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COVID-19 Infection in Fingolimod- or Siponimod-Treated Patients

Case Series

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Abstract

Background and Objectives

A descriptive analysis of COVID-19 infection in patients with multiple sclerosis (MS) receiving fingolimod or siponimod.

Methods

We reviewed the cases of COVID-19 from postmarketing or ongoing clinical trials reported to Novartis through December 27, 2020.

Results

As of December 27, 2020, 283 cases had been reported in fingolimod-treated patients. The mean age was 44 years (from $n = 224$; range 11–69 years), and 190 were women. Of 161 cases with available information, 138 were asymptomatic (6), mild (100), or moderate (32); 50 cases required hospitalization. At the last follow-up, 140 patients were reported as recovered/recovering, condition was unchanged in 22, and deteriorated in 3 patients; 4 patients had a fatal outcome. Information was not available for 114 patients. Of the 54 cases of COVID-19 reported in siponimod-treated patients, 45 were from the postmarketing setting and 9 from an ongoing open-label clinical trial. The mean age was 54 years (from $n = 45$; range 31–70), and 30 were women. Of 28 cases with available information, 24 were asymptomatic (2), mild (17), or moderate (5); 9 cases required hospitalization. At the last follow-up, 27 patients were reported as recovered/recovering, condition remained unchanged for 1, and 3 patients had a fatal outcome. Information was not available for 23 patients.

Discussion

Based on a review of available information, the risk of more severe COVID-19 in patients receiving fingolimod or siponimod seems to be similar to that reported in the general population and the MS population with COVID-19. However, limitations of spontaneous reporting, especially missing data, should be considered in the interpretation of these observations.

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Glossary

ARDS = acute respiratory distress syndrome; **DMT** = disease-modifying therapies; **EDSS** = Expanded Disability Status Scale; **FDA** = Food and Drug Administration; **HCP** = health care professional; **ICH** = International Council on Harmonization; **ICU** = intensive care unit; **MS** = multiple sclerosis; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **WHO** = World Health Organization.

In December 2019, the novel COVID-19 disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seemed as a new infectious disease in China and spread within months, becoming a global pandemic. As of February 2021, more than 114 million confirmed cases of COVID-19 were reported worldwide.¹ The disease is mild to moderate in most people; however, pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan dysfunction occur in a subgroup of cases, often with poor outcomes including death and disability.² Elderly people and those with obesity and/or serious comorbidities, such as cardiovascular or respiratory disease, are at greater risk of COVID-19 complications and death.²

The impact of COVID-19 on people living with multiple sclerosis (MS), including how disease-modifying therapies (DMT) might influence the risk of symptomatic infection or COVID-19 outcomes, is being assessed through large local registries³⁻⁶ and a global data sharing initiative.⁷ Older age and comorbidities, including obesity, progressive forms of MS, and higher degree of disability, seem to be associated with severe COVID-19 outcomes among people living with MS.^{4,8}

Fingolimod (Gilenya®) and siponimod (Mayzent®) are immunomodulatory MS DMTs that target sphingosine 1-phosphate receptors expressed on lymphocytes and reduce the egress of autoreactive T lymphocytes and their naïve progenitors from secondary lymphoid organs into the circulation.⁹ Despite the reduction in circulating lymphocytes, the risk of common viral respiratory infections in people living with MS treated with fingolimod or siponimod was generally comparable with placebo.^{10,11} Fingolimod-treated patients mount antigen-specific immune responses similar to healthy controls.¹²

We report the clinical characteristics of confirmed cases of COVID-19 reported to Novartis from postmarketing setting or ongoing clinical trials as of December 27, 2020, from patients with MS receiving fingolimod or siponimod.

Methods

This is a case series with descriptive summaries of confirmed COVID-19 reported to Novartis from the postmarketing setting or ongoing clinical trials. The Novartis safety database and cases from clinical trials were reviewed to identify confirmed or suspected COVID-19 in patients treated with fingolimod or siponimod reported to Novartis through December 27, 2020. The Novartis safety database is a system to collect, code, assess, and report adverse events to health authorities from the postmarketing

