Presented at CMSC Annual Meeting 2022 • June 1–4, 2022 • National Harbor, MD, USA

DMT12

Evaluating Humoral Immune Response to mRNA COVID-19 Vaccines in Siponimod-Treated Patients With Advancing Forms of RMS: A COVID-19 Vaccine Substudy of the EXCHANGE Trial

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

[1]Center for Neuroinflammation and Experimental Therapeutics, and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Autoimmunity Center of Excellence, Multiple Sclerosis Center, University of Michigan, Ann Arbor, MI, USA; [3]Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA; [4]Cleveland Clinic, Cleveland, OH, USA; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [6]Providence Multiple Sclerosis Center, Providence Brain and Spine Institute, Portland, OR, USA

SUMMARY

1 **A single-arm pilot substudy is being conducted to understand COVID-19 vaccine response in patients switching to siponimod in the EXCHANGE study**

2 **Albeit limited by small sample size, the preliminary findings of this study offer emerging evidence that the majority of siponimod-treated patients seroconvert following 2 doses of COVID-19 vaccination, demonstrating IgG toward SARS-CoV-2 spike protein**

3 **This study also suggests that, although younger patients (age <40 years) are more likely to develop a vaccine response, some patients may benefit from a COVID-19 booster, where the vaccine response rate is highest**

INTRODUCTION

- Siponimod (SIPO; Mayzent®), an oral sphingosine-1-phosphate ($S1P_{1,5}$) receptor modulator approved in the United States for adults with relapsing multiple sclerosis (RMS; including clinically isolated syndrome, relapsing-remitting MS, and active secondary progressive multiple sclerosis [SPMS]), reduces relapses and disability progression in patients with SPMS[1-3]
- EXCHANGE (NCT03623243) is a 6-month, open-label, single-arm, phase 3b trial of the safety and tolerability of immediate conversion to dose-titrated SIPO from other disease-modifying therapies (DMTs) in patients with advancing RMS
- Given the ongoing coronavirus disease 2019 (COVID-19) global pandemic, it is important to assess whether patients can mount an antiviral humoral immune response to COVID-19 vaccines while receiving or switching to SIPO
- Although data suggest there is limited effect of SIPO on development of the immune response following influenza and pneumococcal vaccinations,[4] this COVID-19 vaccination substudy will provide early evidence on considerations for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and beyond

OBJECTIVE

- To report results of a substudy assessing humoral immune response to messenger RNA (mRNA) COVID-19 vaccines (Pfizer/Moderna) in a subset of patients enrolled in EXCHANGE

METHODS

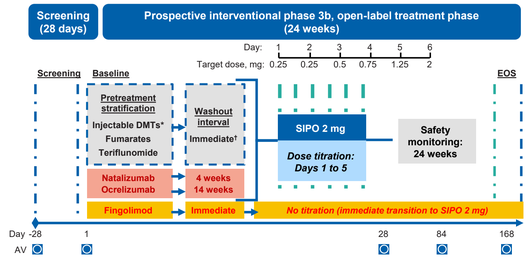
STUDY DESIGN

- EXCHANGE enrolled patients aged 18 to 65 years with advancing forms of RMS, an Expanded Disability Status Scale score 2.0 to 6.5, and on continuous oral/injectable/infusion DMTs for ≥3 months at time of consent (**Figure 1**)
- SARS-CoV-2 spike immunoglobulin G (IgG) was used to assess vaccine response; SARS-CoV-2 nucleocapsid IgG was assessed simultaneously to inform any confounding COVID-19 infection and natural immunity

COVID-19 VACCINATION SUBSTUDY

- A single-arm pilot substudy in patients currently participating in the core EXCHANGE study who have received at least a full course (2 doses) of mRNA COVID-19 vaccine
  - Notably, some patients were vaccinated before switching to SIPO and some patients once commencing SIPO on study; this is reflected in the data
- Patients with known previous COVID-19 diagnosis (clinically or by laboratory test with negative nucleocapsid antibody [Ab]) or contraindication to receiving an mRNA COVID-19 vaccine are excluded from the substudy
- Patients in the substudy are continuing to take SIPO 2 mg as per the EXCHANGE study protocol
- The substudy is evaluating the number of patients achieving positive IgG response to SARS-CoV-2 spike protein ≥14 days after full course vaccination
- Exploratory endpoints include rate of seroconversion and evaluation of magnitude of humoral response to COVID-19 vaccination

Figure 1. EXCHANGE Study Design



AV, assessment visit; DMT, disease-modifying therapy; EOS, end of study; GA, glatiramer acetate; IFN, interferon; pegIFN, peginterferon; SIPO, siponimod
*Injectable DMTs: IFN beta-1a, IFN beta-1b, GA, pegIFN beta-1a; †Defined as cessation of existing DMT and initiation of SIPO within 24 hours, followed by subsequent 5-day dose titration

