COVID-19 Outcomes and Vaccination in Ofatumumab-treated RMS Patients: ALITHIOS Trial and Post-marketing Setting

Mario Habek[1], Anne H. Cross[2], Silvia Delgado[3], Maria Davydovskaya[4], Brian J. Ward[5], Bruce A.C. Cree[6], Natalia Totolyan[7], Linda Mancione[8], Roseanne Sullivan[8], Ronald Zielman[9], Xixi Hu[8], Ayan Das Gupta[10], Xavier Montalban[11], Kevin Winthrop[12]

[1]University Hospital Center Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia; [2]Washington University School of Medicine, Saint Louis, Missouri, USA; [3]University of Miami Miller School of Medicine, Miami, Florida, USA; [4]Moscow State Public Healthcare InszCity Clinical Hospital 24, Moscow, Russia; [5]Infectious Diseases Division, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada; [6]UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, California, USA; [7]First Saint Petersburg State Medical University, St. Petersburg, Russia; [8]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [9]Novartis Pharma B.V., Amsterdam, Netherlands; [10]Novartis Healthcare Private Limited, Hyderabad, India; [11]Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain; [12]School of Public Health at Oregon Health & Science University, Portland, Oregon, USA

ePresentation number: EPR169

Session name: MS and Related Disorders 4

Session date and time: Sunday, June 26; 13:30 - 14:15 CET

Poster Presentation at the European Academy of Neurology – Vienna, Austria.
June 25–28, 2022

Scan to download a copy of this presentation

Disclosures

Mario Habek participated as a clinical investigator and/or received consultation and/or speaker fees from Biogen, Sanofi Genzyme, Merck, Bayer, Novartis, Pliva/Teva, Roche, Alvogen, Actelion, Alexion Pharmaceuticals and TG Pharmaceuticals. **Anne H. Cross** has received consulting fees, research support and honoraria from Biogen, Celgene, Bristol Myers Squibb, EMD Serono, Merck, Genentech, Roche, Greenwich Biosciences, Horizon, Janssen (subsidiary of Johnson & Johnson), Novartis, TG Therapeutics, Academic CME, Projects in Knowledge, CME Outfitters, WebMD, Conrad N. Hilton Foundation, The Potomac Center for Medical Education, Consortium of Multiple Sclerosis Centers and ACTRIMS; serves on the scientific advisory board for ASCLEPIOS I/II for Novartis; has received grants from the National Institutes of Health, the Department of Defense, USA; has held an elected office (secretary) on the Board of Governors of the Consortium of Multiple Sclerosis Centers; was a member of the scientific advisory board of Race to Erase MS, program committee (chair) of ACTRIMS, member of the COVID-19 advisory committee of the National Multiple Sclerosis Society USA and National Multiple Sclerosis Society representative on the Progressive MS Alliance; and has received a patent for “Yablonskiy DA, Sukstansky AL, Wen J, Cross AH. Methods for simultaneous multi-angular relaxometry of tissue using magnetic resonance imaging. Patent 15060-630 (015875). **Silvia Delgado** has received fees as a consultant on scientific advisory boards for Novartis and research support from EMD Serono, NIH/NINDS and Novartis. **Maria Davydovskaya** received grants for consulting or speaking fees from Biogen Idec, Celgene/Receptos, Janssen/Actelion, Merck/EMD Serono, Novartis, Roche Sanofi Genzyme and TG Pharmaceuticals; participated on the advisory board of Biogen Idec, Merck/EMD Serono and served as a president of Medicine Association of Professional and MS centers. **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. **Bruce A.C. Cree** has received personal compensation for consulting from Alexion, Atara Biotherapeutics, Autobahn, Avotres, Biogen, EMD Serono, Novartis, Sanofi, TG Therapeutics and Therini and received research support from Genentech. **Natalia Totolyan** has received fees for advisory boards or speaking for Merck and Novartis and institutional grants for conducting clinical trials for Alexion, BIOCAD, Janssen, MAPI Pharma, Merck, Novartis, Receptos, Roche, Sanofi and TG Therapeutics. **Linda Mancione, Xixi Hu, Ronald Zielman** and **Ayan Das Gupta** are employees of Novartis. **Roseanne Sullivan** is employee of Novartis and has Novartis stock ownership. **Xavier Montalban** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Medday, Merck, Mylan, NervGen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, EXCEMED, MSIF and NMSS. **Kevin Winthrop** has received honoraria and/or support for contracted research from BMS, Pfizer, AbbVie, Union ChimiqueBelge, Eli Lilly & Company, Galapagos, Glaxosmithkline, Roche, Gilead, Regeneron, Sanofi, AstraZeneca and Novartis.

Funding source: This study is supported by Novartis Pharma AG, Basel, Switzerland.

