Presented at 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis • 26-28 October 2022 • Amsterdam, The Netherlands

EP1146

Disability Status and Cognitive Functioning in Patients With Advancing Multiple Sclerosis Switching to Siponimod: Interim Results of the EXCHANGE Study

Robert J. Fox,[1] Bianca Weinstock Guttman,[2] Yang Mao-Draayer,[3] Stanley L. Cohan,[4] Gina Mavrikis Cox,[5] Xiangyi Meng,[5] Linda-Ali Cruz,[5] Amit Bar-Or[6]

[1]Mellen Center for Multiple Sclerosis, Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA; [2]Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA; [3]Autoimmunity Center of Excellence, Multiple Sclerosis Center, University of Michigan, Ann Arbor, MI, USA; [4]Providence Brain and Spine Institute, and Providence Multiple Sclerosis Center, Providence Health & Services, Portland, OR, USA; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [6]Center for Neuroinflammation and Experimental Therapeutics, and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

SUMMARY

1 Patient-reported disability and cognitive function are being assessed as exploratory outcomes in EXCHANGE, a phase 3b study evaluating the safety and tolerability of conversion to siponimod from other DMTs in patients with RMS

2 Compared with baseline, the proportion of patients in each Patient Determined Disease Steps category on Days 84 and 168 pointed to improvement in patient-reported disability. For cognitive processing speed, patients achieved numerically higher Processing Speed Test scores at Day 168 compared with baseline

3 Findings from these interim analyses suggest patients with advancing RMS converting to siponimod from other DMTs experience relative stability in disease progression and numerical improvements in self-reported physical disability and cognitive functioning

INTRODUCTION

- Siponimod, a sphingosine-1-phosphate ($S1P_{1,5}$) receptor modulator, is approved in adults for treatment of relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive MS (SPMS)[1]
- >50% of patients with poorly treated RRMS transition to SPMS within 15-20 years[2] and patients may convert between different disease-modifying therapies (DMTs) as their condition progresses
- Conversion to siponimod from other disease-modifying therapies (DMTs) in patients with advancing relapsing MS* (RMS) or a history of RMS† is being evaluated in EXCHANGE (NCT03623243), a phase 3b, prospective, 6-month, multicentre, open-label, single-arm study
- Patient-reported disability and cognitive function are being assessed as exploratory outcomes in EXCHANGE

*As defined by principal investigator; †With or without progressive features

OBJECTIVE

- To explore the effects of siponimod on short-term disease evolution and cognition in patients with advancing RMS

METHODS

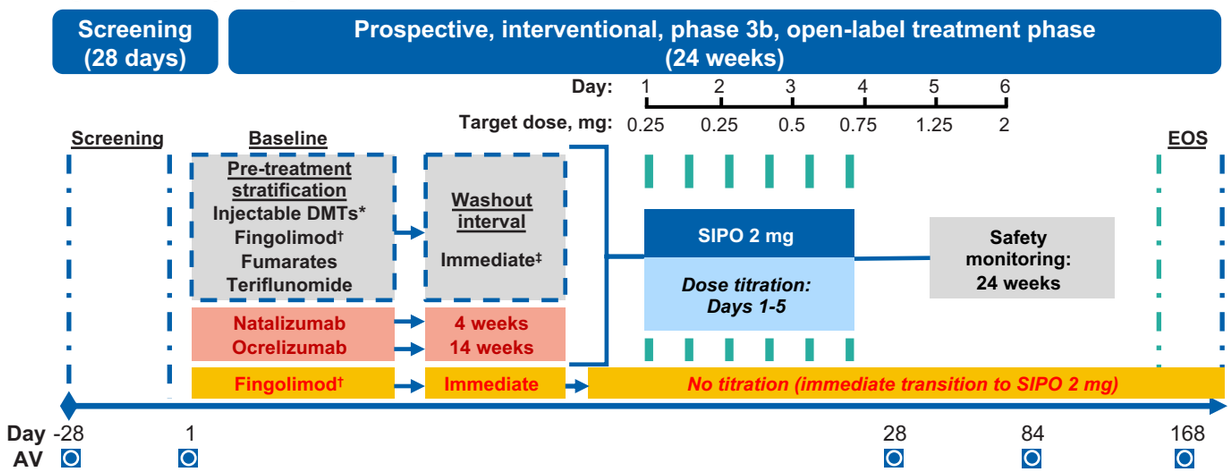
STUDY DESIGN

- The study includes patients aged 18-65 years with advancing RMS and an Expanded Disability Status Scale (EDSS) score of 2.0-6.5 who received continuous treatment with DMTs for ≥3 months
- Patients were converted from other DMTs to siponimod over a 6-month treatment period (**Figure 1**)
  - Most patients initiating siponimod were titrated from 0.25 mg to 2 mg (maintenance dose) over the first 6 days of the treatment period
- Patient-reported disability and cognitive function were assessed at baseline, Day 84 and Day 168 of the treatment period