setting (i.e., spontaneously reported to Novartis, from a post-marketing surveillance program or cases identified in the published literature), serious adverse events, and protocol-triggered events of interest from clinical trials in accordance with international guidelines. The database captures adverse events reported to Novartis from health care professionals (HCPs), patients, or other sources. COVID-19 cases were classified as confirmed if a SARS-CoV-2-positive test result was available or the patient was reported to have been diagnosed with COVID-19. Cases without a positive test or a definitive diagnosis were classified as suspected. Cases were considered “serious” based on the International Council on Harmonization regulatory reporting definition, which is “fatal, life-threatening, hospitalization, and medically significant.” The severity of cases were assessed using the US Food and Drug Administration (FDA)¹³ and World Health Organization (WHO)¹⁴ COVID-19 severity scales, and where data were available, categorization was done as follows: asymptomatic (infection without symptoms), mild (not requiring hospitalization, symptoms did not include dyspnea), moderate (hospitalization with pneumonia not reported to be severe and/or with respiratory rate [RR] >20 and/or oxygen saturation [SpO₂] >90%, shortness of breath or dyspnea, and hospitalization less than 7 days without further details), severe (pneumonia reported as severe—RR ≥ 30, SpO₂ ≤ 93%, and hospitalization 7 days or more without further details), or critical (respiratory failure and/or intubation). The severity of clinical trial cases was based on investigator-reported common terminology criteria for adverse events grade. If reported, the outcome status of each patient was noted to be recovered/recovering (including patients noted to be “stable” or “doing well”), condition unchanged, condition deteriorated, or fatal. We present data as mean or median with their range of dispersion or absolute number and percentage.

Data Availability

Anonymized data can be made available on request for research purposes by sending a request to the corresponding author.

Results

Fingolimod

As of December 27, 2020, there are more than 870,000 patient-years of exposure for fingolimod from clinical trials and postmarketing experience (Novartis, data on file). The drug exposure during the time of the SARS-CoV-2 pandemic—February 28 to December 27, 2020—is more than 94,000 patient-years.

As of December 27, 2020, Novartis received a notification of 342 confirmed or suspected COVID-19 cases in fingolimod-

treated patients in the postmarketing setting and no cases in the ongoing clinical trials. Of these 342 cases, 59 were considered suspected and 283 were confirmed. Case overview, severity rating, and outcomes are presented in the Table 1 and Figure 1 for the confirmed cases.

From the available information, the mean age was 44 years (range 11–69 years), and 190 (73%) cases were women. Four patients had a fatal outcome. At the time of the most recent follow-up, 140 patients had recovered or were recovering, condition was unchanged in 22 patients, and condition deteriorated in 3 patients, and information was not available for 114 cases. Of the total 283 cases, information to assess case severity was reported for 161 cases. The COVID-19 outcome information was provided for 169 cases of the total 283 cases.

Siponimod

As of December 27, 2020, there are more than 10,000 patient-years of exposure for siponimod from clinical trials and postmarketing experience (Novartis, data on file). The drug exposure during the time of the SARS-CoV-2 pandemic—February 28 to December 27, 2020—is more than 3,000 patient-years.

As of December 27, 2020, Novartis received a notification of 58 confirmed or suspected COVID-19 cases in siponimod-treated patients. Of these 58 cases, 4 were considered suspected and 54 were confirmed, consisting of 45 cases from the postmarketing setting and 9 from clinical trials. Further details are provided in Table 2 and Figure 2.

From the available information, the mean age was 54 years (range 31–70 years), and 30 (68%) were women. Three patients had a fatal outcome. At the time of the most recent follow-up, 27 patients had recovered or were recovering, condition was reported as unchanged in 1 patient, and information was not available for 23 patients. Of the total 54 cases, information to assess case severity was reported for 28 cases. COVID-19 outcome information was provided for 31 of the 54 cases.

Discussion

The disease course of COVID-19 in people living with MS receiving either fingolimod or siponimod seems to be similar to those reported in the general population¹⁵ and in the overall MS population affected with COVID-19.³⁻⁷ The mean

Table 1 Overview of 283 Confirmed Cases (as of December 27, 2020) in Fingolimod-Treated People Living With Multiple Sclerosis

Characteristics		Comments
Age, mean (range)	44 (11–69)	Based on 224 cases for which information was provided
Gender, n (%)		
Female	190 (67)	
Male	71 (25)	
Not reported	22 (8)	
Reporter type, n (%)		
HCP	151 (53)	
Non-HCP	132 (46)	
Serious criteria, n (%)^a		
Fatal	4 (1.4)	For details please refer to Table 3
Hospitalization	50 (18) ^c	Twelve of 13 cases (where information was reported) with 1 or more COVID-19 risk factors
Life-threatening	2 (<1)	Reported by non-HCPs; 1 patient with no further details provided; 1 patient had mild disease
Medically significant ^b	33 (12)	Twenty-three cases received from non-HCPs; all cases, where sufficient information was provided for severity assessment, were asymptomatic, mild, or moderate
Region, n (%)		
Europe	111 (39)	
United States	102 (36)	
Rest of world	70 (25)	

Abbreviation: HCP = health care practitioner.

