

# **Analyses of the Effect of Baseline Age on the Efficacy and Safety of Siponimod in Patients with Active Secondary Progressive Multiple Sclerosis from the Phase 3 EXPAND Study**

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## Background

- For patients with relapsing forms of multiple sclerosis (RMS), risk of transitioning to secondary progressive MS (SPMS) remains high, despite treatment availability<sup>1</sup>
- Siponimod (Mayzent®) is a selective sphingosine 1-phosphate receptor (S1P1 and S1P5) modulator, approved in the USA for the treatment of adults with RMS, including clinically isolated syndrome, relapsing-remitting MS, and active SPMS<sup>2</sup>
- Increasing age is associated with disability accumulation, independent of MS duration, and may negatively affect treatment outcomes<sup>3</sup>
- In EXPAND, a phase 3 trial examining the efficacy and safety of siponimod in an SPMS population, siponimod significantly reduced risk of confirmed disability progression (CDP) versus placebo<sup>4</sup>
- We investigated efficacy and safety of siponimod in the subpopulation of patients from EXPAND with active SPMS (relapse in 2 years before screening and/or  $\geq 1$  T1 Gd+ lesion at baseline), in line with approved indication of Siponimod, and compared by age subgroups<sup>2</sup>

## Objective

- Assess efficacy and safety of siponimod in patients with active SPMS in subgroups of patients aged <50 and  $\geq 50$  years at Baseline from the EXPAND study

Gd+, gadolinium-enhancing.

1. University of California SFMSET, et al. Ann Neurol. 2016;80:499-510. 2. Novartis Pharmaceuticals Corporation. Prescribing information. Mayzent® 2019. Available from:

<https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mayzent.pdf> (Accessed May 1, 2019). 3. Scalfari A, et al. Neurology. 2011;77:1246-1252. 4. Kappos L, et al. Lancet. 2018;391:1263-1273.

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## Study design

- EXPAND was a phase 3, 36 month, randomized, placebo-controlled trial of siponimod 2 mg/day in adults (18-60 years) with SPMS, EDSS score of 3.0-6.5, and EDSS progression in the 2 years before study<sup>1</sup>

## Analyses

- Post hoc analyses were performed in subgroups of patients aged <50 and ≥50 years at Baseline with active SPMS (≥1 relapse in the 2 years before Baseline and/or ≥1 T1 Gd+ lesion at Baseline)
- Proportional hazard model was used in the analysis of time to 3- and 6-month CDP (as per EDSS scores)
- Number and percentage of patients with AEs were reported
- Analyses for hypothesis generation only

## Patient Disposition

- EXPAND included 1651 patients (siponimod, n=1105; placebo, n=546)
- Of these, 779 patients had active SPMS and were stratified by median baseline age:
  - <50 years, 471 patients (siponimod, n=326; placebo, n=145)
  - ≥50 years, 308 patients (siponimod, n=190; placebo, n=118)

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

1. Kappos L, et al. Lancet. 2018;391:1263-1273.

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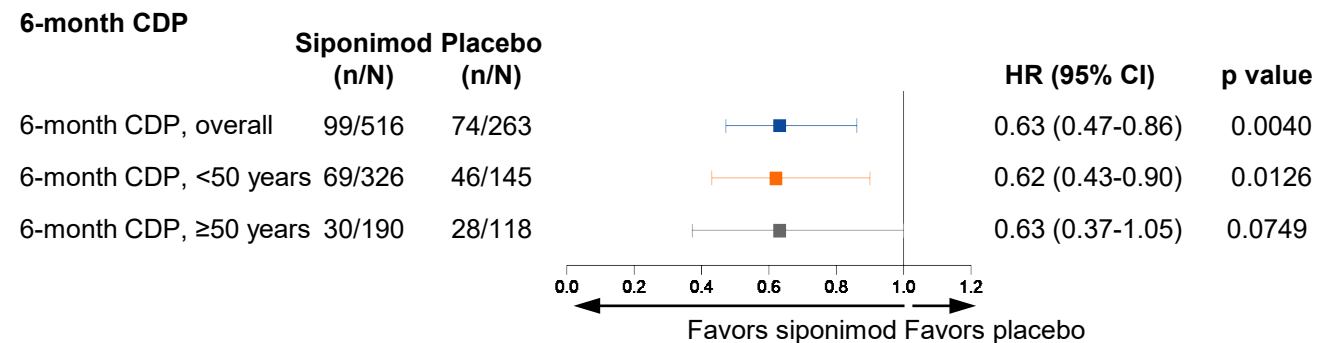
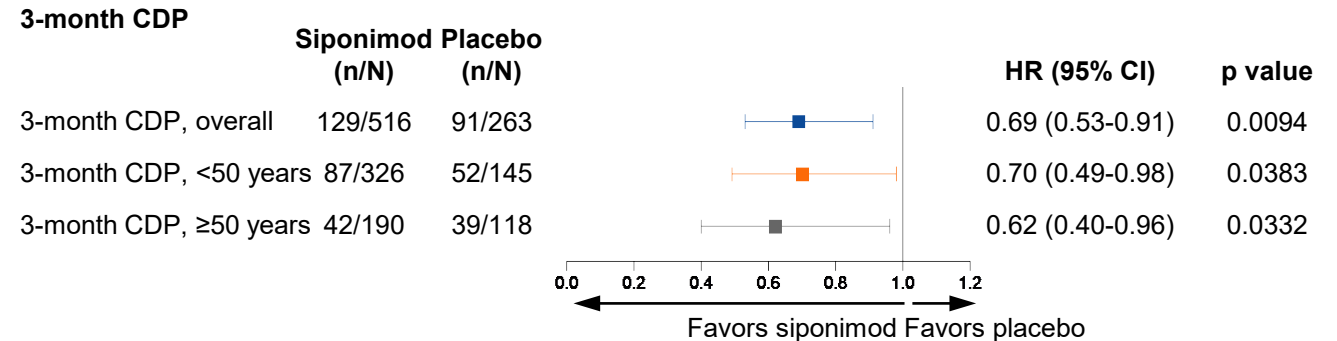
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## CDP in the overall active SPMS subpopulation of EXPAND, and baseline age subgroups

