Outcomes of COVID-19 in Ofatumumab-treated RMS Patients: Data from the ALITHIOS Open-label Extension Study

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Disclosures

Heinz Wiendl has received honoraria for acting as a member of scientific advisory boards for Biogen, Evgen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, and Sanofi-Aventis, as well as speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Merck Serono, Novartis, Roche Pharma AG, Genzyme, Teva, and WebMD Global. He is acting as a paid consultant for AbbVie, Actelion, Biogen, IGES, Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, and the Swiss Multiple Sclerosis Society. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, the European Union, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation, Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, and Sanofi-Genzyme. **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 research support from EMD Serono and Novartis. **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. **Natalia Khachanova** participated as a clinical investigator and/or received consultation and/or speaker fees from Merck, Novartis, Hoffmann-La Roche, Actelion, TG Pharmaceuticals , Generium, Osmotica Pharmaceuticals US LLC, Sanofi-Aventis, Teva, Octapharma AG, Janssen, MAPI Pharma, BIOCAD. **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 Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

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Background and Objective

- The COVID-19 pandemic has created challenges in the management of patients with MS[1]
- B-cell–depleting therapies may compromise immune responses and may lead to a higher risk of severe and prolonged COVID-19[2,3]
- The development of SARS-CoV-2 vaccines has been a key milestone in fighting the COVID-19 pandemic
- There is a need for evidence from clinical studies and real-world settings to better understand the impact and effect of COVID-19 and vaccinations in MS patients treated with DMTs, especially including B-cell–depleting therapies
- Data collected on COVID-19 outcomes in ofatumumab-treated RMS patients were previously reported up to 25-Sep-2021 from the ongoing ALITHIOS open-label extension study, and up to 25-Mar-2022 from PMS[4,5]

Objective

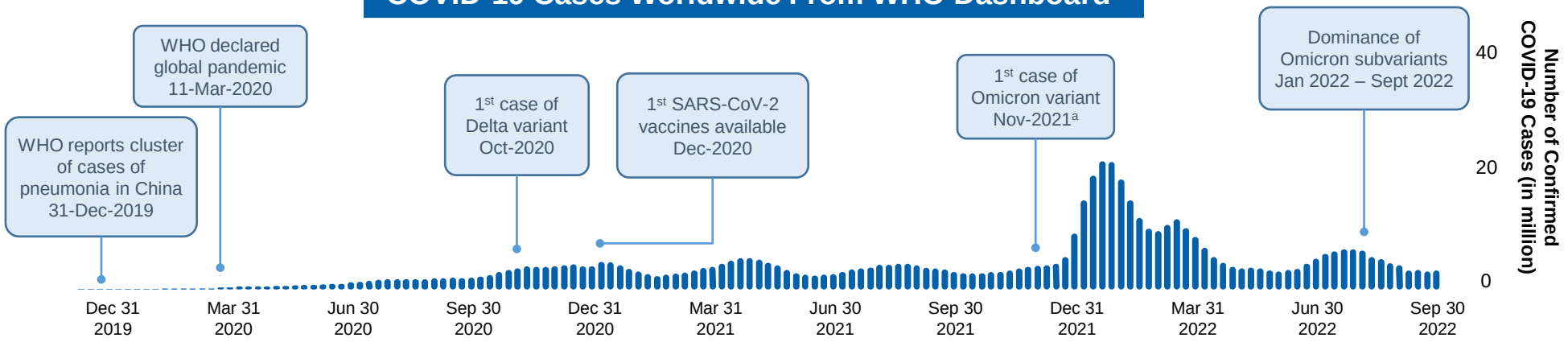
To present updated cumulative COVID-19 outcomes and vaccination status in patients with RMS on ofatumumab from the ALITHIOS study and the post-marketing population up to 25-Sep-2022

DMT, disease-modifying therapy; MS, multiple sclerosis; PMS, post-marketing surveillance; RMS, relapsing MS
Please refer to backup slides for additional information on data collection, outcomes and assessments

