COVID-19 Outcomes and Vaccination Status in Patients With Relapsing Multiple Sclerosis Receiving Ofatumumab

DMT36

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Background

- As of September 25, 2021, the World Health Organization (WHO) reported that >231 million people worldwide had been affected by COVID-19, with fatal outcome in >4.7 million people[1]
- In MS patients, the rate of hospitalization due to COVID-19 varied from 12.8% to 15.5% and mortality due to COVID-19 from 1.62% to 1.97%[2,3]
- B-cell depleting therapies may compromise immune responses and lead to higher risk of severe and prolonged COVID-19 infection [4,5]
- Development of SARS-CoV-2 vaccines was a key milestone in fighting the COVID-19 pandemic, but little is known about the efficacy of these vaccines in people with immune-mediated disorders, such as multiple sclerosis (MS)
- There is a need for further evidence from clinical studies and the real-world setting to better understand the effect of COVID-19 and vaccination in MS patients treated with disease-modifying therapies (DMTs), especially the B-cell depleting therapies

Objective

- To report the characteristics of COVID-19 cases, vaccination status, and breakthrough infections in people with relapsing MS (RMS) on ofatumumab from the ALITHIOS study and post-marketing setting

Methods

ALITHIOS open-label extension trial

Data collection

- Data from ofatumumab-treated ALITHIOS patients and their reported COVID-19 status from December 2019 (first WHO recognized reporting of COVID-19 event worldwide) to September 25, 2021 (data cut-off; based on latest available predefined database lock) were analyzed[6]

Outcomes and assessment

- Cases of COVID-19 infection in patients receiving ofatumumab (data cut-off: September 25, 2021) were reviewed
- Cases were defined as confirmed (laboratory confirmation) or suspected COVID-19 (signs and symptoms but no laboratory confirmation) as reported by the site investigators
- Seriousness category (including hospitalization), severity, COVID-19 outcomes, reinfections, COVID-19 vaccination status, and vaccine breakthrough infection with associated outcomes were presented as reported by the site investigators

Post-marketing reports

Data collection

- The analysis included post-marketing COVID-19 cases (mostly serious) in RMS patients from the Novartis Global Safety Database received from the time of ofatumumab first approval in August 2020 up to March 25, 2022
- The database captures adverse events (AEs) reported to Novartis by healthcare providers (HCPs), patients, and other sources
- Reporting of post-marketing cases is voluntary, with a large proportion of cases having incomplete data or incomplete follow-up

Outcomes and assessment

- Cases of COVID-19 infection in patients receiving ofatumumab (data cut-off: March 25, 2022) were reviewed
- COVID-19 cases were assessed as confirmed or suspected if they contained ≥1 of the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms from the COVID-19 narrow standardized MedDRA query (SMQ)
  - **Confirmed:** Coronavirus infection, Coronavirus test positive, COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, and SARS-CoV-2 test positive
  - **Suspected:** Exposure to SARS-CoV-2, SARS-CoV-2 antibody test positive, suspected COVID-19
- Seriousness category, including hospitalization and outcomes status, was presented as reported by the HCPs or non-HCPs or as per European Union list of important medical events

Results

ALITHIOS open-label extension trial

Baseline characteristics

- As of data cut-off, 245 of 1703 (14.4%) in ALITHIOS reported COVID-19 (confirmed: 210 [85.7%]; suspected: 35 [14.3%])
- In the overall patients with COVID-19, mean ± SD age at baseline: 37.9 ± 8.75 years and mean ± SD BMI: 25.42 ± 5.94 kg/m^2 (**Table 1**)

Table 1. Demographics and baseline characteristics of patients in the open-label ALITHIOS study

Characteristic	Ofatumumab 20 mg, Overall N = 1703[a]	Any COVID-19–related AE: Overall COVID-19 n = 245	Confirmed COVID-19 n = 210	Suspected COVID-19 n = 35	Hospitalized overall COVID-19 n = 23
Age (years), mean ± SD	38.6 ± 9.06	37.9 ± 8.75	38 ± 8.79	37.5 ± 8.58	41.7 ± 7.5
Female, n (%)	1186 (69.6)	171 (69.8)	147 (70.0)	24 (68.6)	13 (56.5)
BMI in kg/m^2, mean ± SD	25.42 ± 5.92	25.42 ± 5.94	25.49 ± 6.02	25 ± 5.49	27.32 ± 5.32
BMI categories, n (%)					
Overweight: BMI 25 to <30 kg/m^2	427 (25.1)	62 (25.3)	52 (24.8)	10 (28.6)	9 (39.1)
Obese: BMI ≥30 kg/m^2	307 (18.0)	45 (18.4)	40 (19.0)	5 (14.3)	7 (30.4)
EDSS, mean ± SD	2.84 ± 1.38	2.63 ± 1.21	2.65 ± 1.23	2.49 ± 1.07	2.67 ± 1.10
EDSS >3.5, n (%)	430 (25.2)	44 (18.0)	40 (19.0)	4 (11.4)	3 (13.0)
Type of MS, n (%)					
RRMS	1621 (95.2)	239 (97.6)	204 (97.1)	35 (100)	22 (95.7)
SPMS	82 (4.8)	6 (2.4)	6 (2.9)	0	1 (4.3)
Selected AEs prior to COVID-19 onset, n (%)[b]	60 (3.5)	60 (24.5)	52 (24.8)	8 (22.9)	3 (13.0)
Cardiac disorders	9 (0.5)	9 (3.7)	8 (3.8)	1 (2.9)	0
Metabolism and nutrition disorders	14 (0.8)	14 (5.7)	13 (6.2)	1 (2.9)	1 (4.3)
Respiratory, thoracic, and mediastinal disorders	28 (1.6)	28 (11.4)	25 (11.9)	3 (8.6)	1 (4.3)
Vascular disorders	18 (1.1)	18 (7.3)	15 (7.1)	3 (8.6)	2 (8.7)

