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Analyses of the Effect of Baseline Age on the Efficacy and Safety of Siponimod in Patients With Active SPMS From the Phase 3 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 ($S1P_1$ and $S1P_5$) 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]

Objectives

- Assess efficacy and safety of siponimod in patients with active SPMS from EXPAND, by subgroups aged <45 years and ≥45 years (median value) at baseline

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 for subgroups of patients with active SPMS (relapse in 2 years before screening and/or ≥1 T1 gadolinium-enhancing lesion at baseline)
- Efficacy endpoints: time to 3 and 6 month CDP (defined using EDSS scores)
- Adverse events (AEs), serious AEs and AEs leading to treatment discontinuation were assessed
- Analyses for hypothesis generation only; no adjustment for multiple comparisons

Results

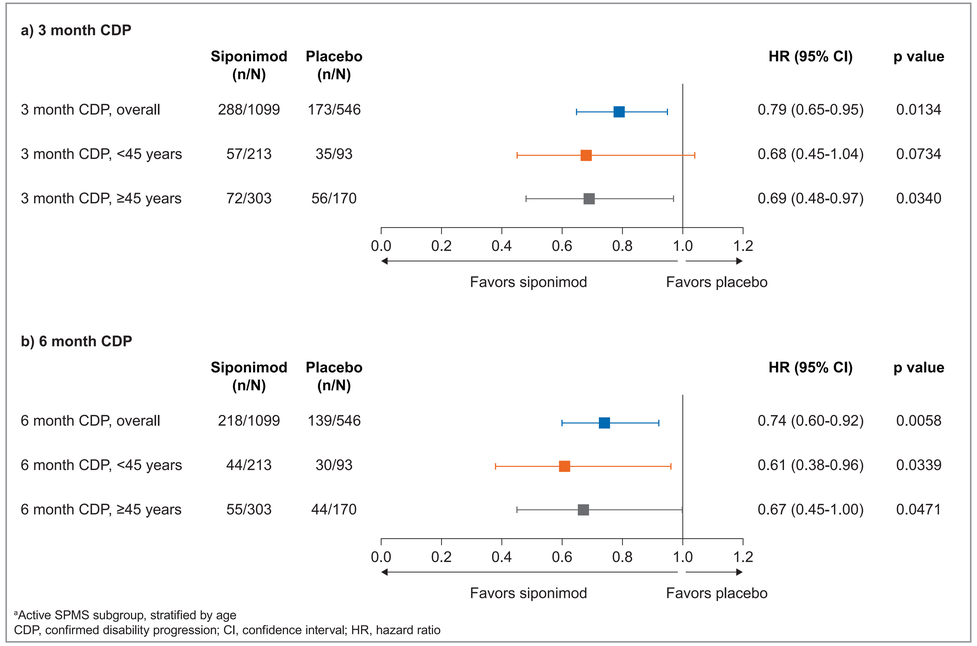
Demographics

- EXPAND included 1651 patients (siponimod, n=1105; placebo, n=546)
- Of these, 779 patients had active SPMS and were stratified by median baseline age:
  - <45 years, 306 patients (siponimod, n=213; placebo, n=93)
  - ≥45 years, 473 patients (siponimod, n=303; placebo, n=170)
- A total of 827 patients had non-active SPMS

