COVID-19 outcomes in fingolimod- or siponimod - treated patients: Clinical trial and post marketing cases

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Joseph Berger[1], Roseanne Sullivan[2], Ajay Kilaru[3], Bernhard Hemmer[4], Bruce A.C. Cree[5], Benjamin M. Greenberg[6], Virginia DeLasHeras[3], Brian J. Ward[7]

[1]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, US; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, US; [3]Novartis Pharma AG, Basel, Switzerland; [4]Department of Neurology, Technical University of Munich, and Munich Cluster for Systems Neurology (SyNergy), Germany; [5]Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, CA, US; [6]Department of Neurology, University of Texas Southwestern, Dallas, TX, US; [7]Department of Medicine, Division of Experimental Medicine, Research Institute of the McGill University Health Centre, Montreal, Canada

Introduction

- Fingolimod and siponimod are sphingosine 1-phosphate receptor (S1P) modulators that act by blocking S1P receptor (S1PR) function, reducing the egress of autoreactive T lymphocytes and their naive progenitor cells from secondary lymphoid organs into the bloodstream.[1] This results in the reduction of absolute circulating lymphocytes
- Therefore, people living with multiple sclerosis (PlwMS) receiving treatment with S1Ps or other immunomodulatory therapies may have a risk COVID-19[2]
- Variable rates of hospitalisation (12.8%–21.5%) and death (1.6%–3.5%) due to COVID-19 in PlwMS treated with disease-modifying therapies (DMTs) have been reported[3–6]
- Evidence from registries or databases containing real-world data is vital for patients and physicians to better understand the impact of COVID-19 on PlwMS treated with DMTs

Objective

- To evaluate the outcomes of COVID-19 in PlwMS receiving either fingolimod or siponimod in ongoing clinical trials (CT) or in the post-marketing (PM) setting

Methods

- Data from Novartis clinical trials (CTs) and safety databases were reviewed to identify confirmed or suspected cases of COVID-19 in PlwMS receiving either fingolimod or siponimod
  - **CTs cut-off dates:**
    - Fingolimod (04-Aug-2021): PARADIGMS study (CT identifier: NCT01892722): Safety and efficacy of fingolimod in paediatric patients with multiple sclerosis
    - Siponimod (29-Oct-2021): Open-label extension part of the EXPAND study (CT identifier: NCT01665144): Exploring the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis
  - **Post-marketing cut-off dates:** Fingolimod (28-Feb-2022); Siponimod (25-Mar-2022)
- COVID-19 cases were assessed as confirmed according to the following criteria:
  - **In CT:** If a patient tested positive for severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) using real-time polymerase chain reaction (RT-PCR), SARS-CoV-2 antigen test or serological test, as reported by the investigator
  - **In PM:** When one or more of the following Medical Dictionary of Regulatory Activities (MedDRA) preferred terms (PTs) from the COVID-19 narrow MedDRA Standardised MedDRA Query (SMQ) were reported: coronavirus infection, coronavirus test positive, COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, and SARS-CoV-2 test positive
- COVID-19 cases were assessed as suspected according to the following criteria:
  - **In CTs:** If a patient tested negative to a SARS-CoV-2 test or definitive diagnosis of SARS-COV-2 but the patient had reported signs and symptoms consistent with SARS-COV-2, as reported by the investigator
  - **In PMs:** When one or more of the following MedDRA PTs from the COVID-19 narrow MedDRA SMQ were reported: exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive, and suspected COVID-19
- Cases were considered 'serious' based on the International Council on Harmonisation regulatory reporting definition, which is 'fatal, life-threatening, hospitalisation, and medically significant'