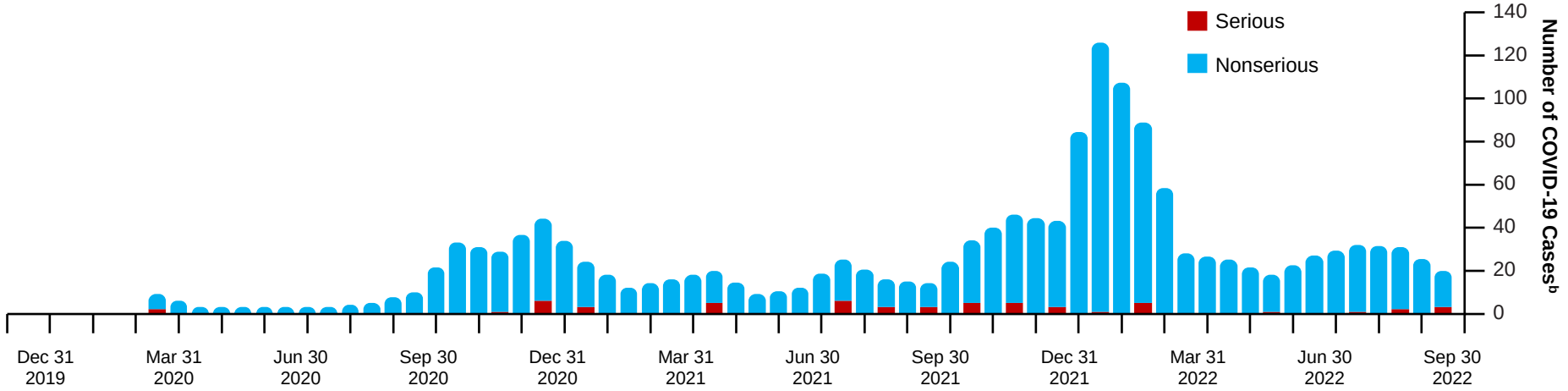
1. Hollen C, Bernard J. Curr Neurol Neurosci Rep. 2022 Aug;22(8):537-543. **2.** Louapre C et al. J Neurol Neurosurg Psychiatry. 2022;93(1):24-31. **3**. D'Abramo A et al. Int J Infect Dis. 2021;107: 247-250. **4.** Habek M et al. European Academy of Neurology (EAN) 2022. 2022, June 26. EPR169. **5.** Winthrop K et al. Consortium of Multiple Sclerosis Centers (CMSC) 2022. 2022, June 1-4. DMT36.

COVID-19 Cases Over Time in the ALITHIOS Study

COVID-19 Cases Worldwide From WHO Dashboard[1]



COVID-19 Cases From the ALITHIOS Study[b]



- The incidence of COVID-19 cases over time in the ALITHIOS study follows the global COVID-19 incidence and incidence peaks over time
- A clear incidence peak is observed when the SARS-CoV-2 Omicron variant was the dominant strain globally

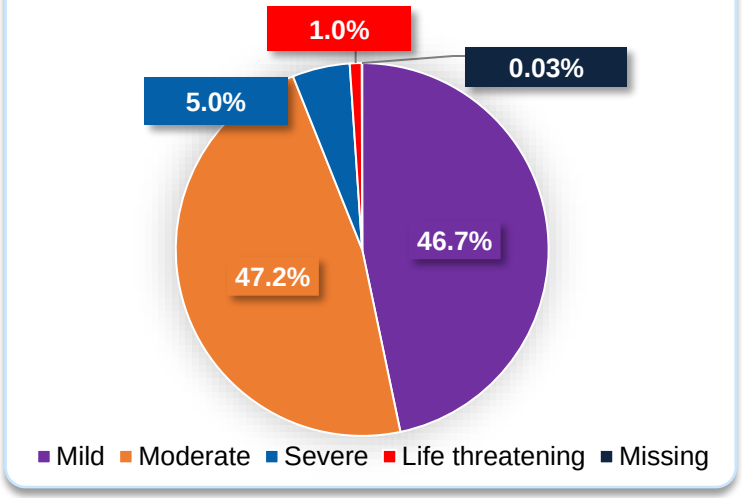
[a]First case of Omicron variant reported after data cut-off: November 26, 2021; [b]includes confirmed and suspected COVID-19 cases reported during the study.

