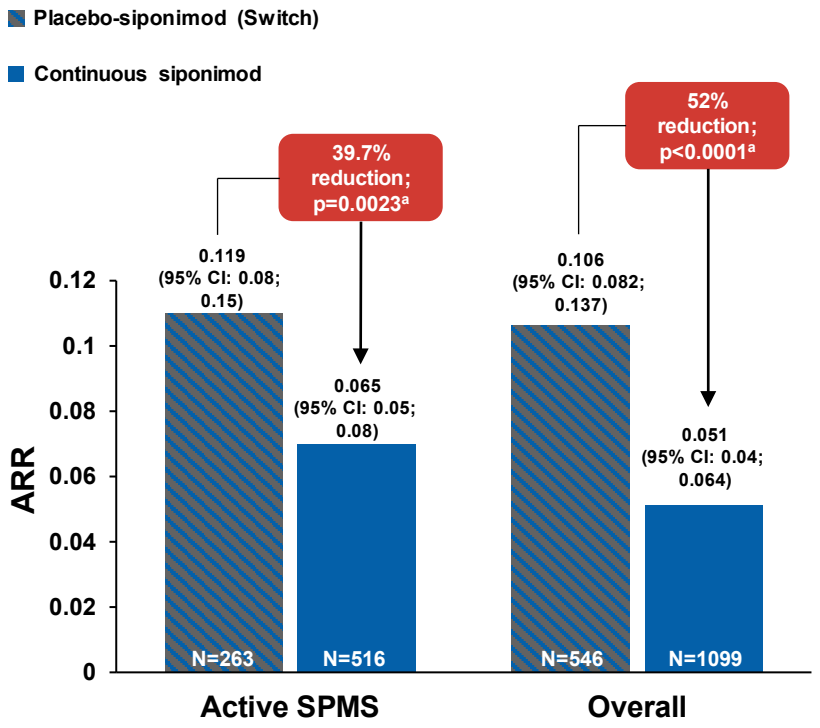
Percentile of population	Active SPMS			Overall		
	Switch (months)	Continuous (months)	Delay (%)	Switch (months)	Continuous (months)	Delay (%)
25th	17.4	25.2	45	18.3	29.6	62
30th	18.7	37.6	100	26.4	39.0	48
40th	33.4	n.r.	-	41.3	n.r.	-
50th	55.5	n.r.	-	n.r.	n.r.	-
	Average delay (%)		73	Average delay (%)		55

- In both the overall and active SPMS populations, siponimod treatment delayed the time to reach 6mCCW
  - Only in the switch group did 50% of the active SPMS population meet 6mCCW