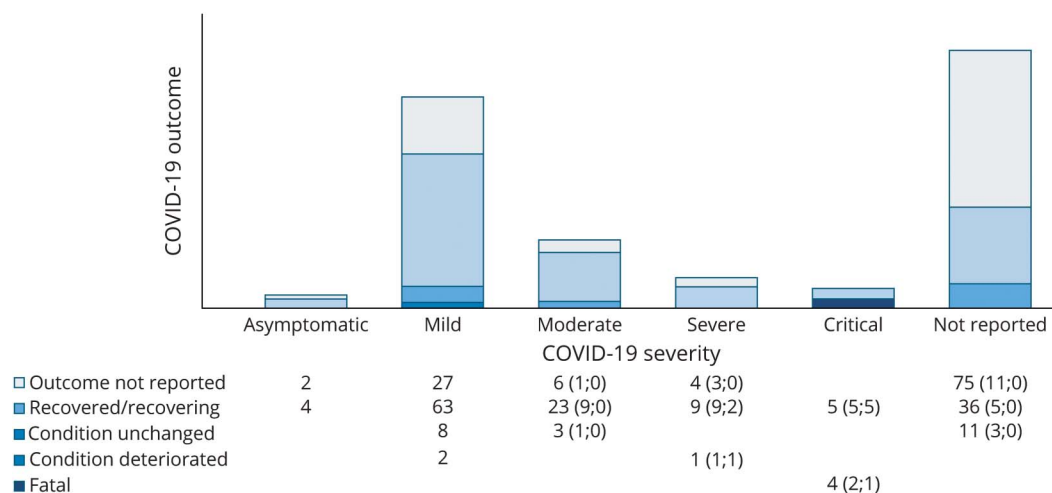
Data refers to number of cases, unless mentioned otherwise.

^a Ascertained based on the most serious criteria. For hospitalization, all cases were included even if the patient had a more severe (i.e., fatal) outcome.

^b Important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes.

^c Also includes 2 patients with fatal outcome.

Figure 1 COVID-19 Severity* and Outcome in Fingolimod-Treated People Living With Multiple Sclerosis



*COVID-19 severity was assessed based on both the FDA and WHO COVID-19 criteria. Information as per the last follow-up. Numbers in parenthesis show—(patients hospitalized; patients requiring ventilation or ICU admission). FDA = US Food and Drug Administration; ICU = intensive care unit; WHO = World Health Organization.

age of patients with COVID-19 receiving fingolimod was 44 years and that of patients receiving siponimod was 54 years. The patient demographics were consistent with those

included in the respective pivotal phase 3 studies, in which the siponimod patient cohort was generally older (mean age 44 years) with higher levels of disability (mean Expanded Disability

Table 2 Overview of 54 Confirmed Cases (as of December 27, 2020) Siponimod-Treated People Living With Multiple Sclerosis

Characteristics		Comments
Age, mean (range)	54 (31–70)	Based on 45 cases for which information was provided
Gender, n (%)		
Female	30 (56)	
Male	14 (26)	
Not reported	10 (18)	
Serious criteria, n (%) ^a		For details please refer to Table 3
Fatal	3 (6)	Four patients had contributory comorbidities; no information on medical history was provided in the other 4 patients
Hospitalization	9 (17) ^c	Patient had mild symptoms and was not hospitalized
Life-threatening	1 (2)	Received from non-HCP
Medically significant ^b	1 (2)	
Reporter type, n (%)		
HCP	23 (43)	
Non-HCP	31 (57)	
Region, n (%)		
United States	40 (74)	
Europe	14 (26)	

Abbreviation: HCP = health care practitioner.