RESULTS

PATIENT DEMOGRAPHICS AND DISPOSITION

- Patient demographics and disposition described in **Table 1**

Table 1. Patient Demographics and Disposition

At screening	Total (N=10)
Disposition, n (%)	
Completed study	5/10 (50.0)
Ongoing	3/10 (30.0)
Discontinued*	2/10 (20.0)
Age, years	
Median (range)	47.0 (27-60)
≤40, n (%)	4 (40.0)
>40, n (%)	6 (60.0)
Female, n (%)	7 (70.0)
Race, n (%)	
White	7 (70.0)
Black or African American	2 (20.0)
American Indian or Alaska Native	1 (10.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (20.0)
Not Hispanic or Latino	8 (80.0)
MS DMT at time of vaccination, n (%)	
SIPO	5 (50.0)
FIN	1 (10.0)
OCR	1 (10.0)
TER	1 (10.0)
GA	1 (10.0)
Any IFN beta	1 (10.0)
Number of vaccine doses, n (%)	
2	7 (70.0)
3	3 (30.0)

DMT, disease-modifying therapy; FIN, fingolimod hydrochloride; GA, glatiramer acetate; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; SIPO, siponimod; TER, teriflunomide
*Study discontinuations were due to patient decision (n=1) and physician decision (n=1)

HUMORAL IMMUNE RESPONSE TO mRNA COVID-19 VACCINE

- Characteristics of the patients achieving immune response as defined by a positive SARS-CoV-2 qualitative IgG ≥14 days after full course vaccination (responders) are described in **Table 2**
- Overall, 7 out of 10 (70.0%) patients achieved a positive humoral immune response to COVID-19 vaccine at the postvaccination assessment (**Table 2**)
- 4 out of 7 (57.1%) and 3 out of 3 (100%) patients achieved a positive response after 2 and 3 vaccine doses, respectively (**Table 2**)
- 3 out of 4 (75.0%) and 4 out of 6 (66.7%) patients aged ≤40 and >40 years, respectively, had a positive humoral response post vaccination (**Table 2**)
- 4 out of 5 (80.0%) patients on SIPO treatment at the time of vaccination had a positive humoral response (**Tables 2-4**)
  - All 3 SIPO-treated patients aged <40 years responded to the vaccination

Table 2. Immune Response to COVID-19 Vaccine

	Responders, n/M (%)
Overall	7/10 (70.0) 95% CI: 35.4-91.9
Number of vaccine doses	
2	4/7 (57.1)
3	3/3 (100.0)
Age, years	
≤40	3/4 (75.0)
>40	4/6 (66.7)
MS DMT at time of vaccination	
SIPO	4/5 (80.0)
Other*	3/5 (60.0)
Type of COVID-19 vaccine†	
Moderna	5/10 (50.0)
Pfizer	6/10 (60.0)

CI, confidence interval; COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; GA, glatiramer acetate; FIN, fingolimod hydrochloride; IFN, interferon; M, number of patients with lab data; MS, multiple sclerosis; n, number of patients with positive humoral immune response; OCR, ocrelizumab; SIPO, siponimod; TER, teriflunomide
*Other: FIN (n=1), OCR (n=1), TER (n=1), GA (n=1), any IFN beta (n=1); †1 patient received 2 doses of the Moderna vaccine and a booster dose of the Pfizer vaccine

- Patient #1013005 was on glatiramer acetate (GA) at the time of all vaccinations; Ab titers were captured while still on GA (at screening, assessment 1) and ~1 month after switching to SIPO (assessment 2)
  - The increased Ab titer at assessment 2 suggests that expansion of the immune response following vaccination was not restricted under SIPO (**Table 3**)
  - The patient was negative for nucleocapsid IgG at both assessments, which suggests that the patient had not had previous COVID-19 exposure at the assessment timepoints; they developed COVID-19 infection afterward

Table 3. Patient Characteristics for Those Who Achieved a Positive Humoral Immune Response to COVID-19 Vaccine at the Postvaccination Assessment (Responders; n=7)

Patient #	Age, y	COVID-19 vaccine	Previous MS DMT	MS DMT at time of vacc	Ab titer
Received 2 vaccine doses					
1044007	27	Moderna	DMF	SIPO	1616
1065018	34	Moderna	TER	SIPO	1616
1026001	51	Pfizer	NAT	SIPO	101
1076005	38	Pfizer	OCR	SIPO	404
Received 3 vaccine doses					
1013005*	47	Moderna/ Pfizer	GA	GA	(1) 3232 (2) 6464
1026003†	49	Pfizer	TER	TER	3232
1026004	60	Pfizer	Any IFN beta	Any IFN beta	3232

Ab, antibody; COVID-19, coronavirus disease 2019; DMF, dimethyl fumarate; DMT, disease-modifying therapy; GA, glatiramer acetate; IFN, interferon; IgG, immunoglobulin G; MS, multiple sclerosis; NAT, natalizumab; OCR, ocrelizumab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIPO, siponimod; TER, teriflunomide; vacc, vaccination; y, year
*Patient received 2 doses of the Moderna vaccine and a booster dose of the Pfizer vaccine; Ab titer captured while still on GA (assessment 1), and ~1 month after switching to SIPO (assessment 2);
†Patient was positive for SARS-CoV-2 nucleocapsid IgG, suggesting previous COVID-19 exposure