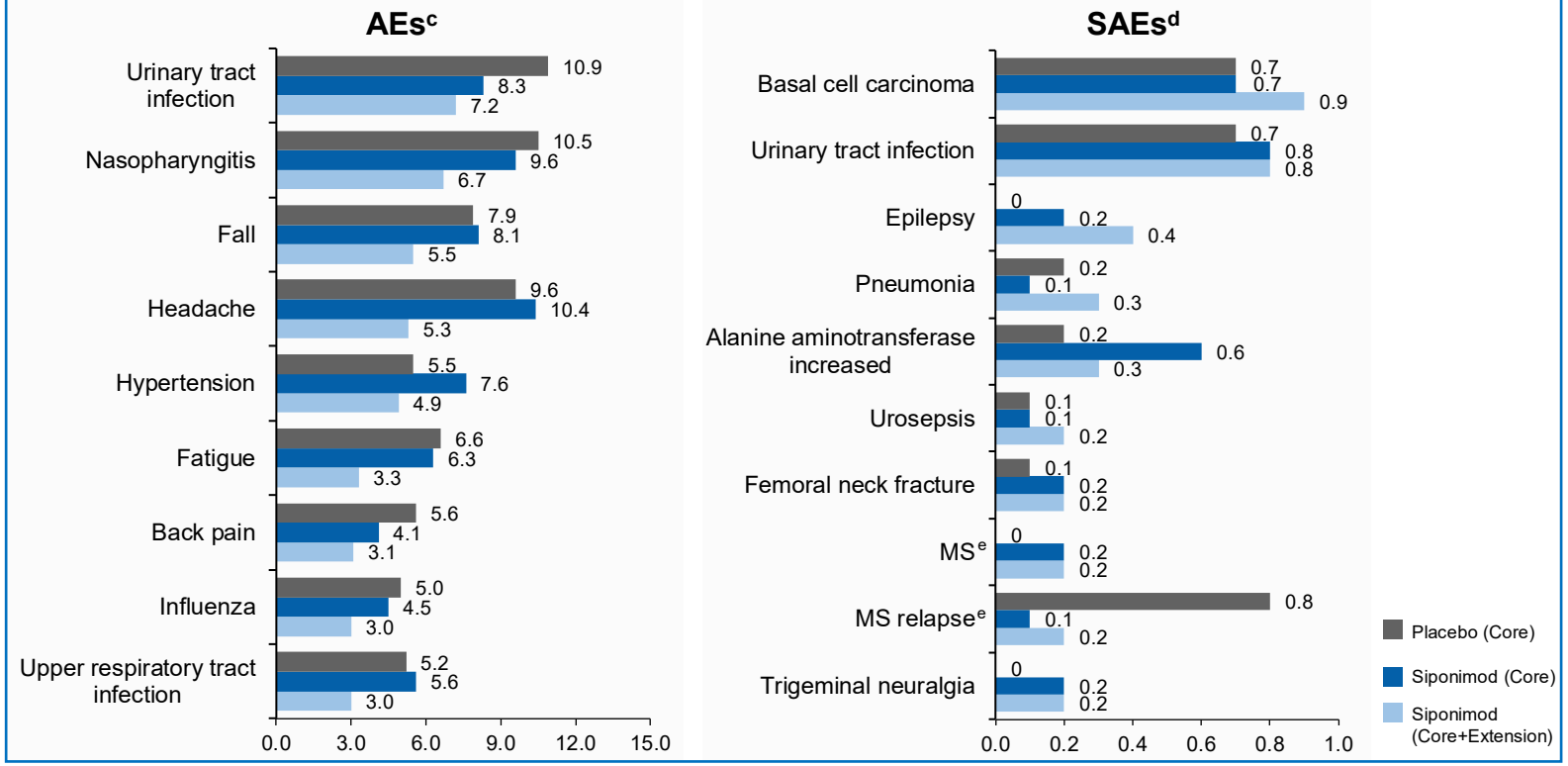
6mCCW, 6-month confirmed clinically meaningful worsening of ≥4 points from baseline in SDMT Oral score; CI, confidence interval; HR, hazard ratio; N, number of subjects included in the analysis (i.e. with non-missing covariates); K-M, Kaplan-Meier; n.r, not reached; RR, risk reduction; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis.
[a]Using a Cox proportional hazards model with treatment, baseline EDSS, baseline SDMT and SPMS group (with-/without superimposed relapses, baseline definition) as covariate on combined SDMT data from Core and Extention parts. [b]Risk reduction is derived as (1−HR)×100. [c]Indicates statistical significance (2-sided) at the 0.05 level.

Long-Term Siponimod Treatment (Up to 5 years) Significantly Reduced ARR in the Overall and Active SPMS Populations. No New Safety Findings Observed

ARR



IRs per 100 PYs[b] (Safety set – overall population; Core+Extension)



- ARR reduction was significant in the continuous versus switch group across active SPMS and overall populations
- IRs of AEs/100 PYs in both populations were consistent over the long-term period with no new safety findings observed

AE, adverse event; ARR, annualized relapse rate; CI, confidence interval; IR, incidence rate; MS, multiple sclerosis; PY, patient-year; SAE, serious AE; SPMS, secondary progressive MS.
[a]Indicates statistical significance (2-sided) at the 0.05 level. [b]Per 100-PYs. IRs were computed as the number of participants with an AE divided by the total exposure for the AE (i.e., cumulative exposure until the first occurrence or until the end of the extension). [c]IR ≥3 in siponimod group during Core+Extension. [d]IR ≥0.2 in siponimod group during Core+Extension. [e]Reported as SAEs by investigator (if MS/MS relapse is unusually severe or medically unexpected as per protocol).

Conclusions

- The effects of siponimod on disability (6mCDP), cognitive processing speed (6mCCW), and relapse (ARR) outcomes are sustained for up to 5 years
  - In both the overall and active SPMS populations, continuous siponimod treatment was associated with a significant delay in the time to disability progression and time to worsening in cognitive processing speed versus switch treatment
  - Continuous siponimod treatment was associated with significant reductions in ARR versus switch treatment
- Sustained treatment effects of continuous siponimod treatment versus patients who switched later highlight the benefit of earlier treatment initiation
- The safety profile of siponimod for up to 5 years remained favorable and consistent with the core study

Disclosures

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6mCCW, 6-month confirmed clinically meaningful worsening of ≥4 points from baseline in SDMT Oral score; 6mCDP, 6-month confirmed disability progression; ARR, annualized relapse rate; SPMS, secondary progressive multiple sclerosis.