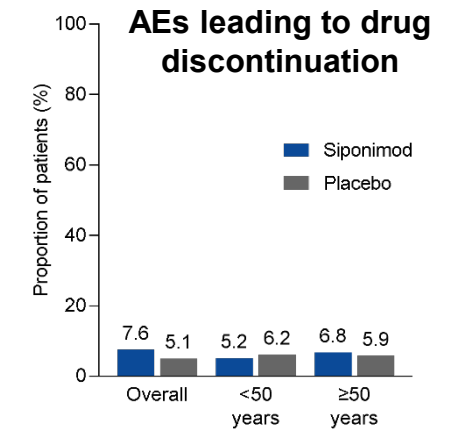
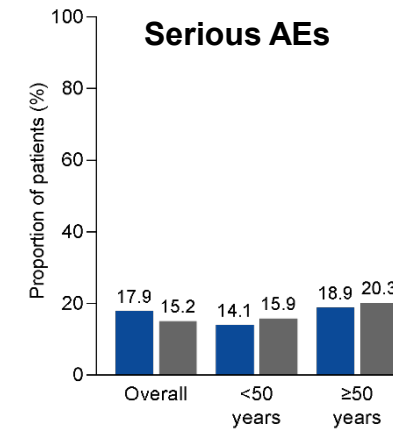
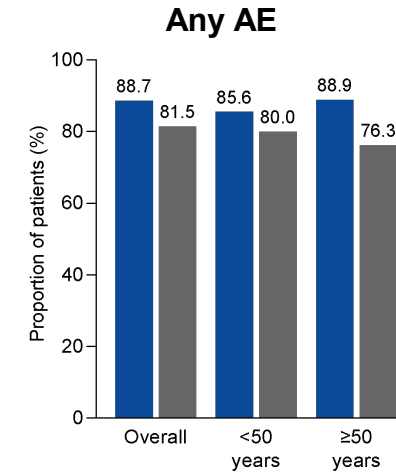
- In the phase 3 EXPAND trial, for overall subpopulation with active SPMS, siponimod reduced risk of:
  - 3-month CDP by 31% (p=0.0094)
  - 6-month CDP by 37% (p=0.0040)
- In patients <50 years, siponimod reduced risk of:
  - 3-month CDP by 31% versus placebo (siponimod, 27%; placebo, 36%; p=0.0383)
  - 6-month CDP by 38% (siponimod, 21%; placebo, 32%; p=0.0126)
- In those ≥50 years, siponimod reduced the risk of:
  - 3-month CDP by 38% versus placebo (siponimod, 22%; placebo, 33%; p=0.0332)
  - 6-month CDP by 37% (siponimod, 16%; placebo, 24%; p=0.0749)

CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis.



## AE frequency in the overall EXPAND population, and baseline age subgroups

- The safety profile of siponimod in EXPAND was generally similar in the overall population and among baseline age subgroups
- Siponimod was generally well tolerated in both age subgroups
  - <50 years: rates of any AE were similar for siponimod and placebo (85.6% vs 80.0%)
  - ≥50 years: rates of any AE were slightly higher for siponimod than placebo (88.9% vs 76.3%)
- In both age subgroups, rates of serious AEs were slightly lower for siponimod than placebo
  - <50 years: siponimod, 14.1% vs placebo, 15.9%
  - ≥50 years: siponimod, 18.9% vs placebo, 20.3%
- Rates of AEs leading to discontinuation were slightly higher in those aged ≥50 years than <50 years
  - <50 years: siponimod, 5.2% vs placebo, 6.2%
  - ≥50 years: siponimod, 6.8% vs placebo, 5.9%



AE, adverse event

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## AEs associated with siponimod in the overall EXPAND population, and baseline age subgroups

- Proportionally more patients receiving siponimod than placebo experienced AEs previously associated with S1P-receptor modulation irrespective of baseline age

Event	Overall Population		<50 years		≥50 years	
	Siponimod (n=1099)	Placebo (n=546)	Siponimod (n=326)	Placebo (n=145)	Siponimod (n=190)	Placebo (n=118)
n (%)						
Bradycardia	48 (4.4)	14 (2.6)	30 (9.2)	7 (4.8)	7 (3.7)	3 (2.5)
Hypertension	137 (12.5)	50 (9.2)	32 (9.8)	8 (5.5)	29 (15.3)	11 (9.3)
Lymphopenia	9 (0.8)	0	4 (1.2)	0	0	0
Macular edema	18 (1.6)	1 (0.2)	3 (0.9)	0	4 (2.1)	1 (0.8)
Herpes zoster	25 (2.3)	4 (0.7)	5 (1.5)	0	4 (2.1)	1 (0.8)

AE, adverse event; N, number of patients; n, number of observations; S1P, sphingosine 1-phosphate;

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- Siponimod provided similar clinical benefits in reducing CDP risk in patients aged <50 years and ≥50 years with active SPMS
- Siponimod was generally well tolerated by patients with active SPMS, regardless of baseline age
- These results are consistent with the overall active SPMS cohort in EXPAND<sup>1</sup>

CDP, confirmed disability progression; SPMS, secondary progressive multiple sclerosis.  
1. Gold R, et al. Presented at ECTRIMS 2019; abstract P750.

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