- 9 out of 10 (90.0%) patients were negative for SARS-CoV-2 nucleocapsid IgG, indicating no confounding previous COVID-19 infection and natural immunity
  - Patient #1026003 demonstrated a positive response to nucleocapsid IgG, suggesting previous COVID-19 exposure
- The 3 nonresponders were each on ocrelizumab, SIPO, or fingolimod hydrochloride at time of vaccination; 2 out of 3 (66.7%) were aged >40 years (**Table 4**)

Table 4. Patient Characteristics for Those Who Did Not Achieve a Positive Humoral Immune Response to COVID-19 Vaccine at the Postvaccination Assessment (Nonresponders; n=3)

Patient #	Age, y	COVID-19 vaccine	Previous MS DMT	MS DMT at time of vacc	Ab titer
Received 2 vaccine doses					
1017006	47	Moderna	GA	OCR	Negative
1041014	29	Moderna	FIN	FIN	Negative
1037010	47	Pfizer	OCR	SIPO	Negative

Ab, antibody; COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; FIN, fingolimod hydrochloride; GA, glatiramer acetate; OCR, ocrelizumab; SIPO, siponimod; MS, multiple sclerosis; vacc, vaccination; y, year

SAFETY

- 5 out of 10 (50.0%) patients experienced adverse events (AEs) during the study
  - AEs by Preferred Term included increased blood alkaline phosphatase, COVID-19, dyspnea, headache, increased hepatic enzyme, influenza-like illness, nasopharyngitis, peripheral swelling, rash, and upper-airway cough syndrome (each n=1 [10.0%]; 95% CI: 0.5, 45.9)
  - 1 patient (#1013005, received booster under GA therapy) developed COVID-19 infection shortly after switching to SIPO. Infection was mild and resolved; the patient was negative for nucleocapsid IgG at time of titer assessment, indicating that reported titer values were captured before COVID-19 exposure
  - AEs leading to permanent SIPO discontinuation included peripheral swelling and rash (each n=1 [10.0%]; 95% CI: 0.5, 45.9)
- No serious AEs were reported

ABBREVIATIONS: Ab, antibody; **AE**, adverse event; **AV**, assessment visit; **CI**, confidence interval; **COVID-19**, coronavirus disease 2019; **DMF**, dimethyl fumarate; **DMT**, disease-modifying therapy; **EOS**, end of study; **FIN**, fingolimod hydrochloride; **GA**, glatiramer acetate; **IFN**, interferon; **IgG,** immunoglobulin G; **M**, number of patients with lab data; **mRNA**, messenger RNA; **MS**, multiple sclerosis; **n**, number of patients with positive humoral immune response; **NAT**, natalizumab; **OCR**, ocrelizumab; **pegIFN**, pegInterferon; **RMS**, relapsing multiple sclerosis; **S1P,** sphingosine-1-phosphate; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **SIPO**, siponimod; **SPMS**, secondary progressive multiple sclerosis; **TER**, teriflunomide; **vacc**, vaccine; **y**, year

DISCLOSURES: Amit Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from Atara, Biogen, Celgene/Receptos, Janssen/Actelion, MAPI, MedImmune, Merck/EMD Serono, Novartis, Roche/Genentech, and Sanofi Genzyme. **Yang Mao-Draayer** has received fees for consulting/non-CME/CE services from Biogen, Celgene, EMD Serono, Genentech, Novartis, Sanofi Genzyme, and Teva, and fees for contracted research from Chugai, Novartis, and Sanofi Genzyme. **Silvia R. Delgado** has received consultant fees from Novartis, and research grant funding (clinical trials) from EMD Serono, MAPI Pharma, National MS Society, NIH/NINDS, and Novartis. **Robert J. Fox** has received personal fees from Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunic, Novartis, and Teva; grants from Novartis; and other support from Biogen and Novartis (clinical trial contracts). **Linda-Ali Cruz, Xiangyi Meng,** and **Gina Mavrikis Cox** are employees of Novartis Pharmaceuticals Corporation. **Stanley L. Cohan** has served on advisory boards or steering committees for AbbVie, Biogen, EMD Serono, Novartis, Roche/Genentech, and Sanofi Genzyme; has received research support from Adamas, Biogen, EMD Serono, MedDay, Novartis, Opexa, Roche/Genentech, and Sanofi Genzyme; and has received speaker honoraria from Biogen, Bristol Myers Squibb, Roche/Genentech, and Sanofi Genzyme

REFERENCES: 1. Kappos L et al; EXPAND Clinical Investigators. *Lancet*. 2018;391(10127):1263-1273. 2. Selmaj K et al. *Lancet Neurol*. 2013;12(8):756-767. 3. Novartis Pharmaceuticals Corporation. Prescribing information. Mayzent® 2021. Accessed April 4, 2022. www.novartis.us/sites/www.novartis.us/files/ mayzent.pdf. 4. Ufer K et al. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(6):e398.

ACKNOWLEDGMENTS: The study was supported by Novartis Pharmaceuticals Corporation. Medical writing support was provided by Grace Jeong, PhD, of Alphabet Health (New York, NY) 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