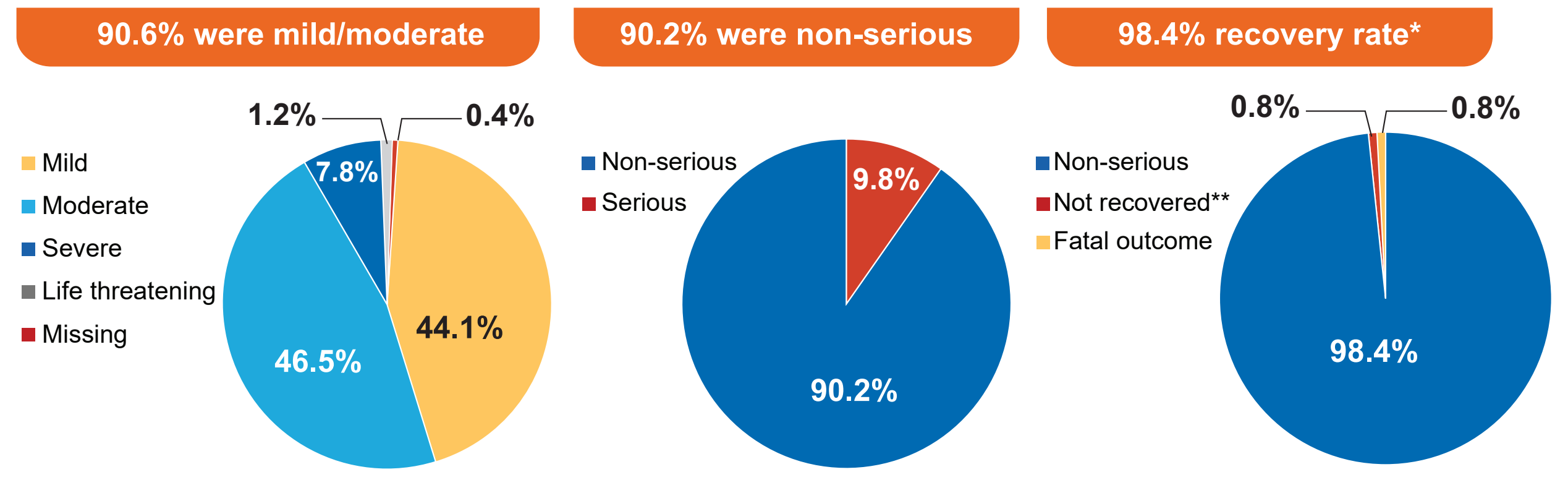
AE, adverse event; BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

[a]N = 1703 represents the enrolled population in the ALITHIOS study. [b]The selection of prior AEs was based on the following MedDRA System Organ Classes (SOCs) Cardiac disorders,' 'Metabolism and nutrition disorders,' 'Respiratory, thoracic and mediastinal disorders,' and 'Vascular disorders'.

COVID-19 outcomes

- Of the 245 reported COVID-19 cases, 221 (90.2%) were non-serious and 24 (9.8%) were serious, including 23 hospitalizations (**Table 2**, **Figure 1a**)
- Among the reported cases, majority (90.6%) had an infection that was mild-to moderate in severity while 19 had severe (7.8%), and 3 had life-threatening (1.2%) COVID-19; CTCAE grading was missing for 1 (0.4%) case (**Table 2**, **Figure 1b**)
- Majority (241, 98.4%) of COVID-19 cases had either recovered or recovered with sequelae, or were recovering, while two (0.8%) had not yet recovered, and two cases (0.8%) had a fatal outcome (**Table 2, Figure 1c**)
  - Two ALITHIOS patients with fatal outcomes were unvaccinated and had underlying comorbidities of diabetes and hypertension in one patient and slightly overweight (BMI of 28.3 kg/m^2) in another patient, which are known risk factors for severe COVID-19
- No patient had reinfection
  - As per the Centers for Disease Control and Prevention, reinfection was defined as a second confirmed infection after 90 days from the end date of the recovered first COVID-19
- Before COVID-19 onset, IgG levels were within the normal range in all COVID-19–affected patients, while IgM was <0.4 g/L in 23 (9.4%) patients
- Ofatumumab was temporarily interrupted in 39 (15.9%) patients