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available at https://covid19.who.int/. Accessed 26 May, 2023

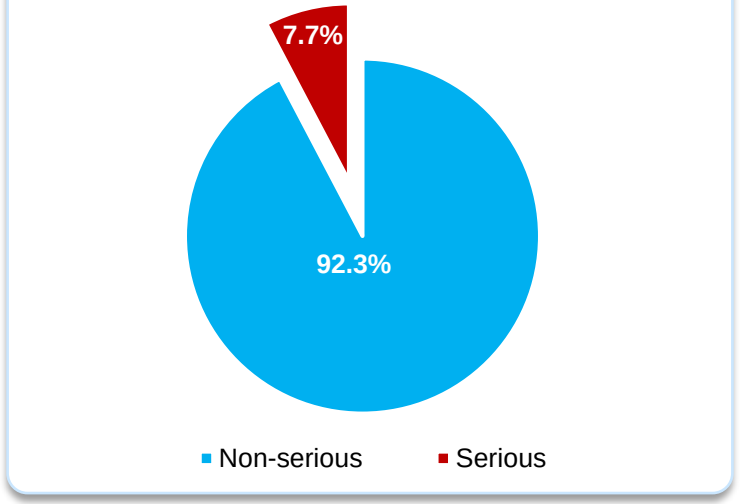
ALITHIOS: COVID-19 Outcomes

As of 25-Sep-2022, **38% (648/1703)** of ofatumumab-treated patients[a] entering ALITHIOS reported COVID-19 **(confirmed [n=603]; suspected [n=45])**

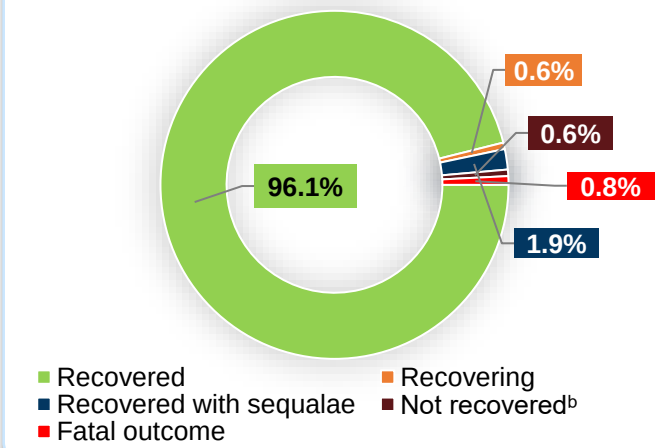
93.9% were mild to moderate in severity



92.3% were non-serious



98.6% patients recovered/recovered with sequalae/recovering



- There were 5 patient deaths (5/648; 0.8%)[c]; three patients were unvaccinated; two patients were fully vaccinated[d]
- Most patients (87.5%) did not interrupt ofatumumab treatment; only 5 patients discontinued the treatment due to COVID-19 or COVID-19 pneumonia
- Only 3.8% (n=64) of patients had a COVID-19 reinfection (at the onset of infection, 26 unvaccinated, 4 partially vaccinated, 22 fully vaccinated, 10 received booster doses, 2 received ≥2 booster doses)

[a]Mean age at baseline: 39.2 years; females, 69.6%; BMI ≥30 kg/m^2, 18%; [b]At the time of the data cutoff; [c]The five fatal cases consisted of: COVID-19 [n=2], COVID-19 pneumonia (n=1), COVID-19 and COVID-19 pneumonia (n=1), COVID-19 pneumonia and pneumothorax (n=1); [d]Fully vaccinated is at least 14 days after completing the primary vaccine series, which may or may not be after a booster dose. These two fatal cases occurred before a booster dose, one case had multiple risk factors for severe COVID-19 and the other case which was complicated by a bilateral pneumothorax.