Results

- A total of 1,375 confirmed or suspected cases of COVID-19 in patients receiving fingolimod (n=1054) or siponimod (n=321) were reported from CTs or the PM setting as of the cut-off dates
  - **Fingolimod:** 45 of 1054 were suspected cases of COVID-19 (all PM=45/1054) and 1009/1054 were confirmed cases of COVID-19 (PM=1,000; CT=9)
  - **Siponimod:** 6 of 321 were suspected cases of COVID-19 (PM=5, CT=1) and 315/321 were confirmed cases of COVID-19 (PM=262, CT=53)
- The cumulative patient exposure in the PM setting was ~958,384 patient-years with fingolimod treatment (as of 28-Feb-2022) and ~15,163 patient-years with siponimod treatment (as of 25-Mar-2022)
- The mean age (range) was 43 years (11–82 years, PM) and 17 years (14–20 years, CT) for fingolimod and 53 years (25–74 years, PM) and 49 years (24–59 years, CT) for siponimod (**Table 1**)
- Most of the patients receiving fingolimod (>70%) or siponimod (>65%) were female
- Hospitalisation and mortality rates with fingolimod and siponimod seem comparable with those reported with other DMTs[4–6] (**Table 1** and **Figure 1**)
  - Where case outcomes were reported, more than 80% of patients with fingolimod (PM=428/515 [83%], CT=9/9 [100%]) or siponimod (PM=81/100 [81%], CT=50/53 [94%]) had recovered or were recovering at the time of the most recent follow-up (**Table 1**)

Table 1. Patient demographics for confirmed cases of COVID-19

	Fingolimod		Siponimod	
	Post-marketing	Clinical trial**	Post-marketing	Clinical trial
COVID-19 case (confirmed + suspected)	1045	9	267	54
COVID-19 case (confirmed)	1000	9	262	53
Age (years), mean (range)	43 (11 years[#] to 82 years) (based on 712 cases where information was provided)	17 (14–20)	53 (25–74)[§] (based on 162 cases where information was provided)	49 (24–59)[§]
Gender				
Female	711	4	180	34
Male	249	5	69	19
Not reported	40	0	13	0
Seriousness				
Non-serious	625	9	187	36
Serious*	375	0	75	17
Fatal	13	0	4[¶]	3[¥]
Hospitalisation	130	0	45	15
Life-threatening	8	0	0	0
Medically significant	243	0	31	1
Case outcomes				
Not reported	485	0	162	0
Reported	515	9	100	53
Recovered/recovering	428	9	81	50
Condition unchanged	66	0	14	0
Condition detiorated	8	0	1	0
Fatal	13	0	4	3
Reporter type				
Healthcare professional	345	9	82	53
Non healthcare professional	655	0	180	0
Country/region				
Europe	349	8	50	46
United states	305	0	162	6
Rest of the world	346	1	50	1

*A case may have more than one serious criterion. [§]Age at time of event for post marketing cases and age at the start of the study for clinical trial cases

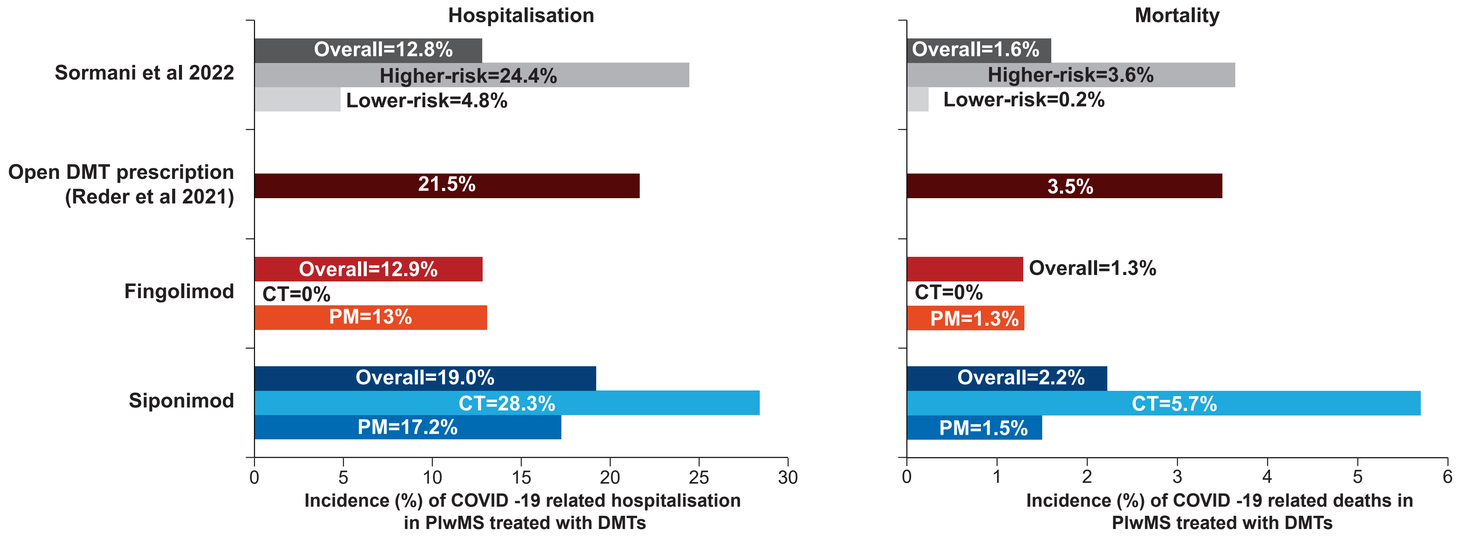
**PARADIGMS study: Safety and efficacy of fingolimod in paediatric patients with multiple sclerosis, cut-off date 04-Aug-2021