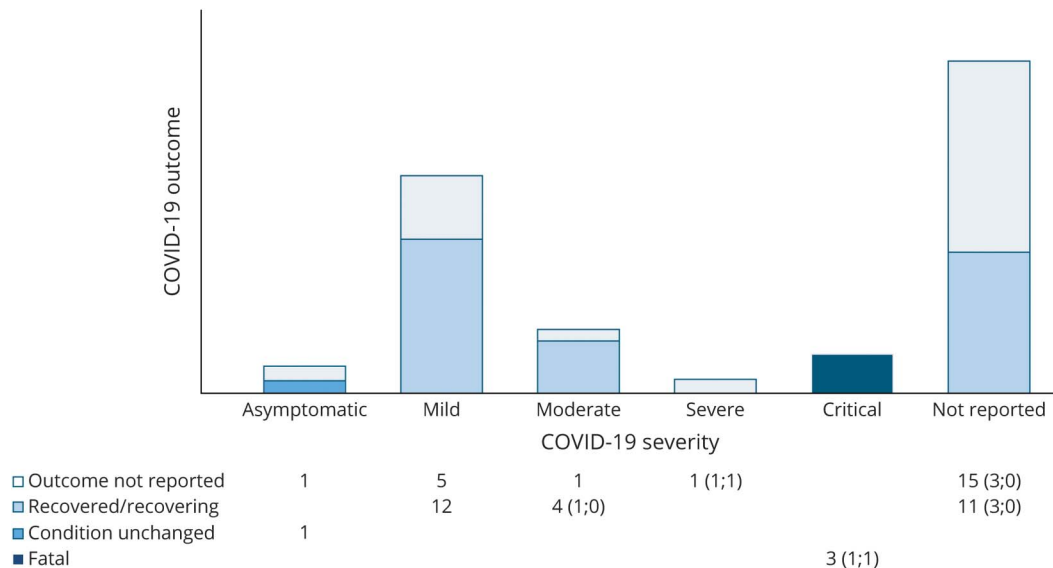
Data refers to number of cases, unless mentioned otherwise.

^a Ascertained based on the most serious criteria. For hospitalization, all cases were included even if the patient had a more severe (i.e., fatal) outcome.

^b Important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes.

^c Also includes 1 patient with fatal outcome.

Figure 2 COVID-19 Severity* and Outcome in Siponimod-Treated People Living With MS



*COVID-19 severity was assessed based on both the FDA and WHO COVID-19 criteria. Information as per the last follow-up. Numbers in parenthesis show—(patients hospitalized; patients requiring ventilation or ICU admission). FDA = US Food and Drug Administration; ICU = intensive care unit; WHO = World Health Organization.

Status Scale [EDSS]) score 5.4) as compared with fingolimod cohort (mean age 37 years, mean EDSS score 2.3).¹⁶⁻¹⁸

The clinical course of most fingolimod- and siponimod-associated cases has overall been uncomplicated. Most patients for whom information was available to assess severity reported asymptomatic, mild, or moderate SARS-CoV-2 infection (138/161, 85.7% of cases with fingolimod; 24/28, 85.7% of cases with siponimod). When information was available about the outcomes in patients on therapy with fingolimod, the large majority (140/169; 83%) completely recovered or were recovering. Based on the available data, the proportions of severe (14/161; 8.7%) and critical cases (9/161; 5.6%) were generally consistent with background rates of severity in the general population, noted to be 14% severe and 5% critical in an early report from China.¹⁵ In a more recent study in the United States, the proportion of people who were hospitalized was 14%, including 2% admitted to intensive care unit (ICU), and overall 5% of patients died.¹⁹ The number of cases in patients on therapy with fingolimod requiring hospitalization (50/283; 18%), including those requiring ICU/ventilation because of COVID-19 or were fatal (12/283; 4%), is also in line with the reported incidence in the general population,^{15,19} as well as in patients with MS receiving a range of DMTs from the COVIMS registry, with 80% not hospitalized, 12% hospitalized, and 8% requiring ICU/ventilation or were fatal.²⁰ Of the 54 patients receiving siponimod with COVID-19, a total of 9 (17%) patients required hospitalization, including those requiring ICU/ventilation, and 3 patients who had fatal outcome (6%). It is noteworthy that siponimod-treated patients are older, with higher degree of disability among the MS population,^{8,20} and are therefore at a higher risk of severe COVID-19 outcome as compared to the

general population.^{15,21} Of the total 337 confirmed cases of COVID-19 in our case series, there were 7 reported fatalities (Table 3). A recent study reported that the infection-fatality risk estimates are 1.4% for overall population, with higher risk of 4.9% (65–74 years of age) and 14.2% (>75 years of age) in the older age groups.²¹ The risk of severe outcomes, including fatalities, with fingolimod or siponimod could only be evaluated with an age-adjusted analysis, which is currently not possible with the limited cases and missing information.