ALITHIOS: COVID-19 Outcomes by Vaccination Status

Before Vaccination

1703 Patients

After Vaccination[a,b]

Before Vaccination	Partially vaccinated (n=41)	Fully vaccinated (n=705)	Booster Dose 1 (n = 329)	Booster Dose 2 (n = 42)
318 had confirmed COVID-19	**23** had confirmed COVID-19	**167** had infection after vaccination	**109** had infection after vaccination	**12** had infection after vaccination
314/318 (98.7%) Recovered[c]	**23/23 (100%)** Recovered[c]	**163/167 (97.6%)** Recovered[c]	**109/109 (100%)** Recovered[c]	**12/12 (100%)** Recovered[c]
Not Recovered (1/318), Fatal (3/318)		Not Recovered (2/167), Fatal (2/167)		
Seriousness: 29, 289	Seriousness: 2, 21	Seriousness: 14, 153	Seriousness: 3, 106	Seriousness: 1, 11
Severity: 20, 3, 154, 141	Severity: 2, 9, 12	Severity: 5, 3, 84, 75	Severity: 39, 2, 68	Severity: 1, 6, 5

Seriousness Non-serious, Serious

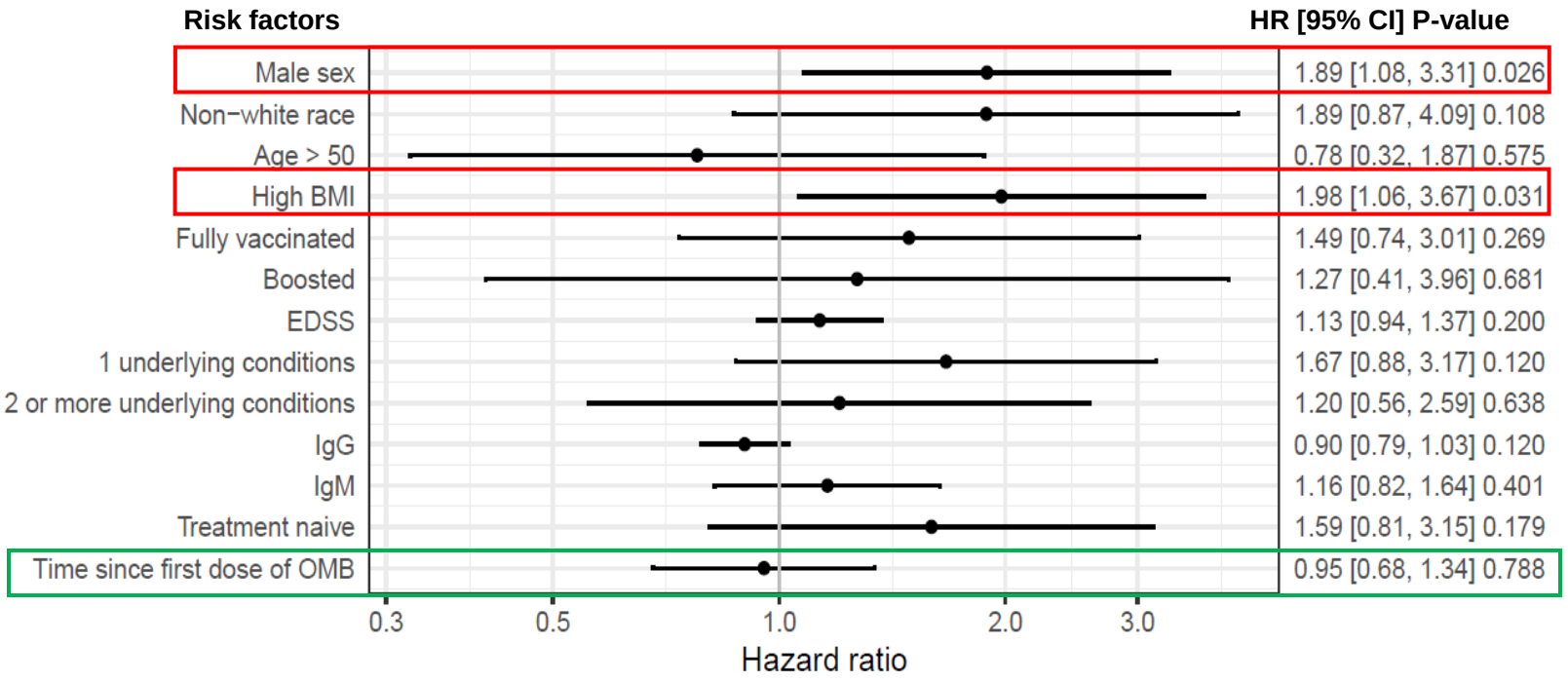
Severity Mild, Moderate, Severe, Life-threatening