Acknowledgments: Writing support was provided by **Vaishnavi Khandal** and **Saimithra Thammera** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Introduction

- As of September 25, 2021, the 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 hospitalisation 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 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 DMTs, especially the B-cell–depleting therapies

Objective

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

DMT, disease-modifying therapy; MS, multiple sclerosis; RMS, relapsing MS; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

1. World Health Organization website. https://covid19.who.int. Accessed April 20, 2022. **2.** Prosperini L et al. J Neurol. 2022 Mar;269(3):1114-1120. **3.** Solomon JM, et al. Mult Scler Relat Disord. 2022;58:103509. **4.** Louapre C et al. J Neurol Neurosurg Psychiatry. 2022;93(1):24-31. **5.** D'Abramo A et al. Int J Infect Dis. 2021;107: 247-250.

Methods: Data Collection, Outcomes and Assessments

	ALITHIOS study[1]		Post-marketing setting*	
Data Collection	**December 2019** First WHO recognised reporting of COVID-19 event worldwide ↓ **September 25, 2021** Data cutoff; based on latest available predefined database lock		COVID-19 cases in RMS patients from the Novartis Global Safety Database received from **August 2020** ↓ **March 25, 2022**	
Definition of COVID-19 cases	Cases were defined as reported by the site investigators		COVID-19 cases were assessed as confirmed or suspected if they contained ≥1 of the following MedDRA preferred terms from the COVID-19 narrow SMQ:	
	Confirmed cases Laboratory confirmation	**Suspected cases** Signs and symptoms but no laboratory confirmation	**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
Outcomes and assessments	Reported by the site investigator • Seriousness category (including hospitalisation) • Severity • COVID-19 outcomes	• Reinfections • COVID-19 vaccination status • Vaccine breakthrough infection with associated outcomes	Reported by the HCPs or non-HCPs • Seriousness category (including hospitalisation) • Outcomes status	

HCP, healthcare professional; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; RMS, relapsing MS; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SMQ, standardised MedDRA query; WHO, World Health Organization

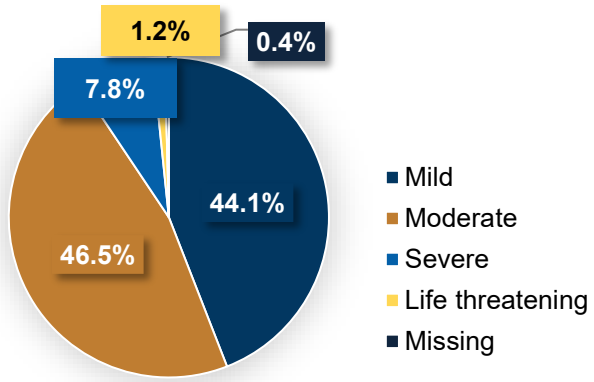
*The database captures adverse events reported to Novartis by healthcare providers, patients and other sources; reporting of post-marketing cases is voluntary, with a large proportion of cases having incomplete data or incomplete follow-up.

1. Cross AH et al. Neurol Ther. 2022 Mar 13;1-18.

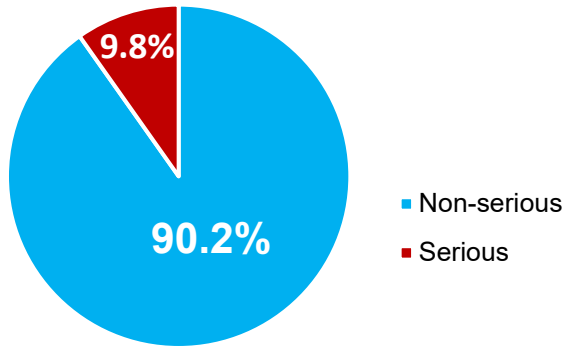
Results: COVID-19 Outcomes From ALITHIOS Study

As of 25 Sep 2021, 245/1703[a] ofatumumab-treated patients from the ALITHIOS study reported COVID-19

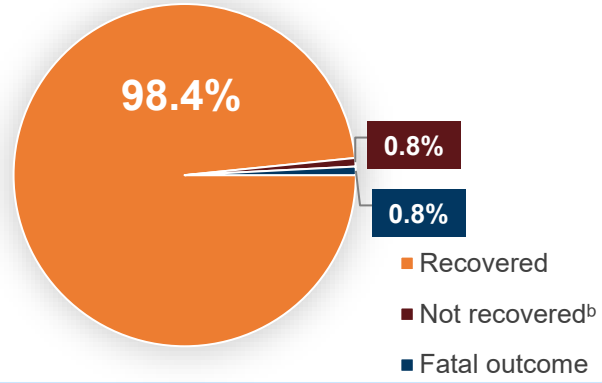
Severity: 90.6% were mild to moderate



Seriousness: 90.2% were non-serious



Outcomes: 98.4% patients recovered[b]

