Long-term Safety of Ofatumumab in Patients With Relapsing Multiple Sclerosis

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Background and Objective

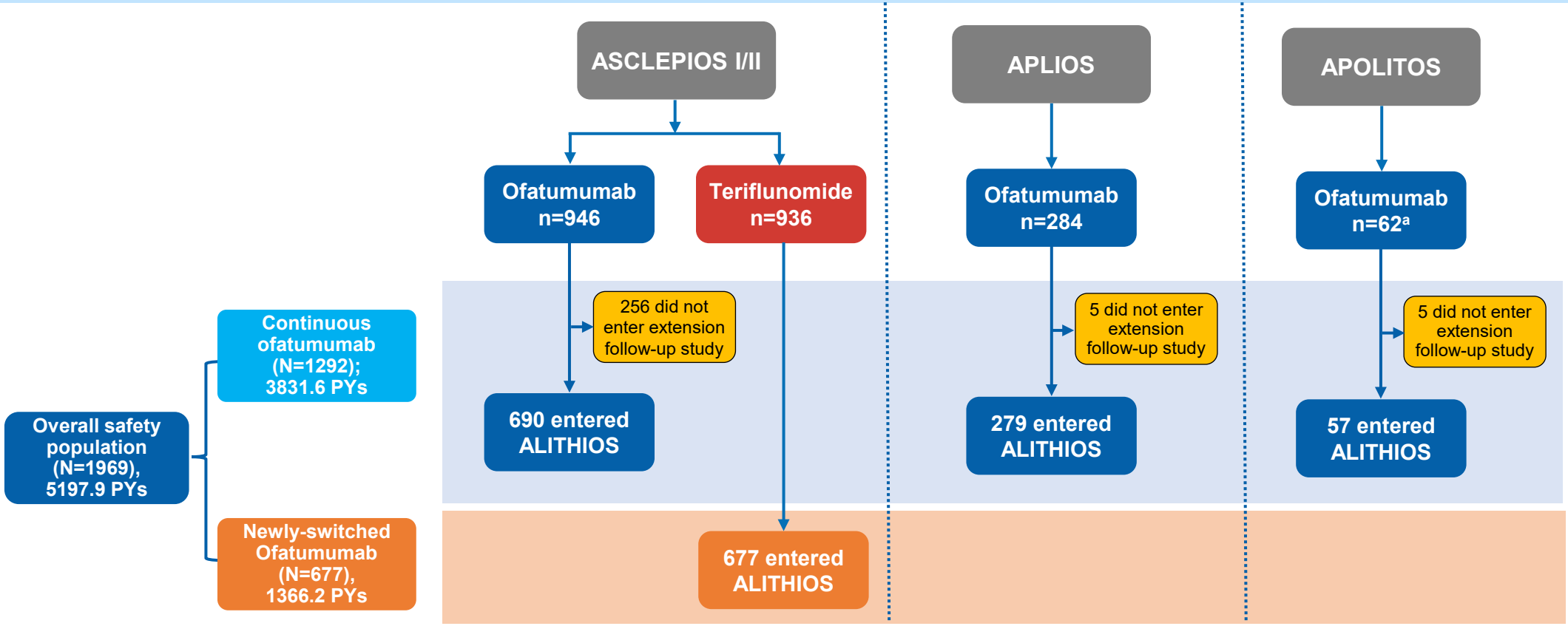
- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[1]
- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab treatment up to 30 months had a favorable safety profile and was generally well tolerated in RMS patients[2]
- Cumulative safety data for up to 3.5 years have shown that[3,4]
  - Ofatumumab was well tolerated, with no new safety risks identified
  - Mean IgG levels remained similar to baseline values, whereas mean IgM levels decreased over time but stayed above the reference limit (LLN)
- Assessment of the long-term safety of ofatumumab is important to further understand its benefit–risk profile (long-term efficacy is discussed in poster P004)

Objective	**To assess the long-term safety and tolerability of ofatumumab treatment for up to 4 years (data cut-off: 25-Sep-2021) in patients with RMS**

CD, cluster of differentiation; Ig, immunoglobulin; LLN, lower limit of normal; RMS, relapsing multiple sclerosis.

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed February 17, 2022).
2. Hauser SL, et al. *N Engl J Med* 2020;383:546−57.
3. Hauser SL, et al. *Mult Scler*. 2022.
4. Wiendl H, et al. Poster presented at ECTRIMS 2021.

Patient Population



- In the overall safety population, 86.5% patients (1703/1969) completed core studies and entered ALITHIOS
- Of these, 88.5% patients (1508/1703) were still receiving ofatumumab treatment at the time of data cutoff (25-Sep-2021)

[a]patients were either randomized to or switched to OMB during the core study.