- Most of the fully vaccinated patients (75.6%) received an mRNA-based vaccine
- The post-vaccination COVID-19 cases mostly occurred when the SARS-CoV-2 Omicron variant was the dominant strain globally
- Majority of cases were mild-to-moderate in severity (n=299/312; 95.8 %) and recovered[c] (n=308/312; 98.7%)
- Of the 746 patients with a COVID-19 vaccination, 55 (7.4%) had a confirmed ofatumumab dose interruption; Median duration of treatment gap was 59 days

[a]746 patients were vaccinated; [b]4 patients had ≥3 booster doses of which 1 patient had COVID-19 infection (Grade 1) who recovered; [c]includes patients who have recovered, recovering, and recovered with sequalae.
mRNA, messenger ribonucleic acid; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

ALITHIOS: Risk Factors of Serious COVID-19

Hazard ratios from a Cox model analysis of risk factors for serious COVID−19[a,b]



- The only identified risk factors for a serious COVID-19 were **male sex** (HR 1.89 [95% CI: 1.08, 3.31]; p=0.026) **and a high BMI ≥30 kg/m² vs <30 kg/m²** (HR 1.98 [95% CI: 1.06, 3.67]; p=0.031)
- Time of ofatumumab exposure was not associated with an increased risk of serious COVID-19

[a]The analysis was based on ALITHIOS subjects who were "on ofatumumab" (including 100 days after the last dose) as of the beginning of 2020. It confirmed the association of some factors with serious COVID-19 but did not rule out the potential causation with other factors as reported in the literature. For covariates other than vaccination status, IgG, IgM, the last available value by 01−Jan−2020 was used; [b]Obtained from a Cox model with adjustment for sex, race, age (> vs <= 50), BMI (>= vs < 30), EDSS, number of underlying conditions, prior DMT, and time since first dose of OMB (years), and with vaccination status, IgG, and IgM as time−varying covariates.
BMI, body mass index; EDSS, Expanded Disability Status Scale; HR, hazard ratio, Ig, immunoglobulin; OMB, ofatumumab.

Post-Marketing Population[a]: COVID-19 Outcomes

Post-marketing setting (data cutoff: September 25, 2022)

Overall, **1154 confirmed COVID-19 cases** in ofatumumab-treated patients were reported in the post-marketing setting; the cumulative post-authorisation patient exposure to ofatumumab since the first launch: **~37,127 PY**

For confirmed COVID-19 cases, the **mean age** (range) at baseline: **45 (17-78) years**

108 (9.4%) were serious cases (74 hospitalisations, 38 medically significant, 2 life-threatening and 4 fatal cases)

Of the **415 cases** with outcomes available at the time of the data cutoff**, most recovered/recovered with sequelae/recovering (n=367, 88.4%); the remaining were condition unchanged/not recovered (n=44) and fatal (n=4)**

PY, patient years

[a]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.