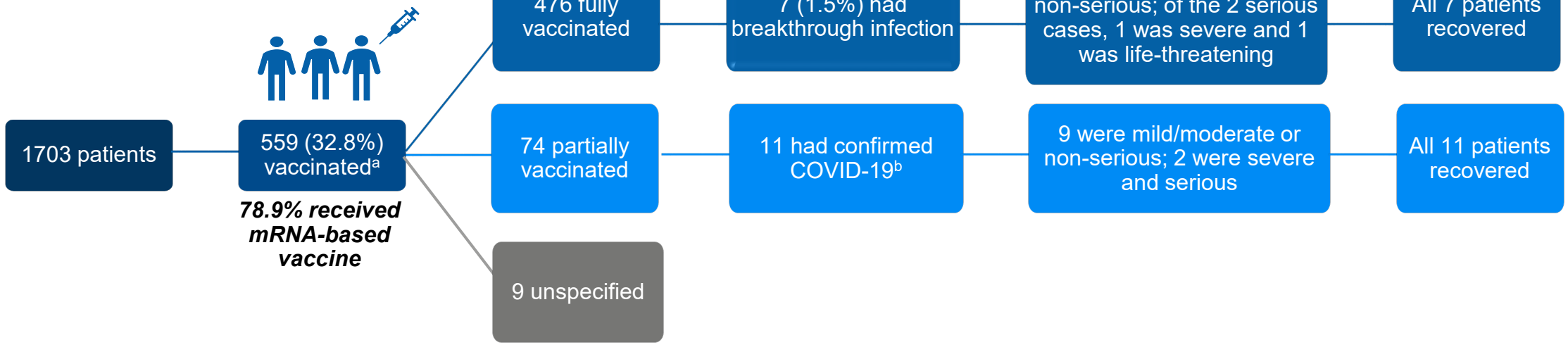


- 90.6% of COVID-19 cases were mild or moderate in severity and 90.2% were characterised as non-serious
- At the time of data cutoff, 98.4% of patients treated with ofatumumab recovered, recovered with sequalae, or were recovering from COVID-19
- Two patients[c] (0.8%) had a fatal outcome, both were unvaccinated and had comorbidities of slight overweight, diabetes and hypertension
- The majority of patients (84.1%) did not have interruption in ofatumumab treatment
- None of the patients had a COVID-19 reinfection as per the data cutoff

[a]N = 1703 represents the enrolled population in the ALITHIOS study and includes both confirmed (n=210 [85.7%]) and suspected (35 [14.3%]) COVID-19 cases. [b]Recovered includes recovered or recovered with sequalae or recovering at the time of data cutoff. [c]Two patients died due to COVID-19; both had normal Ig levels throughout the study and 1 fatal case was not admitted to hospital due to personal circumstances and financial reasons.

ALITHIOS: Vaccination and Infections Post Vaccination

Habek M, et al
EPR169



- Most of the fully vaccinated patients (79.8%) received an mRNA-based vaccine
- Of the 559 patients with a COVID-19 vaccination, **37 (6.6%)** had a confirmed ofatumumab **dose interruption;** Median duration of treatment gap[c] was **56 days**

mRNA, messenger ribonucleic acid
[a]Nine patients were vaccinated with unspecified vaccines. [b]One patient was from one of the 9 patients with unspecified vaccines where the vaccination status was partial at COVID-19 onset. [c]Number of days between two non-zero ofatumumab doses.
Additional details on the types of vaccination are presented in slide 11 in the back-up section

Results: COVID-19 Outcomes From Post-Marketing Setting

Post-marketing setting (Data cutoff: March 25, 2022)

Overall, **467 confirmed and 13 suspected COVID-19 cases** in ofatumumab-treated patients were reported in the post-marketing setting

For confirmed COVID-19 cases, **mean age** (range) at baseline: **45 (19-75) years**; the cumulative post-authorisation patient exposure since the first launch of ofatumumab: **~18,530 PY**

55 (11.8%) out of 467 were serious cases (42 hospitalisations, 14 medically significant, 1 life-threatening and 2 fatal cases)

Of the **199 cases** with outcomes available at the time of data cutoff, **most recovered/recovered with sequelae/recovering (n=173); the remaining were condition unchanged/not recovered (n=24) or fatal (n=2)**

