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Analyses of the Effect of Disease Duration on the Efficacy and Safety of Siponimod in Patients With Active SPMS From the Phase 3 EXPAND Study

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Introduction

- 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 multiple sclerosis (RMS), including clinically isolated syndrome, relapsing remitting MS and active secondary progressive MS (SPMS)[1]
- Longer disease duration is associated with greater disability accumulation[2] and treatment benefits are potentially less pronounced[3,4]
- 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 in SPMS[3]
- We investigated efficacy and safety of siponimod, by disease duration, 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[1]

Objectives

- Assess efficacy and safety of siponimod in patients with active SPMS from EXPAND, by subgroups of median MS duration at baseline of <16 years or ≥16 years (time since onset of symptoms)
  - 16 years was chosen as the cut-off because this was the median time since MS symptoms onset in EXPAND[3]

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 2 years before study[3]

Analyses

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

Results

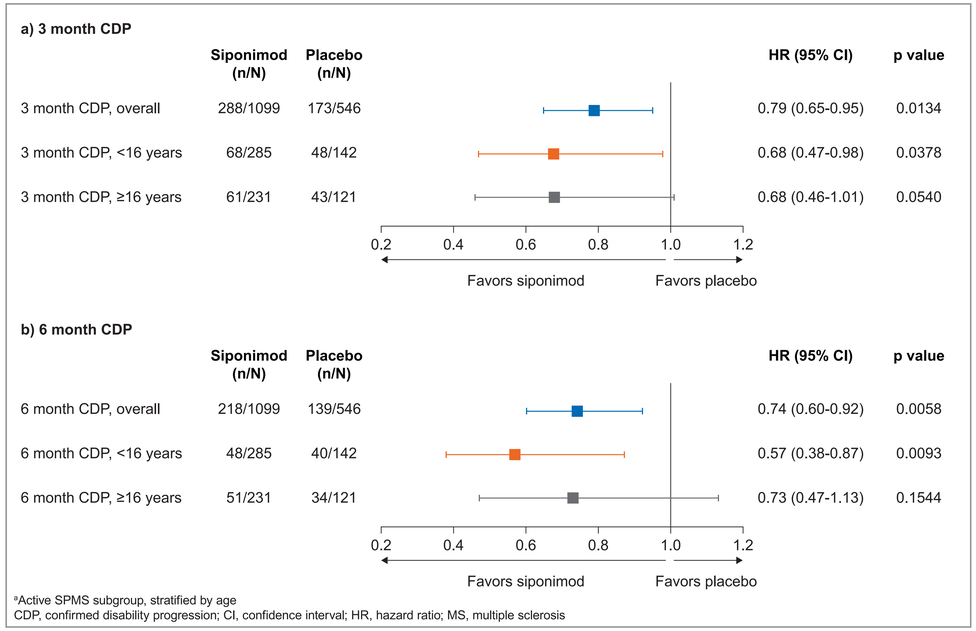
Demographics

- EXPAND included 1651 patients (siponimod, n=1105; placebo, n=546)
- Of these, 779 patients had active SPMS and were stratified by median MS duration at baseline:
  - MS duration <16 years, 427 patients (siponimod, n=285; placebo, n=142)
  - MS duration ≥16 years, 352 patients (siponimod, n=231; placebo, n=121)
- Corresponding numbers for patients with non-active MS:
  - <16 years, 365 patients (siponimod, n=229; placebo, n=136)
  - ≥16 years, 462 patients (siponimod, n=328; placebo, n=134)