Conclusions

- Data from ALITHIOS (as of 25-Sep-2022) from ~1700 RMS patients treated with ofatumumab:
  - Most COVID-19 cases were non-serious (92.3%)
  - Most were mild-to-moderate in severity (93.9%)
  - Most patients recovered (98.6%)
- Except for the known risk factors for serious COVID-19, such as male sex and higher BMI, no other risk factors have been identified.
- No evidence of an association between the seriousness of COVID-19 cases and ofatumumab exposure was apparent
- The COVID-19 cases observed after full vaccination (23.7%) were mostly mild to moderate in severity and the majority were reported to have recovered
- The proportion of serious COVID-19 cases in the real world are consistent with the ALITHIOS trial population (9.4% vs 7.7%)

BMI, body mass index; MS, multiple sclerosis; RMS, relapsing MS

Back-up Slides

Data Collection, Outcomes and Assessments

	ALITHIOS study		Post-marketing setting*	
Data collection	**December 2019** First WHO recognized reporting of a COVID-19 event worldwide ↓ **September 25, 2022** Data cutoff; based on the latest available predefined database lock		COVID-19 cases in RMS patients from the Novartis Global Safety Database received from **August 2020** ↓ **September 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 as reported by the site investigator	**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, and suspected COVID-19
Outcomes and assessments	**Reported by the site investigator** • Seriousness category (including hospitalisation) • Severity • COVID-19 outcomes • Risk factors associated with serious COVID-19	• Reinfections • COVID-19 and booster vaccination status • Infection after vaccination with associated outcomes	**Reported by HCPs or non-HCPs** • Seriousness category (including hospitalisation) • Outcomes status	

HCP, healthcare professional; MedDRA, Medical Dictionary for Regulatory Activities; RMS, relapsing multiple sclerosis; 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.

ALITHIOS: Demographics and Baseline Characteristics

Characteristics	Ofatumumab 20 mg, Overall N=1703[a]	Any COVID-19–related AE			
		Overall COVID-19 n=648	Confirmed COVID-19 n=603	Suspected COVID-19 n=45	Hospitalised overall COVID-19 n=49
Age (years), mean ± SD	39.2±9.05	39.1±8.74	39.1±8.71	38.9±9.11	41.1±7.55
Female, n (%)	1186 (69.6)	453 (69.9)	418 (69.3)	35 (77.8)	28 (57.1)
Country, n (%)					
Russia	386 (22.7)	122 (18.8)	111 (18.4)	11 (24.4)	18 (36.7)
United States	275 (16.1)	100 (15.4)	91 (15.1)g	9 (20.0)	4 (8.2)
Poland	213 (12.5)	85 (13.1)	78 (12.9)	7 (15.6)	8 (16.3)
BMI (kg/m^2), mean ± SD	25.42 (5.920)	25.80 (6.258)	25.87 (6.267)	24.89 (6.124)	26.98 (7.139)
BMI categories, n (%)					
Overweight: BMI 25 to <30 kg/m^2	427 (25.1)	173 (26.7)	162 (26.9)	11 (24.4)	14 (28.6)
Obese: BMI ≥30 kg/m^2	307 (18.0)	123 (19.0)	118 (19.6)	5 (11.1)	12 (24.5)
EDSS score, mean ± SD	2.84±1.382	2.69±1.290	2.68±1.293	2.81±1.258	3.03±1.321
EDSS score >3.5, n (%)	432 (25.4)	126 (19.4)	117 (19.4)	9 (20.0)	11 (22.4)
Type of MS, n (%)					
RRMS	1621 (95.2)	624 (96.3)	580 (96.2)	44 (97.8)	46 (93.9)
SPMS	82 (4.8)	24 (3.7)	23 (3.8)	1 (2.2)	3 (6.1)
Selected AE prior to COVID-19 onset, n (%)[b]	179 (10.5)	179 (27.6)	171 (28.4)	16 (25.8)	10 (20.4)
Cardiac disorders	25 (1.5)	25 (3.9)	23 (3.8)	3 (4.8)	1 (2.0)
Metabolism and nutrition disorders	62 (3.6)	62 (9.6)	62 (10.3)	3 (4.8)	5 (10.2)
Respiratory, thoracic and mediastinal disorders	92 (5.4)	92 (14.2)	89 (14.8)	6 (9.7)	4 (8.2)
Vascular disorders	60 (3.5)	60 (9.3)	56 (9.3)	6 (9.7)	5 (10.2)

AE, adverse event; BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS; SD, standard deviation; SPMS, secondary progressive MS
[a]This represents the enrolled population in the ALITHIOS study. [b]The selection of prior AEs was based on the following MedDRA System Organ Classes: “Cardiac disorders,’ ‘Metabolism and nutrition disorders,’ ‘Respiratory, thoracic and mediastinal disorders,’ and ‘Vascular disorders’.