PY, patient years

Conclusions

- In the ALITHIOS study, where RMS patients are treated with ofatumumab, a B-cell–depleting therapy, we report the following results[1]:
  - No evidence of an increased risk of severe, or serious COVID-19 or fatal outcomes (fatal, 0.8%; hospitalisation, 9.4%) when compared to hospitalisation and fatality rates reported in general MS population[2]
  - 90.2% of COVID-19 cases were non-serious, 90.6% were mild or moderate in severity and 98.4% of patients recovered from COVID-19 despite being on ofatumumab (mean onset time of COVID-19 since the first dose: 2.32 years)
  - None of the COVID-19 patients were reinfected during the study
  - The few COVID-19 cases (1.5%) observed after full vaccination were mostly mild to moderate in severity and all patients have recovered
- In the most COVID-19 cases from post-marketing setting, 86.9% recovered; 0.4% were fatal; 9.0% were hospitalised and 1 case was life-threatening
- To summarise, people living with MS who contract COVID-19 while receiving ofatumumab treatment appear to have similar outcomes to the overall MS population affected with COVID-19[2,3]

MS, multiple sclerosis; RMS, relapsing MS

1. Cross AH et al. Neurol Ther. 2022 Mar 13;1-18. **2.** Prosperini L et al. J Neurol. 2022 Mar;269(3):1114-1120. **3.** Barzegar M et al. Neurol Neuroimmunol Neuroinflamm. 2021;8(4):e1001.

Demographics and Baseline Characteristics From ALITHIOS Study

Habek M, et al
EPR169

Characteristics	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	Hospitalised 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)
Country, n (%)[b]					
Russian Federation	386 (22.7)	71 (29.0)	60 (28.6)	11 (31.4)	7 (30.4)
United States	275 (16.1)	36 (14.7)	29 (13.8)	7 (20.0)	3 (13.0)
Poland	213 (12.5)	35 (14.3)	30 (14.3)	5 (14.3)	5 (21.7)
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 AE 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'.

Summary of COVID-19 Cases

ALITHIOS study

Characteristics	Any COVID-19–related AE in ALITHIOS study: Overall COVID-19 (N=245)	Confirmed COVID-19 (n=210)	Suspected COVID-19 (n=35)	Hospitalised overall COVID-19 (n=23)
COVID-19 seriousness, n (%)				
Nonserious	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 AE 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)

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[b]	55 (11.8)
Fatal	2 (0.4)
Hospitalisation	42 (9.0)
Life-threatening	1 (0.2)
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)

AE, adverse event; CTCAE, common terminology criteria for AE; HCP, healthcare professional
[a]One fatal case was not admitted to hospital due to personal circumstances and financial reasons. [b]A case may have more than one seriousness criteria.

ALITHIOS: Vaccination Status Details (Data cutoff: September 25, 2021)

Manufacturer	Vaccine platform	Recommended doses	Any vaccination[a] n (%)	Partial vaccination[b] n (%)	Complete vaccination[c] n (%)
All			559 (32.8)	74 (4.3)	476 (28.0)
Moderna US, Inc	**RNA-based vaccine**	2	81 (4.8)	11 (0.6)	70 (4.1)
Pfizer-BioNTech	**RNA-based vaccine**	2	353 (20.7)	43 (2.5)	310 (18.2)
Oxford-AstraZeneca	**Viral vector (non-replicating)**	2	48 (2.8)	9 (0.5)	39 (2.3)
Janssen	**Viral vector (non-replicating)**	1	17 (1.0)	1 (0.1)	16 (0.9)
Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products	**Inactivated virus**	2	3 (0.2)	1 (0.1)	2 (0.1)
Gamaleya National Institute of Epidemiology	**Viral vector (non-replicating)**	1	2 (0.1)	0	2 (0.1)
Gamaleya National Institute of Epidemiology	**Viral vector (non-replicating)**	2	26 (1.5)	6 (0.4)	20 (1.2)
Vector center of virology	**Protein subunit**	2	3 (0.2)	1 (0.1)	2 (0.1)
Sinopharm	**Inactivated virus**	2	2 (0.1)	0	2 (0.1)
Sinovac	**Inactivated virus**	2	5 (0.3)	2 (0.1)	3 (0.2)
Mixed[d]		2	10 (0.6)	0	10 (0.6)
Unspecified			9 (0.5)		

CDC, Centers for Disease Control and Prevention.
[a]Any vaccination is defined as ≥1 dose of COVID-19 vaccine is taken. [b]Partial vaccination is defined as ≥1 dose is taken, but either not all recommended doses are taken or <14 days after completion of all recommended doses of a COVID-19 vaccine. [c]Complete vaccination is defined as per CDC guidance, ≥14 days after completion of all recommended doses of a COVID-19 vaccine. [d]Mixed includes patients with COVID-19 vaccines from ≥2 different manufacturers where recommended dose is 2 for each mixture component. Complete vaccination is defined as ≥14 days after completion of the second dose in the mixture; otherwise, it is partial.