Efficacy

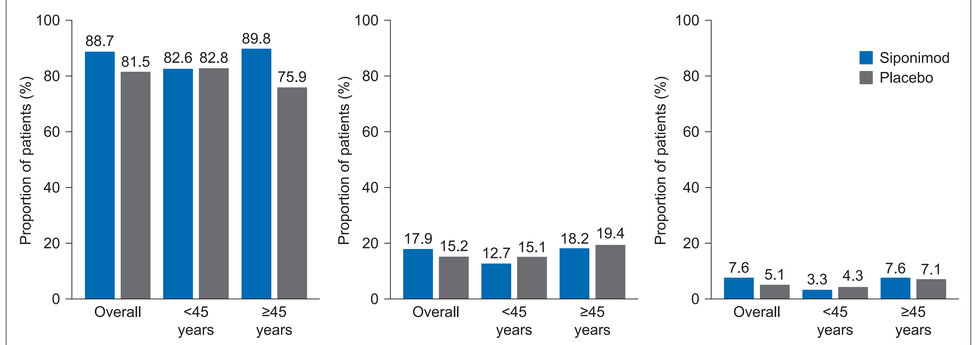
- In the overall EXPAND population, siponimod reduced risk of (**Figure 1**):
  - 3 month CDP by 21% (p=0.0134)
  - 6 month CDP by 26% (p=0.0058)
- Siponimod also reduced risk of 3 and 6 month CDP versus placebo irrespective of baseline age
- In patients <45 years, siponimod reduced risk of:
  - 3 month CDP by 32% versus placebo (siponimod, 27%; placebo, 38%; p=0.0734)
  - 6 month CDP by 40% (siponimod, 21%; placebo, 32%; p=0.0339)
- In those ≥45 years, siponimod reduced the risk of:
  - 3 month CDP by 31% versus placebo (siponimod, 24%; placebo, 33%; p=0.0340)
  - 6 month CDP by 33% (siponimod, 18%; placebo, 26%; p=0.0471)

Figure 1. Confirmed disability progression in the overall population, and baseline age subgroups[a]



[a]Active SPMS subgroup, stratified by age
CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio

Figure 2. AE frequency in the overall siponimod population, and baseline age subgroups[a]



[a]Active SPMS subgroup, stratified by age
AE, adverse event

Table 1. Adverse events associated with siponimod in the overall population, and in patients <45 or ≥45 years[a]

Event	Overall population		<45 years		≥45 years	
	Siponimod (n=1099)	Placebo (n=546)	Siponimod (n=213)	Placebo (n=93)	Siponimod (n=303)	Placebo (n=170)
Bradycardia	48 (4.4)	14 (2.6)	24 (11.3)	5 (5.4)	13 (4.3)	5 (2.9)
Hypertension	137 (12.5)	50 (9.2)	15 (7.0)	4 (4.3)	46 (15.2)	15 (8.8)
Lymphopenia	9 (0.8)	0	4 (1.9)	0	0	0
Macular edema	18 (1.6)	1 (0.2)	2 (0.9)	0	5 (1.7)	1 (0.6)
Herpes zoster	25 (2.3)	4 (0.7)	4 (1.9)	0	5 (1.7)	1 (0.6)

[a]Active SPMS subgroup, stratified by age
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**)
  - <45 years: rates of any AE were similar for siponimod and placebo (82.6% vs 82.8%)
  - ≥45 years: rates of any AE were slightly greater for siponimod than placebo (89.8% vs 75.9%)
- In both age subgroups, rates of serious AEs were slightly lower for siponimod than placebo (**Figure 2**)
  - <45 years: siponimod, 12.7% vs placebo, 15.1%
  - ≥45 years: siponimod, 18.2% vs placebo, 19.4%
- Rates of AEs leading to discontinuation were slightly higher in those aged ≥45 years than <45 years (**Figure 2**)
  - <45 years: siponimod, 3.3% vs placebo, 4.3%
  - ≥45 years: siponimod, 7.6% vs placebo, 7.1%
- Proportionally more patients receiving siponimod than placebo experienced AEs previously associated with S1P-receptor modulation irrespective of baseline age (**Table 1**)

Conclusions

- In EXPAND, siponimod provided similar clinical effects in reducing CDP risk in patients with active SPMS aged <45 years and ≥45 years
- Siponimod was generally well tolerated by patients with active SPMS, regardless of baseline age
- In EXPAND, differences in age were not associated with differences in CDP reductions or safety outcomes in patients with active SPMS

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