ALITHIOS: Summary of COVID-19 Cases

Characteristics	Overall ALITHIOS N=648/1703	After primary vaccine series and before booster N=167/705	After 1 booster dose N=109/329	After ≥2 booster doses N=13/46
Median COVID-19 AE onset time since first dose	2.9 years	3.2 years	3.9 years	3.4 years
COVID-19 seriousness, n (%)				
Non-serious	598 (92.3)	153 (91.6)	106 (97.2)	12 (92.3)
Serious	50 (7.7)	14 (8.4)	3 (2.8)	1 (8.3)
COVID-19 maximum severity[a], n (%)				
Mild	303 (46.8)	75 (44.9)	68 (62.4)	6 (46.2)
Moderate	306 (47.2)	84 (50.3)	39 (35.8)	6 (50.0)
Severe	33 (5.1)	5 (3.0)	2 (1.8)	1 (8.3)
Life-threatening	6 (0.9)	3 (1.8)	0	0
COVID-19 outcome, n (%)				
Recovered/recovered with sequelae/recovering	639 (98.6)	163 (97.6)	109 (100)	13 (100)
Condition unchanged/not recovered	4 (0.6)	2 (1.2)	0	0
Fatal	5 (0.8)	2 (1.2)[b]	0	0

[a]Grading by CTCAE v5.0. [b]Two ALITHIOS patients with fatal outcomes who were fully vaccinated had underlying comorbidities of diabetes, obesity (BMI of 40.0 kg/m^2) and hypertension in one patient (age, 52) and breast disorder, chronic tonsilitis, kidney cysts in another patient (age, 46).
AE, adverse event

ALITHIOS: Vaccination Type

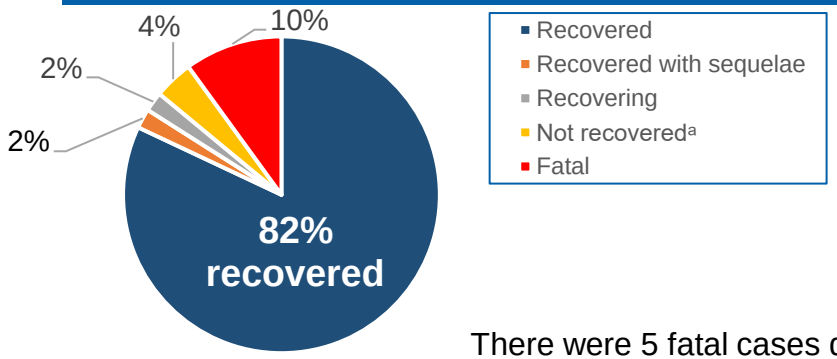
Vaccine platform	Any vaccination N=746[a] n (%)	Partial vaccination N=41 n (%)	Complete vaccination N=705 n (%)	Booster dose 1 N=329 n (%)	Booster dose 2 N=46 n (%)
RNA based vaccine	551 (73.9)	31 (75.6)	520 (73.8)	273 (83.0)	30 (71.7)
Viral-vector (non-replicating)	161 (21.6)	5 (12.2)	156 (22.1)	50 (15.2)	11 (26.0)
Inactivated virus	15 (2.01)	2 (4.9)	13 (1.8)	3 (0.9)	1 (2.2)
Protein subunit	5 (0.7)	0	5 (0.7)	0	0
Mixed	10 (1.3)	0	10 (1.4)	3 (0.9)	0
Unspecified	4 (0.5)	3 (7.3)	1 (0.1)	0	0

[a]4 patients received >2 booster doses; 3 received RNA-based vaccine and 1 patient received viral-vector (non-replicating) vaccine