[#]Excludes a 10-week-old neonate with paternal exposure to fingolimod during pregnancy developed COVID-19 concurrently with beta haemolytic Streptococcus infection and deep vein thrombosis. The neonate was hospitalised, treated, recovered, and was discharged. It was reported that the neonate's father was COVID-19 positive

[¶]Two patients from the COVID-MS registry where only approximate age of the patient was provided (>50 and >70 years); third patient was a 60-year-old morbidly obese female with diabetes and hypertension; fourth patient was a 57-year-old female with no information provided regarding possible risk factors

[¥]All 3 patients had confounding factors for increased COVID-19 severity risk including hypertension, acute respiratory failure or >60 years of age

Figure 1. COVID-19 hospitalisation and mortality rates in PlwMS treated with DMT[3, 6]



Abbreviations: CT, clinical trial; DMT, disease-modifying therapy, MS, multiple sclerosis; PM, post-marketing study, PlwMS, patients living with multiple sclerosis
Open DMT prescription, defined as a DMT prescription in PlwMS with a defined start date and no end date at the time of diagnosis or hospitalisation
Note: Severity and mortality have changed over the course of the pandemic due to various reasons including viral strains, improved care and vaccination; therefore, the results presented here are not fully comparable to the reference rates

Clinical response to COVID-19 vaccinated patients receiving siponimod or fingolimod from clinical trials only

- Seven patients receiving siponimod had breakthrough COVID-19 infection (i.e., ≥2 weeks after 2nd dose of vaccine, or ≥ 2 weeks after one dose of a single dose regimen) of the 360 fully vaccinated patients (320 on siponimod, 40 on fingolimod) and 51 patients (45 on siponimod, 6 on fingolimod) receiving partial vaccine dose. Of these 7 patients, one patient with co-morbidities had a fatal outcome and the other 6 patients recovered completely

Conclusions

- There are 1,324 confirmed cases of COVID-19 infection and seven cases of breakthrough COVID-19 infection (with siponimod post COVID-19 vaccination in the CTs) reported in patients treated with fingolimod and siponimod. Most of the COVID-19 cases were non-serious
  - Data on outcomes of COVID-19 to date suggests that the rates of hospitalisation (13%–28.3%) and mortality (1.3%–5.7%) reported here in PlwMS receiving fingolimod or siponimod seems to be consistent with those reported with other DMTs[4-6]
  - Although data on COVID-19 outcomes including breakthrough COVID-19 infection post vaccination in patients treated with S1Ps is limited, available information support that there could be a satisfactory immune response in patients on therapy with fingolimod and siponimod modulators. However, firm conclusions cannot be drawn at this time given the relatively low numbers of cases identified, the limitations of the data available and the nature of the study

Note: The majority of COVID-19 cases reported from siponimod clinical trial occurred at a time when only limited COVID-19 treatments and no, or only limited vaccination were available and the virus was more virulent

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Presenter email address: Joseph.Berger@pennmedicine.upenn.edu

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