Safety and Efficacy of Siponimod in Patients with Active Secondary Progressive Multiple Sclerosis Identifying as Hispanic from the Phase 3 EXPAND Study

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Disclosures

Author Name	Disclosures
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Le H Hua	Received personal fees for speaking, consulting and advisory board activities from Bristol Myers Squibb, EMD Serono, Genentech, Genzyme, Novartis, TG Therapeutics, Horizon, Greenwich, Alexion. Received research support from Biogen paid directory to her institution.
Amit Bar-Or	Participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Janssen/Actelion, MAPI, Medimmune, Merck/EMD Serono, Novartis, Roche/Genentech and Sanofi-Genzyme.
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Background & Objective

Background

- Over 50% of patients with relapsing-remitting multiple sclerosis (RRMS) are expected to transition to secondary progressive MS (SPMS) within 15 to 20 years after disease onset[1,2]
- In SPMS, relapses are infrequent or absent, yet disability continues to gradually worsen[3]
  - Available disease-modifying therapies for relapsing MS have shown limited potential to delay gradual disability accrual[4]
- Siponimod is an oral selective sphingosine 1-phosphate (S1P) 1 and 5 receptor modulator[5,6]
- EXPAND was a placebo-controlled, Phase 3 study of siponimod in an ambulatory SPMS population[7]
  - Siponimod significantly reduced risk of 3-month and 6-month confirmed disability progression (CDP) by 31% and 37%, respectively, in patients with active SPMS versus placebo
- Minority groups are persistently underrepresented in clinical trials, resulting in limited data to inform decision-making for minority patients, presenting an urgent need for clinical evidence

Objective

- In an exploratory post hoc analysis, the efficacy and safety profile of siponimod 2 mg daily was analyzed in a subgroup of patients with active SPMS from EXPAND who identified as Hispanic

1. Tremlett H, et al. *Mult Scler*. 2008;14:314–324.; 2. Scalfari A, et al. *J Neurol Neurosurg Psychiatry* 2014;85:67–75.; 3. Plantone D, et al. *CNS Drugs* 2016;30(6):517–526.; 4. Dumitrescu L, et al. *Expert Opin Pharmacother*. 2019;20:143–150.; 5. Gergely P, et al. *Br J Pharmacol*. 2012;167:1035–1047.; 6. Nuesslein-Hildesheim B, et al. *Mult Scler*. 2009;15:438.; 7. Kappos L, et al. *Lancet*. 2018;391:1263–1273.

Methods

Study design and patient population

- Post hoc analysis included data from patients who identified as Hispanic and had active SPMS and were randomized (2:1) to receive siponimod 2 mg or placebo in the core study
  - Active SPMS defined as having ≥1 relapse in the 2 years before Baseline and/or ≥1 T1 Gd+ lesion at Baseline
- Proportional hazard and ANCOVA models were applied to the analyses of time to 3- and 6- month CDP (as per EDSS scores) and change in SDMT, respectively
- Number and percentage of patients with AEs were reported

Study endpoints

- **Primary endpoint:** 3- and 6-month CDP Risk
- **Secondary endpoints:**
  - Symbol Digit Modalities Test (SDMT) score
  - Safety (any AEs, SAEs, and AEs leading to discontinuation)

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

Results: Patient Characteristics

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Patient demographics and baseline characteristics in Hispanic patients with active SPMS

- Of 1651 patients in the overall EXPAND population, 106 (6.4%) identified as Hispanic, of which 40 had active SPMS (siponimod [n=31], placebo [n=9])

	Siponimod, N=31	Placebo, N=9
Age, mean (SD), years	46.9 (7.8)	49.0 (7.3)
Female, n (%)	19 (61.3)	7 (77.8)
Race, n (%) Other White	 1 (3.2) 30 (96.8)	 1 (11.1) 8 (88.9)
Duration since MS onset, mean (SD), years	14.9 (6.1)	16.5 (7.6)
Time since conversion to SPMS, mean (SD), years	3.6 (2.7)	1.9 (1.1)
EDSS score, mean (SD)	5.5 (1.1)	5.2 (1.1)
SDMT score (SD)	38.7 (13.5)	41.1 (12.3)
Patients with ≥1 MS relapse in the last 2 years prior to screening, n (%)	23 (74.2)	8 (88.9)
Relapses in the last 2 years prior to screening, n (%)		
1 2-3 4-5	10 (32.3) 11 (35.5) 2 (6.5)	3 (33.3) 4 (44.4) 1 (11.1)
Patients with number of Gd^+ T1 lesions, n (%)		
0 ≥1	18 (58.1) 11 (35.5)	6 (66.7) 3 (33.3)
T2 lesion volume, cm^3, mean (SD)	16175.7 (14916.81)	16240.7 (9325.39)
Normalized brain volume, cm^3, mean (SD)	1441.6 (99.8)	1383.1 (75.7)

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; N, number of patients; n, number of observations; SPMS, secondary progressive multiple sclerosis; SD, standard deviation; SDMT, Symbol Digit Modalities Test.