ALITHIOS: Serious COVID-19 Outcomes

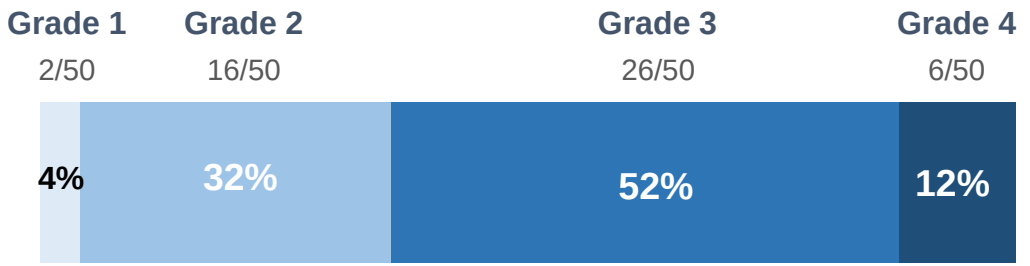
Serious COVID-19 cases	n= 50/1703 (2.9%)

Outcomes of serious COVID-19 cases (n=50)



There were 5 fatal cases due to serious COVID-19 course[b]

Severity of serious COVID-19 cases



Discontinuation of ofatumumab: 5 patients[c]

- A low number of patients had serious COVID-19 with over 85% recovered or recovering or recovering with sequelae at the time of data cut-off

[a]at the cut off; [b]5 fatal cases consisted of the following: COVID-19 [n=2], COVID-19 pneumonia [n=1], COVID-19 and COVID-19 pneumonia [n=1], COVID-19 pneumonia and pneumothorax [n=1]; [c]5 patients who discontinued the study are the same fatal cases reported due to serious COVID-19 course

ALITHIOS: Summary of Fatal Cases

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	46	44	47	52	31
Sex	Female	Female	Female	Female	Male
Race	White	White	White	White	Asian
BMI	23.2	29.8	25.8	40.0	16.9
Medical history/comorbidities	Multiple sclerosis, uterine leiomyoma, renal cyst, chronic tonsilitis, breast disorder	Multiple sclerosis, chronic gastritis, hiatus hernia, chronic sinusitis, meniscus injury, spinal osteoarthritis	Multiple sclerosis, drug-induced liver injury after doxycycline, upper respiratory tract infection, lyme disease	Multiple sclerosis, type 2 diabetes mellitus, hypertension, headache, uterine leiomyoma, spinal pain, hyperthyroidism, biliary colic, anaemia	Multiple sclerosis, hypertension, hyperglycaemia
EDSS prior to COVID-19 AE	4.5	4	3.5	4.5	4
OMB treatment duration prior to AE start date, days	1407	700	1339	1407	535
Reported AE terms	COVID-19 COVID-19 pneumonia Pneumothorax (bilateral)	COVID-19 COVID-19 pneumonia	COVID-19 COVID-19 pneumonia	COVID-19	COVID-19
Time since last OMB dose prior to COVID-19 AE	3	16	23	15	15
Action taken with study drug	Drug withdrawn	Drug withdrawn	Drug withdrawn	Drug withdrawn	Drug withdrawn
AE duration, days	94	26	33	21	10
Vaccination Status	Fully vaccinated	Unvaccinated	Unvaccinated	Fully vaccinated	Unvaccinated
Hospitalisation	Yes	Yes	Yes	Yes	No[a]
Reported relation to OMB	Not related	Not related	Not related	Not related	Not related

[a]Patient had no access to hospital during height of the pandemic.
AE, adverse event, BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis, OMB, ofatumumab

Post-marketing Population: Summary of COVID-19 Cases

Characteristics	Confirmed COVID-19 N=1154 (37,127 PY)
COVID-19 seriousness, n (%)	
Non-serious	1046
Serious	108
Fatal	4
Hospitalisation	74
Life-threatening	2
Medically significant	38
COVID-19 worst outcome, n (%)	
Recovered/recovered with sequelae/recovering	367
Condition unchanged/not recovered	44
Fatal	4
Not reported	739

PY, patient-years