OUTCOME MEASURES

- Short-term disease evolution and cognition were evaluated using the Patient Determined Disease Steps (PDDS) and Processing Speed Test (PST), respectively
- The PDDS is a validated questionnaire measuring patient-reported disability on a scale from "normal" to "bedridden." Patients were classified as normal (no disability) or having mild (gait impairment without device), moderate (assistive device) or severe (non-ambulatory) disability[3,4]
- The PST is a validated, self-administered, iPad-based tool used to measure MS-related deficits in processing speed, scoring the number of correct digits recorded over 120 seconds.[5] Higher test scores therefore indicate faster processing speed
- A summary of adverse events (AEs) possibly related to siponimod treatment is also presented

Figure 1. Study Design of EXCHANGE



AV, assessment visit; DMT, disease-modifying therapy; EOS, end of study; GA, glatiramer acetate; IFN, interferon; pegIFN, peginterferon; S1P, sphingosine-1-phosphate; SIPO, siponimod
*Injectable DMTs: IFN beta-1a, IFN beta-1b, GA, pegIFN beta-1a; †Patients previously treated with fingolimod were either converted immediately to maintenance dose of siponimod (2 mg) or underwent dose titration to enhance understanding of the role of titration when converting between S1P receptor modulators; ‡Defined as cessation of existing DMT and initiation of SIPO within 24 hours, followed by subsequent 5-day dose titration

RESULTS

PATIENTS

- Of the 163 patients enrolled in EXCHANGE, mean age was 46.6 years and most were female (74.2%)
- Patients had a mean MS duration of 12.2 (8.7) years and mean EDSS score of 3.9 (1.5)
- Additional baseline characteristics for patients are described in **Table 1**

Table 1. Patient Demographics

Characteristic	Siponimod (N=163)
Age, years	46.6 (10.3)
Female, n (%)	121 (74.2)
Race, n (%)	
White	138 (84.7)
Black or African American	23 (14.1)
Asian	2 (1.2)
Ethnicity, n (%)	
Hispanic or Latino	36 (22.1)
Not Hispanic or Latino	126 (77.3)
Not reported	1 (0.6)
Type of MS at study entry, n (%)	
Single demyelinating event	1 (0.6)
PPMS	4 (2.5)
SPMS	33 (20.2)
RRMS	125 (76.7)
MS duration since diagnosis, years	12.2 (8.7)
EDSS score, median (range)	3.5 (2.0-6.5)
Relapses in 12 months before screening, n (%)	
0	88 (54.0)
1	57 (35.0)
2	10 (6.1)
3	6 (3.7)
≥4	2 (1.2)

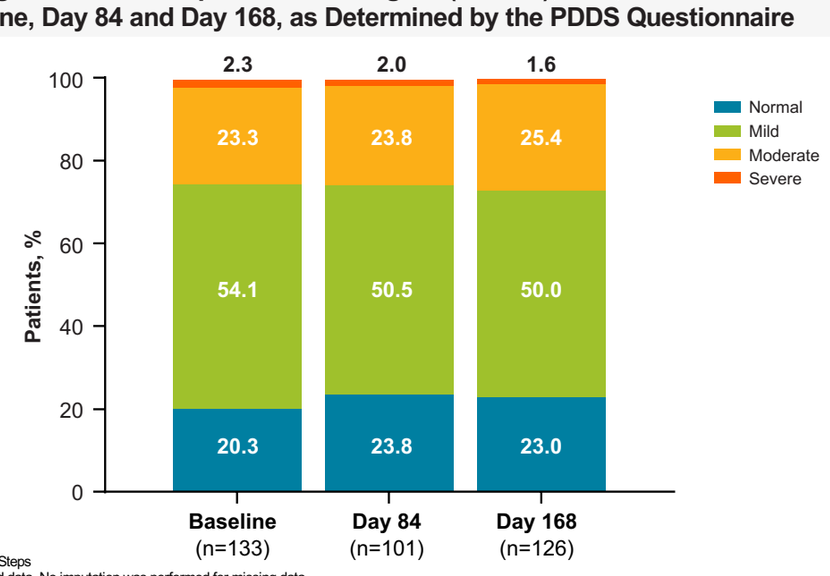
Previous MS treatments	n (%)	Duration, Months*
Fingolimod	50 (30.7)	48.3 (31.0)
Glatiramer acetate	26 (16.0)	83.4 (68.7)
Dimethyl fumarate	34 (20.9)	34.9 (25.9)
Any IFN beta	19 (11.7)	82.7 (65.6)
Teriflunomide	28 (17.2)	29.6 (26.9)
Natalizumab	1 (0.6)	3.9 (NA)
Ocrelizumab	5 (3.1)	15.2 (12.7)

EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; NA, not applicable; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis
Values are shown as mean (SD) except where indicated
*Duration of previous MS treatments before switching to sipominod (months)

PATIENT DETERMINED DISEASE STEPS

- The PDDS showed improvement from baseline levels through to the final assessment at Day 168 (**Figure 2**)
- At baseline, 20.3% (27/133) of patients were classified as having no disability and 54.1% (72/133), 23.3% (31/133) and 2.3% (3/133) of patients had mild, moderate and severe disability, respectively
- By Day 168, 23.0% (29/126) of patients were classified as having no disability, and 50.0% (63/126), 25.4% (32/126) and 1.6% (2/126) of patients had mild, moderate and severe disability, respectively

Figure 2. Percentage of Patients Reported as Having No (Normal), Mild, Moderate or Severe Disability at Baseline, Day 84 and Day 168, as Determined by the PDDS Questionnaire

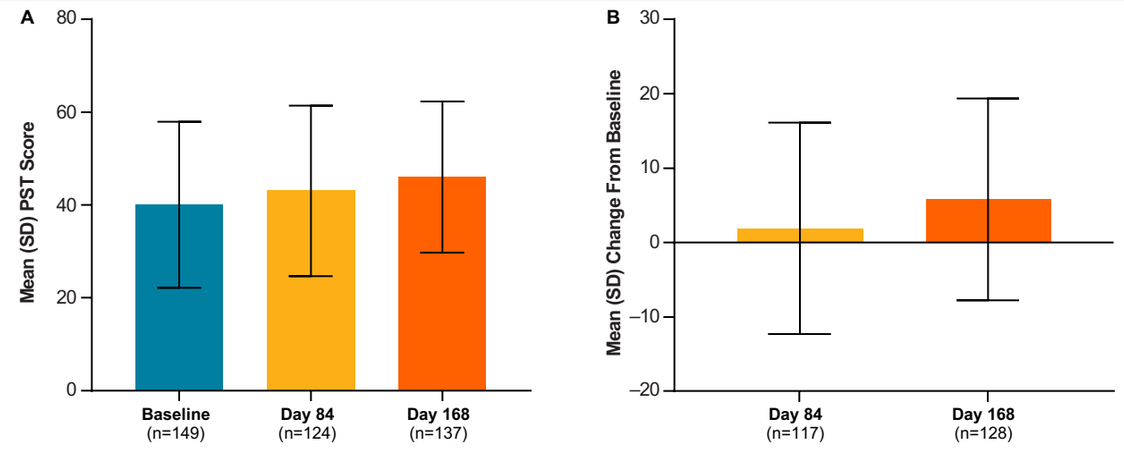


PDDS, Patient Determined Disease Steps
All analyses were based on observed data. No imputation was performed for missing data

PROCESSING SPEED

- For cognitive processing speed, patients achieved numerical improvement in mean (standard deviation [SD]) PST scores on Day 84 (43.1 [18.4]) and Day 168 (46.0 [16.3]) vs baseline (40.0 [17.8]; **Figure 3**)
- Patients achieved a mean (SD) increase of 1.9 (14.2) correct digits recorded compared with baseline on Day 84 and a mean increase of 5.8 (13.6) correct digits recorded compared with baseline on Day 168
- Significant practice effects have been observed for the PST and should be considered when interpreting these results[5]

Figure 3. (A) PST Scores at Baseline, Day 84 and Day 168; (B) Change From Baseline in PST Score at Days 84 and 168