There are limitations to this case series because they include spontaneous cases reported voluntarily with adverse events not confirmed by HCPs and cases found in the scientific literature. There is typically underreporting and/or incomplete reporting in this setting, making interpretation challenging. Many of the COVID-19 cases had limited information regarding previous MS DMTs, comorbidities, MS duration, EDSS/disability status, COVID-19 symptoms and outcome, and some were lost to follow-up. Typically, in the postmarketing setting, serious cases are likely to be reported more frequently than nonserious cases.²² In addition, the number of patients on therapy and the patient exposure data are typically derived from sales data and are therefore estimates. Furthermore, details on morbidity and mortality outcomes in this case series were limited because these could not be further queried.

However, efforts to make accurate and up-to-date information are ongoing to help health care practitioner's make informed decisions, especially in the uncertain and demanding context of COVID-19 pandemic. To date, large ongoing registries of COVID-19 in people living with MS have not shown an increase or decrease in morbidity or mortality with the

Table 3 Characteristics of MS Patients Receiving Fingolimod or Siponimod With COVID-19 Related Fatality

Age range/Gender Reporter type	S1P therapy duration	Disease phase	Comorbidities	COVID-19 symptoms	Treatment
Fingolimod					
65–70 y/unknown HCP	8 y	MS	“Multiple risk factors” not further specified EDSS 6	Fever, cough fatigue, myalgia, shortness of breath, respiratory failure, acute respiratory distress syndrome, and sepsis	Noninvasive ventilation Hydroxychloroquine Ceftriaxone azithromycin
45–50 y/F HCP (lost to follow up)	Not reported	RRMS	Mixed connective tissue disease	Complications linked to COVID-19 (not further specified)	ICU Further details not reported
35–40 y/M Non HCP	Approximately 4 y	Active SPMS	Not reported	Not reported	Acute respiratory distress syndrome
60–65 y/M HCP	23 mo	MS	Not reported	Acute respiratory distress syndrome COVID-19 pneumonia	Not reported
Siponimod					
>50 y/unknown	Not reported	Not reported	Not reported	Not reported	Not reported
>70 years/unknown HCP	Not reported	MS	Not reported	Not reported	Not reported
60–65 y/F HCP	Not reported	Not reported	Morbidly obese Diabetes hypertension	Cough, shortness of breath, fatigue, hypoxia, pyrexia, respiratory failure, and acute respiratory distress syndrome	Hospitalized Mechanical ventilation

Abbreviations: DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; HCP = health care professionals; ICU = intensive care unit; MS = multiple sclerosis; RRMS = relapsing-remitting MS; S1P = sphingosine 1-phosphate; SPMS = secondary progressive MS. EDSS not reported for the other cases; Previous DMT not provided for any case; Duration of MS not provided for any case.

administration of modulators.^{3–8,20} The data presented herein are consistent with the registry observations²³; the risk of more severe COVID-19 symptoms in patients receiving fingolimod seems to be similar to that reported in the general population and the MS population with COVID-19. For siponimod, the less number of cases reported coupled with insufficient information precludes meaningful conclusions.

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Disclosure

R. Sullivan is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. A. Kilaru is an employee of Novartis Pharma AG, Basel, Switzerland. B. Hemmer has served on scientific advisory boards for Novartis. He has served as Data Monitoring and Safety Committee member for AllergyCare, Polpharma, and TG therapeutics. He or his institution have received speaker honoraria from Desitin. His institution received research grants from Regeneron for MS research. He has been funded by the EU project Multiple MS, the excellence cluster Synergy, and the BMBF funded project Clinspect. He holds part of 2 patents. One for the detection of antibodies against KIR4.1 in

