Analyses of the Effect of Baseline Age on the Efficacy and Safety of Siponimod in Patients With Active SPMS From the EXPAND Study

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Introduction

- For patients with relapsing multiple sclerosis (MS), risk of transitioning to secondary progressive MS (SPMS) remains high, despite treatment availability[1]
- Siponimod (Mayzent®) is a selective sphingosine 1-phosphate receptor (S1P1 and S1P5) modulator, approved in the USA for the treatment of adults with relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting MS and active SPMS[2]
- Increasing age is associated with disability accumulation, independent of MS duration, and may negatively affect treatment outcomes[3]
- 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[4]
- We investigated efficacy and safety of siponimod, by age subgroups, in the subpopulation of patients from EXPAND with active SPMS (relapse in 2 years before screening and/or ≥1 T1 gadolinium-enhancing lesion at baseline), in line with approved indication of siponimod[2]

Objective

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

Methods

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, Expanded Disability Status Scale (EDSS) score of 3.0-6.5, and EDSS progression in the 2 years before study[4]

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 gadolinium-enhancing 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 adverse events (AEs) were reported
- Analyses for hypothesis generation only

Results

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)

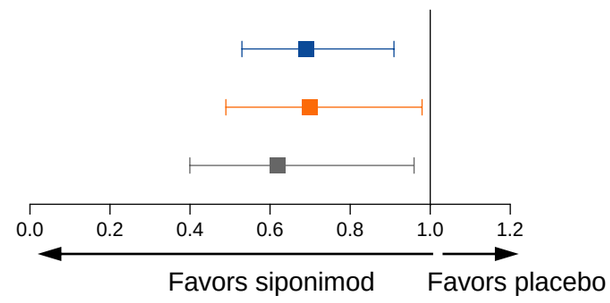
Efficacy

- In the phase 3 EXPAND trial, for patients with active SPMS, siponimod reduced risk of (**Figure 1**):
  – 3-month CDP by 31% (p=0.0094)
  – 6-month CDP by 37% (p=0.0040)
- In patients <50 years, siponimod reduced risk of (**Figure 1**):
  – 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 (**Figure 1**):
  – 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)

Figure 1. CDP in the overall active SPMS subpopulation of EXPAND, and baseline age subgroups

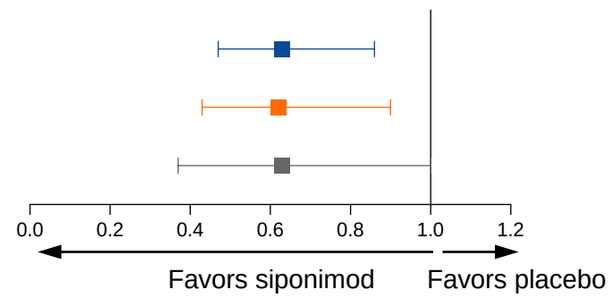
a) 3-month CDP

	Siponimod (n/N)	Placebo (n/N)	HR (95% CI)	p value
3-month CDP overall	129/516	91/263	0.69 (0.53-0.91)	0.0094
3-month CDP <50 years	87/326	52/145	0.70 (0.49-0.98)	0.0383
3-month CDP, ≥50 years	42/190	39/118	0.62 (0.40-0.96)	0.0332



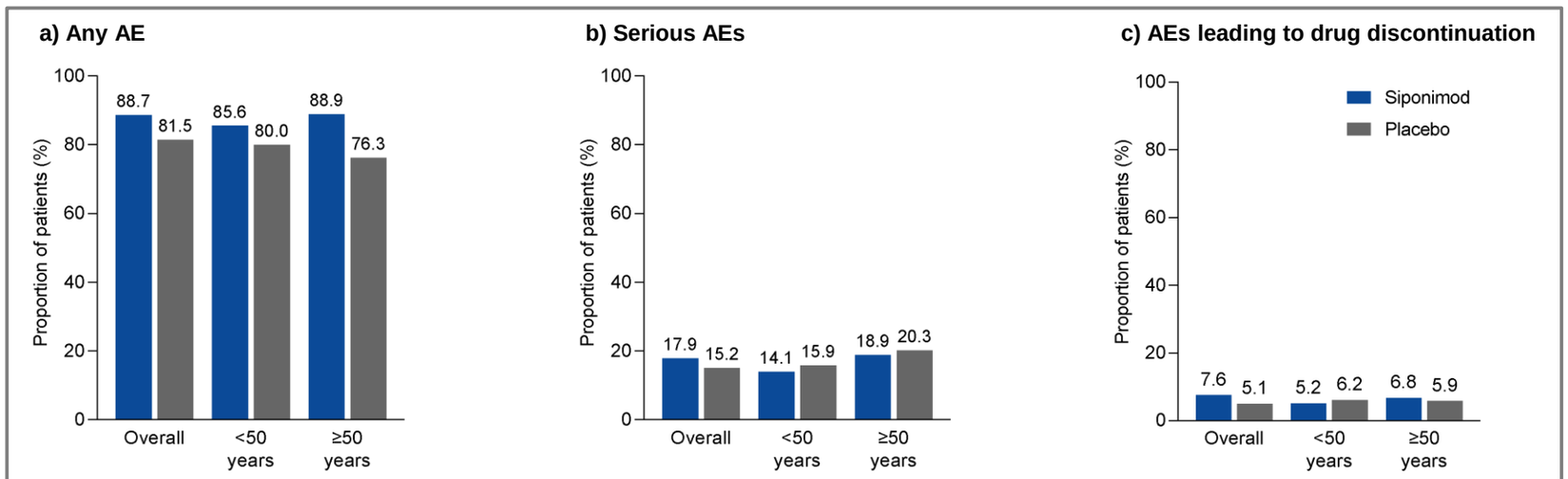
b) 6-month CDP

	Siponimod (n/N)	Placebo (n/N)	HR (95% CI)	p value
6-month CDP overall	99/516	74/263	0.63 (0.47-0.86)	0.0040
6-month CDP <50 years	69/326	46/145	0.62 (0.43-0.90)	0.0126
6-month CDP, ≥50 years	30/190	28/118	0.63 (0.37-1.05)	0.0749



CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio

Figure 2. AE frequency in the overall EXPAND population, and baseline age subgroups



AE, adverse event

Table 1. AEs associated with siponimod in the overall EXPAND population, and baseline age subgroups

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)
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)

Data are number of patients (%)

Safety

- 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 (**Figure 2**)
  – <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 (**Figure 2**)
  – <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 (**Figure 2**)
  – <50 years: siponimod, 5.2% vs placebo, 6.2%
  – ≥50 years: siponimod, 6.8% vs placebo, 5.9%
- Proportionally more patients receiving siponimod than placebo experienced AEs previously associated with S1P-receptor modulation irrespective of baseline age (**Table 1**)

Conclusions

- 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[5]

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