PST, Processing Speed Test; SD, standard deviation
All analyses were based on observed data. No imputation was performed for missing data

SAFETY

- 31.3% (51/163) of patients experienced AEs possibly related to siponimod treatment during the study
- Most common AEs possibly related to siponimod treatment included headache (8.0%; n=13), dizziness (4.3%; n=7), nausea (3.7%; n=6), bradycardia (3.1%; n=5), fatigue (3.1%; n=5), diarrhoea (2.5%; n=4), oedema peripheral (2.5%; n=4) and urinary tract infection (2.5%; n=4)
- 4.9% (8/163) of patients reported ≥1 serious AE, including asthenia, non-cardiac chest pain, cellulitis, pyelonephritis, respiratory fume inhalation disorder, hemiparesis, MS, MS relapse, seizure and renal urinary disorders
- A low proportion of patients (6.7%; 11/163) reported AEs leading to drug discontinuation

ABBREVIATIONS: AE, adverse event; **AV**, assessment visit; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **EOS**, end of study; **GA**, glatiramer acetate; **IFN**, interferon; **MS**, multiple sclerosis; **PDDS,** Patient Determined Disease Steps; **pegIFN,** peginterferon; **PPMS**, primary progressive multiple sclerosis; **PST**, Processing Speed Test; **RMS**, relapsing multiple sclerosis; **RRMS**, relapsing-remitting multiple sclerosis; **S1P**, sphingosine-1-phosphate; **$S1P_{1,5}$**, sphingosine-1-phosphate receptor type 1,5; **SD**, standard deviation; **SIPO**, siponimod; **SPMS**, secondary progressive multiple sclerosis.

ACKNOWLEDGEMENTS: The study was supported by Novartis Pharmaceuticals Corporation. Medical writing support was provided by Frankie Sorrell, PhD, of Envision Pharma Group and was funded by Novartis Pharmaceuticals Corporation. This poster was developed in accordance with Good Publication Practice (GPP3) guidelines. Authors had full control of the content and made the final decision on all aspects of this poster. **DISCLOSURES: Robert J. Fox** has received personal fees from AB Science, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Greenwich Biosciences, Immunic Therapeutics, Janssen, Novartis, Sanofi and TG Therapeutics; grants from Novartis; and other support from Biogen, Novartis and Sanofi (clinical trial contracts). **Bianca Weinstock-Guttman** has received consulting fees from Biogen, Celgene, EMD Serono, Genentech and Janssen; and research support from Biogen, Celgene, EMD Serono, Genentech and Novartis. **Yang Mao-Draayer** has received fees for consulting/non-CME/CE services from Biogen, Celgene/Bristol Myers Squibb, EMD Serono, Genentech/Roche, Horizon Therapeutics, Janssen, Novartis, Sanofi Genzyme and Teva Pharmaceuticals; and fees for contracted research from Chugai Pharmaceutical, Novartis and Sanofi Genzyme. **Stanley L. Cohan** has participated in advisory boards or steering committees for Biogen, EMD Serono, Genentech/Roche, Novartis and Sanofi Genzyme; and has received research support from Adamas Pharmaceuticals, Biogen, EMD Serono, Novartis, Roche/Genentech and Sanofi Genzyme; and speaker honoraria from Biogen, Bristol Myers Squibb, Roche/Genentech and Sanofi Genzyme. **Gina Mavrikis Cox**, **Xiangyi Meng** and **Linda-Ali Cruz** are employees of and stockholders in Novartis Pharmaceuticals Corporation. **Amit Bar-Or** has participated as a speaker in meetings sponsored by and/or received consulting fees and/or grant support from Atara Biotherapeutics, Biogen, Celgene/Receptos, Janssen/Actelion, Mapi Pharma, MedImmune, Merck/EMD Serono, Novartis, Roche/Genentech and Sanofi Genzyme

REFERENCES: 1. Novartis Pharmaceuticals Corporation. Prescribing information. Mayzent® 2022. Accessed August 24, 2022. www.novartis.com/us-en/sites/novartis_us/files/mayzent.pdf; **2.** Tremlett H et al. *Mult Scler.* 2008;14(3):314-324. **3.** Learmonth YC et al. *BMC Neurol.* 2013;13:37. **4.** Marrie RA et al. *Neurology.* 2006;66(8):1235-1240. **5.** Rao SM et al. *Mult Scler.* 2017;23(14):1929-1937.