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Bernhard Hemmer, MD, PhD	Technical University of Munich; Munich Cluster for Systems Neurology (SyNergy), Germany	Conceptualized the study, interpretation of data, and revision of the manuscript for intellectual content
Bruce Anthony Campbell Cree, MD, PhD	University of California San Francisco San Francisco, CA	Interpretation of data, COVID-19 severity adjudication, and revision of the manuscript for intellectual content
Benjamin M. Greenberg, MD	University of Texas Southwestern, Dallas, TX	Conceptualized the study, interpretation of data, and revision of the manuscript for intellectual content
Uma Kundu, MPharm	Novartis Healthcare Pvt. Ltd., Hyderabad, India	Literature search, drafting and revision of manuscript, and preparation of the manuscript for journal submission
Thomas Hach, MD	Novartis Pharma AG, Basel, Switzerland	Conceptualized the study, interpretation of data, and revision of the manuscript for intellectual content
Virginia DeLasHeras, MD	Novartis Pharma AG, Basel, Switzerland	Conceptualized the study, interpretation of data, and revision of the manuscript for intellectual content
Brian J. Ward, MD, PhD	McGill University Health Centre, Montreal, Canada	Conceptualized the study, interpretation of data, COVID-19 severity adjudication, and revision of the manuscript for intellectual content
Joseph Berger, MD	University of Pennsylvania, Philadelphia, PA	Conceptualized the study, interpretation of data, and revision of the manuscript for intellectual content

References

1. Johns Hopkins University & Medicine Coronavirus Resource Center. Accessed September 30, 2020. Available at: coronavirus.jhu.edu/
2. Center for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Accessed September 30, 2020. www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
3. Sormani MP, De Rossi N, Schiavetti I, et al. For the Musc-19 Study Group. Disease modifying therapies and COVID-19 severity in multiple sclerosis. SSRN: dx.doi.org/10.2139/ssrn.3631244.
4. Louapre C, Collongues N, Stankoff B, et al. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. *JAMA Neurol.* 2020; 77(9):1079-1088.
5. Simpson-Yap S, De Brouwer E, Kalincik T, et al. presented at MSVirtual2020, First results of the COVID-19 in MS Global Data Sharing Initiative suggest anti-CD20 DMTs are associated with worse COVID-19 outcomes (SS02.04).
6. COViMS Registry. The COViMS database public data update. Accessed December 15, 20. www.COVIMS.org.
7. Peeters LM, Parciak T, Walton C, et al. COVID-19 in people with multiple sclerosis: a global data sharing initiative. *Mult Scler.* 2020;26(10):1157-1162.
8. Simpson-Yap S, De Brouwer E, Kalincik T, et al. Associations of DMT therapies with COVID-19 severity in multiple sclerosis. medRxiv 2021.02.08.21251316.
9. Hla T, Brinkmann V. Sphingosine 1-phosphate (S1P): physiology and the effects of S1P receptor modulation. *Neurology.* 2011;76(8 suppl 3):S3-S8.
10. GILENYA[®] US prescribing information. Accessed October 10, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/022527s26lbl.pdf
11. MAYZENT[®] US prescribing information. Accessed October 10, 2020. www.accessdata.fda.gov/drugsatfda_docs/label/2019/209884s000lbl.pdf
12. Mehling M, Hilbert P, Fritz S, et al. Antigen-specific adaptive immune responses in fingolimod-treated multiple sclerosis patients. *Ann Neurol.* 2011;69(2):408-413.
13. COVID-19: developing drugs and biological products for treatment or prevention. Accessed October 10, 2020. www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention.
14. *Clinical Management of COVID-19: Interim Guidance*, 2020. Accessed October 10, 2020. apps.who.int/iris/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5-eng.pdf.
15. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA.* 2020;323(13):1239-1242.
16. Kappos L, Radue E-W, O'Connor P, et al. For the Freedoms Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010; 362(5):387-401.
17. Cohen JA, Barkhof F, Comi G, et al. For the TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):402-415.
18. Kappos L, Bar-Or A, Cree BAC, et al. EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391(10127):1263-1273.
19. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22–May 30, 2020. *MMWR.* 2020;69(24):759-765.
20. Salter A, Fox RJ, Newsome SD, et al. Outcomes and risk factors associated with SARS-CoV-2 infection in a north American registry of patients with multiple sclerosis. *JAMA Neurol.* 2021;78(6):699-708.
21. Yang W, Kandula S, Huynh M, et al. Estimating the infection-fatality risk of SARS-CoV-2 in New York City during the spring 2020 pandemic wave: a model-based analysis. *Lancet Infect Dis.* 2021;21(2):203-212.
22. Alomar M, Tawfiq AM, Hassan N, Palaian S. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. *Ther Adv Drug Saf.* 2020;11:2042098620938595.
23. MS International Federation. *Global COVID-19 Advice for People with MS*. Last updated on June 4, 2021. Accessed June 10, 2020. www.msif.org/wp-content/uploads/2021/06/June-2021-MSIF-Global-advice-on-COVID-19-for-people-with-MS-FINAL.pdf.