Figure 1. COVID-19 cases: Clinical severity (a), seriousness (b) and outcomes (c) in the open-label ALITHIOS study



*Recovered includes recovered or recovered with sequalae or recovering at the time of data cut-off;
**At the time of data cut-off

Table 2. Summary of COVID-19 cases in the open-label ALITHIOS study

Characteristic	Any COVID-19–related AE: Overall COVID-19 (N = 245)	Confirmed COVID-19 (n = 210)	Suspected COVID-19 n = 35	Hospitalized overall COVID-19 n = 23
COVID-19 seriousness, n (%)				
Non-serious	221 (90.2)	187 (89.0)	34 (97.1)	0
Serious	24 (9.8)	23 (11.0)	1 (2.9)	23 (100)
Hospitalized	23 (9.4)	22 (10.5)	1 (2.9)	23 (100)
COVID-19 maximum severity, n (%)				
Mild	108 (44.1)	90 (42.9)	18 (51.4)	1 (4.3)
Moderate	114 (46.5)	99 (47.1)	15 (42.9)	5 (21.7)
Severe	19 (7.8)	17 (8.1)	2 (5.7)	14 (60.9)
Life-threatening	3 (1.2)	3 (1.4)	0	3 (13.0)
Missing CTCAE grading	1 (0.4)	1 (0.5)	0	0
COVID-19 outcome, n (%)				
Recovered/recovered with sequelae/recovering	241 (98.4)	206 (98.1)	35 (100.0)	22 (95.7)
Not recovered	2 (0.8)	2 (1.0)	0	0
Fatal	2 (0.8)	2 (1.0)	0	1[a] (4.3)
COVID-19 duration in days, median (range)	15 (1-216)	15 (1-216)	14 (3-47)	14 (4-57)
COVID-19 onset time since first dose of ofatumumab (years), mean ± SD	2.32 ± 1.00	2.38 ± 1.00	1.91 ± 0.90	2.52 ± 0.86
AE leading to ofatumumab interruption, n (%)	39 (15.9)	34 (16.2)	5 (14.3)	9 (39.1)
AE leading to ofatumumab discontinuation, n (%)	2 (0.8)	2 (1.0)	0	1 (4.3)

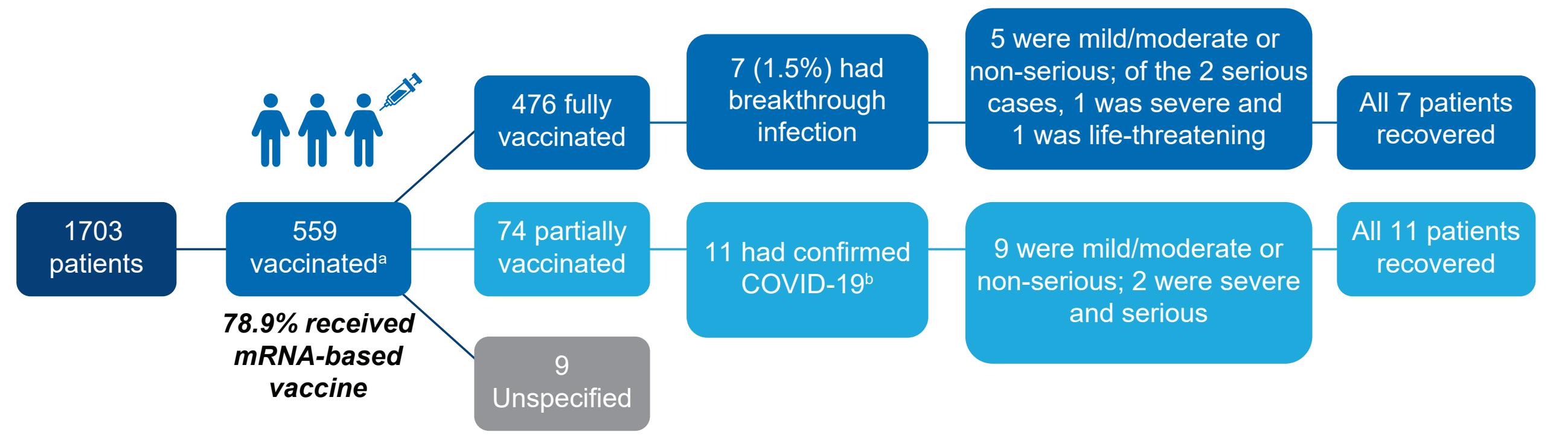
AE, adverse event; CTCAE, common terminology criteria for AE.