Efficacy

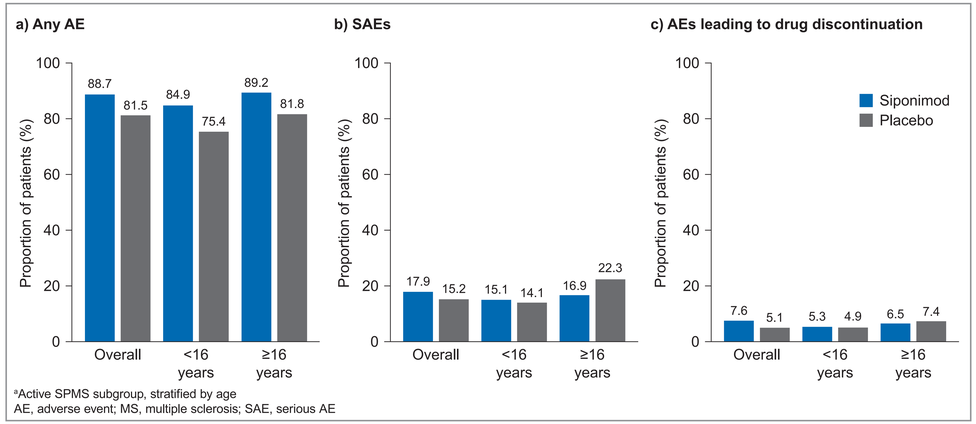
- In the overall EXPAND population, siponimod versus placebo reduced risk of (**Figure 1**):
  - 3 month CDP by 21% (p=0.0134)
  - 6 month CDP by 26% (p=0.0058)
- For MS duration <16 years, siponimod significantly reduced risk of:
  - 3 month CDP by 32% versus placebo (siponimod, 24%; placebo, 34%; p=0.0378)
  - 6 month CDP by 43% versus placebo (siponimod, 17%; placebo, 28%; p=0.0093) (**Figure 1**)
- Similar trends were observed for MS duration ≥16 years
  - 3 month CDP was reduced by 32% versus placebo (siponimod, 26%; placebo, 36%; p=0.0540)
  - 6 month CDP was reduced by 27% versus placebo (siponimod, 22%; placebo, 28%; p=0.1544) (**Figure 1**)
  - However, treatment effects did not achieve statistical significance, possibly because of the small sample size available for these analyses

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



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

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



[a]Active SPMS subgroup, stratified by age
AE, adverse event; MS, multiple sclerosis; SAE, serious AE

Table 1. AEs associated with siponimod in the overall population, and in patients with <16 years and ≥16 years of disease duration[a]

Event	Overall population		<16 years MS duration		≥16 years MS duration	
	Siponimod (n=1099)	Placebo (n=546)	Siponimod (n=285)	Placebo (n=142)	Siponimod (n=231)	Placebo (n=121)
Bradycardia	48 (4.4)	14 (2.6)	27 (9.5)	7 (4.9)	10 (4.3)	3 (2.5)
Hypertension	137 (12.5)	50 (9.2)	32 (11.3)	8 (5.6)	29 (12.6)	11 (9.1)
Lymphopenia	9 (0.8)	0	3 (1.1)	0	1 (0.4)	0
Macular edema	18 (1.6)	1 (0.2)	1 (0.4)	0	6 (2.6)	1 (0.8)
Herpes zoster	25 (2.3)	4 (0.7)	7 (2.5)	1 (0.7)	2 (0.9)	0

[a]Active SPMS subgroup, stratified by age
Data are number of patients (%)
AE, adverse event; MS, multiple sclerosis

Safety

- The safety profile of siponimod in EXPAND was generally similar in the overall population and among baseline MS duration subgroups (**Figure 2**)
- Siponimod was generally well tolerated in both MS duration subgroups, although rates of any AEs were slightly higher for siponimod than placebo (**Figure 2**)
  - <16 years: 84.9% vs 75.4%, respectively
  - ≥16 years: 89.2% vs 81.8%, respectively
- Rates of SAEs and AEs leading to discontinuation were slightly higher with siponimod than placebo in the MS duration <16 years subgroup but slightly lower with siponimod in the MS duration ≥16 years subgroup (**Figure 2**)
  - SAEs
    - <16 years: siponimod, 15.1% vs placebo, 14.1%
    - ≥16 years: siponimod, 16.9% vs placebo, 22.3%
  - AEs leading to discontinuation
    - <16 years: siponimod, 5.3% vs placebo, 4.9%
    - ≥16 years: siponimod, 6.5% vs placebo, 7.4%
- Proportionally more patients receiving siponimod experienced AEs previously associated with S1P-receptor modulation irrespective of baseline MS duration (**Table 1**)

Conclusions

- In patients with active SPMS and MS duration <16 years, siponimod significantly reduced 3 and 6 month CDP risk compared with placebo
- Siponimod showed a trend towards reduced CDP versus placebo in those with MS duration ≥16 years
- These results suggest that early intervention with siponimod may help optimize the benefit of treatment in patients with active SPMS

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