Results: 3- and 6-month CDP Risk & SDMT Score

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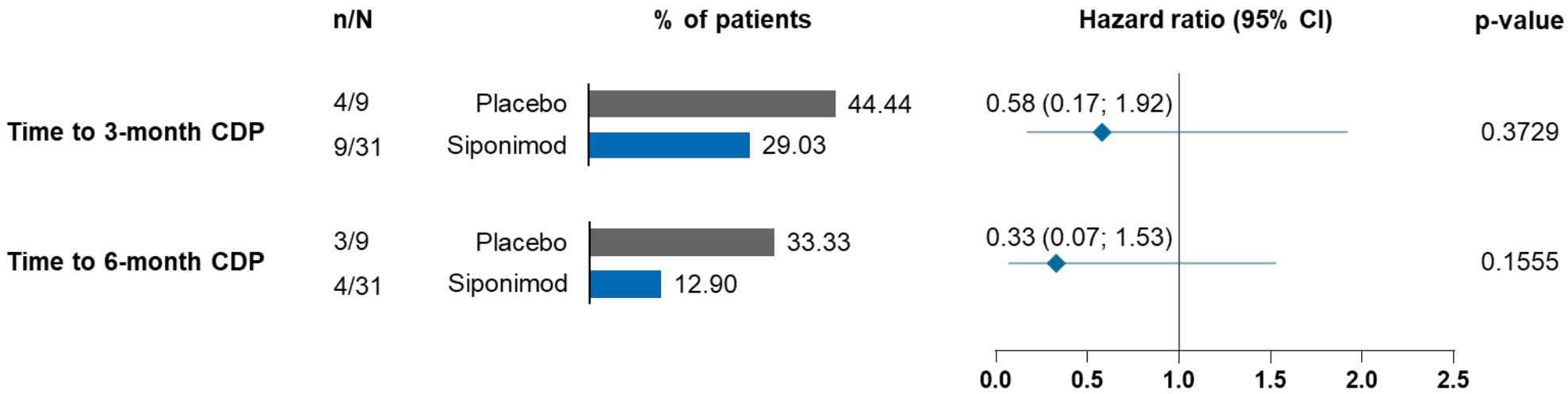
3- and 6-month CDP Risk

- Siponimod showed a reduction of 42% in 3-month CDP risk and of 67% in 6-month CDP risk vs placebo



SDMT score

- At Month 12, the adjusted mean SDMT score changed minimally from Baseline for patients on siponimod (+0.24), whereas the placebo group had a 4.7-point worsening, with a difference between treatment groups of 4.9 (SE 2.6, p=0.07)

CI, confidence interval; CDP, confirmed disability progression; N, number of patients; n, number of observations; SD, standard deviation; SDMT, Symbol Digit Modalities Test.

Results: Safety

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Incidence of adverse events

- Siponimod was generally well tolerated
- Rates of AE, SAEs, and AEs leading to discontinuation were similar between treatment groups

n (%)	Siponimod, N=31	Placebo, N=9
Event		
Any AE	22 (71.0)	7 (77.8)
Any SAE	3 (9.7)	1 (11.1)
Any AE leading to discontinuation	1 (3.2)	0 (0.0)
AEs of interest		
Alanine aminotransferase increased	3 (9.7)	0 (0.0)
Depression	3 (9.7)	1 (11.1)
Bradycardia	2 (6.5)	0 (0.0)
Headache	2 (6.5)	3 (33.3)
Urinary tract infection	2 (6.5)	3 (33.3)
Gait disturbance	1 (3.2)	0 (0.0)
Multiple sclerosis	1 (3.2)	0 (0.0)
SAEs of interest		
Alanine aminotransferase increased	1 (3.2)	0 (0.0)
Ischemic stroke*	1 (3.2)	0 (0.0)
Suicidal behavior	1 (3.2)	0 (0.0)
Urinary tract infection	0 (0.0)	1 (11.1)

*Also a treatment emergent AE causing permanent study drug discontinuation

AE, adverse event; N, number of patients; n, number of observations; SAE, serious adverse event.

Conclusions

- There was a numeric relative reduction in CDP risk in siponimod-treated patients with active SPMS identifying as Hispanic, consistent with results observed in the overall active SPMS cohort in EXPAND
- The study was not designed to detect differences between subgroups, and the small sample size does not allow us to draw conclusions on the statistical significance of the results in the Hispanic subgroup
- This brings into focus the challenges of minority under-representation in clinical trials

CDP, confirmed disability progression; SPMS, secondary progressive multiple sclerosis.