[a]One fatal case was not admitted to hospital due to personal circumstances and financial reasons

Confirmed COVID-19 cases after COVID-19 vaccination

- 559 patients were vaccinated (fully vaccinated, 476; partially vaccinated 74; unspecified, 9)
- Breakthrough infection was reported in 1.5% (7/476) fully vaccinated patients, and 11 reported COVID-19 after partial vaccination; all patients recovered as of cut-off date (**Figure 2**)
  - Fully vaccinated: Most cases were mild/moderate in severity or non-serious (n = 5); among 2 serious cases, 1 was severe and 1 was life-threatening
  - Partially vaccinated: Most cases were mild/moderate in severity or non-serious (n = 9); 2 cases were serious and severe
- Of the 559 patients with a COVID-19 vaccination, 37 (6.6%) had a confirmed ofatumumab dose interruption based upon physician decision and received a COVID-19 vaccination during the treatment gap
- Median duration of treatment gap was 56 days

Figure 2. Vaccination and infections post-vaccination in the open-label ALITHIOS study



1703 patients

559 vaccinated[a]

78.9% received mRNA-based vaccine

476 fully vaccinated

7 (1.5%) had breakthrough infection

5 were mild/moderate or non-serious; of the 2 serious cases, 1 was severe and 1 was life-threatening

All 7 patients recovered

74 partially vaccinated

11 had confirmed COVID-19[b]

9 were mild/moderate or non-serious; 2 were severe and serious

All 11 patients recovered

9 Unspecified

mRNA, messenger ribonucleic acid

[a]Nine patients were vaccinated with unspecified vaccines. [b]One patient was from one of the nine patients with unspecified vaccines where the vaccination status was partial at COVID-19 onset.

Post-marketing setting

Patient characteristics

- As of data cut-off, 480 patients (confirmed: 467; suspected: 13) were reported to have COVID-19
- The cumulative post-authorization patient exposure since the first launch of ofatumumab is estimated to be approximately 18,530 patient years (PY)
- Among 467 confirmed cases
  - Mean age (range) at baseline: 45 (19-75) years
  - Majority were female: 340 patients

COVID-19 outcomes

- COVID-19 infections were mostly non-serious (88%)
- Forty-two patients (9.0%) reported hospitalization due to COVID-19 and there were 2 (0.4%) fatal cases

Table 3. Summary of COVID-19 cases in the post-marketing setting

Characteristic	Post-marketing Confirmed COVID-19 N = 467
Reporter type, n (%)	
HCP	62 (13.3)
Non-HCP	405 (86.7)
COVID-19 seriousness, n (%)	
Nonserious	412 (88.2)
Serious	55 (11.8)
Hospitalization	42 (9.0)
Life-threatening	1 (0.2)
Fatal	2 (0.4)
Medically significant	14 (3.0)
COVID-19 AE last outcome, n (%)	
Recovered/recovered with sequelae/recovering	173 (37.0)
Condition unchanged/not recovered	24 (5.1)
Fatal	2 (0.4)
Not reported	268 (57.4)

*A case may have more than one seriousness criteria.
AE, adverse event; HCP, healthcare professional.

Conclusions

- In the Phase 3b ALITHIOS study, where RMS patients are treated with ofatumumab[6]:
  - There is no evidence of an increased risk of severe, or serious COVID-19 or fatal outcomes (fatal, 0.8%; hospitalization 9.4%) when compared to hospitalization and fatality rates reported in general MS population[2]
  - It is reassuring in that most COVID-19 cases were nonserious (90.2%) mild or moderate in severity (90.6%) and most patients recovered (98.4%) from COVID-19 despite being on ofatumumab (mean onset time of COVID-19 since the first dose: 2.32 years), a B-cell–depleting therapy
  - As per the data cut-off, none of the COVID-19 patients were reinfected
  - The few COVID-19 cases (1.5%) observed after full vaccination were mostly mild to moderate in severity, and all patients have recovered
- In a post-marketing setting, most patients recovered or were reported as condition unchanged; 0.4% fatal; 9.0% hospitalized, and 1 life-threatening cases were reported
- COVID-19 outcomes in people living with MS receiving ofatumumab appear to be similar to the overall MS population affected with COVID-19[2,7]

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Brian J. Ward serves on a scientific advisory board for Novartis and reports personal fees from Novartis for this activity. He is also medical officer for Medicago Inc and holds parts of patents for vaccines targeting influenza, Clostridioides difficile and Schistosoma mansoni. In the last 5 years, he has held academic industry awards with Medicago, MIT Canada, and Aviex Technologies.

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