Safety and Laboratory Assessments

Overall Safety	• Percentage of patients with at least one treatment emergent AEs or SAEs[a] • AEs of Grade 3 or 4 (combined) severity • AEs leading to ofatumumab discontinuation • EAIRs[b] per 100 PYs were estimated for all AEs
Laboratory Parameters	• Absolute serum IgG and IgM levels, lymphocyte, and neutrophil levels and percent change from baseline in IgG/IgM levels, lymphocyte, and neutrophil levels ○ Serum IgG/IgM, lymphocyte, and neutrophil levels were collected every 12 weeks up to W48, and every 24 weeks thereafter until EOS in the extension study • Serious infections occurring within 1 month prior and until 1 month after any series of low IgG/IgM levels below the LLN
Serious Infections and COVID-19	• Incidence of serious infections including opportunistic infections • COVID-19 cases including infections post COVID-19 vaccination
Malignancies	• Incidence of malignancies along with year wise IR of malignancy

[a]Injection-related reactions are reported in Poster: P7.011 presented at AAN 2022.
[b]Exposure-adjusted incidence rates per 100 PYs are defined as the number of patients with a particular event during 100 years of exposure to a treatment.
AEs, adverse events; EOS, end of study; Ig, immunoglobulin; IR, incidence rate; LLN, lower limit of normal; PYs, patient years; SAEs, serious adverse events; W, week.

Baseline Demographics and Disease Characteristics

	Continuous ofatumumab (N=1292)	Newly Switched ofatumumab (N=677)		Overall ofatumumab (N=1969)
		Baseline from core study	Baseline from extension study	
Age, years (mean±SD)	38.0±9.06	38.2±9.22	40.1±9.21	38.7±9.16
BMI, kg/m^2	25.61±6.16	25.69±5.83	25.61±5.85	25.61±6.05
Female, n (%)	889 (68.8)	456 (67.4)	456 (67.4)	1345 (68.3)
Time since MS symptom onset, years (mean±SD)	8.48±7.33	8.06±7.21	9.94±7.23	8.98±7.33
Time since diagnosis, years (mean±SD)	5.87±6.31	5.45±6.00	7.33±6.01	6.37±6.25
EDSS score at baseline, (mean±SD)	2.90±1.33	2.77±1.32	2.81±1.46	2.87±1.38
IgG levels at baseline, g/L (mean±SD)	10.31± 2.24	10.35±2.09	10.23±2.14	10.28±2.21
IgM levels at baseline, g/L (mean±SD)	1.34± 0.65	1.36±0.74	1.14±0.67	1.27±0.66
Median duration of time at risk, months	35.8	26.0	26.0	28.1
Total time at risk, PYs	3831.6	1366.2	1366.2	5197.9

BMI, body mass index; EDSS, Expanded Disability Status Scale; Ig, immunoglobulin; MS, multiple sclerosis; PYs, patient years; SD, standard deviation.
For OMB newly-switched patients, their baseline values from extension study contribute to the overall summary.

Safety Profile of Ofatumumab Remained Consistent Across 4 years of Treatment in the Overall Safety Population

Adverse event	Core, ASCLEPIOS OMB (N=946)		Core + extension, Overall OMB, (N=1969)	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Patients with at least one AE	791 (83.61)	188.55 [175.86, 202.16]	1698 (86.23)	135.11 [128.83, 141.69]
Patients with at least one SAE	86 (9.10)	5.39 [4.36, 6.65]	242 (12.30)	4.96 [4.37, 5.63]
AEs leading to OMB discontinuation	54 (5.70)	–	128 (6.50)	–
Infections and infestations	488 (51.58)	51.14 [46.80, 55.88]	1149 (58.35)	40.95 [38.65, 43.39]
Serious infections	24 (2.54)	1.44 [0.97, 2.15]	78 (4.01)	1.53 [1.23, 1.91]
Injection-related systemic reactions	195 (20.61)	15.49 [13.46, 17.83]	487 (24.73)	12.38 [11.33, 13.53]
Injection site reactions	103 (10.88)	7.21 [5.94, 8.74]	233 (11.83)	5.00 [4.40, 5.68]
Malignancies	5 (0.53)	0.32 [0.13, 0.77]	17 (0.86)	0.33 [0.20, 0.53]
Deaths	0	0	6[a] (0.30)	–

- The overall rate of AEs and SAEs remained consistent with the rates observed during the core trials[1]
- No new safety signals were identified
- The most common AEs were infections; the most frequent infections in the overall safety population were nasopharyngitis (17.5%), upper respiratory tract infections (11.1%), urinary tract infections (10.9%), and COVID-19 (10.6%)

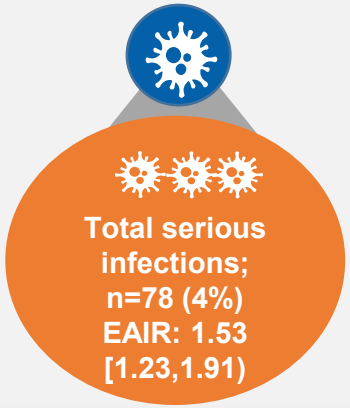
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; OMB, ofatumumab; PT, preferred term; SAE, serious adverse event; [a]PT for these 6 cases include: sudden death (n=1), completed suicide (n=1), COVID-19 and COVID-19 pneumonia (n=1), COVID-19 (n=1), intestinal metastasis (n=1), pneumonia and septic shock (n=1).

1. Data on file. OMB 157G Summary of clinical safety. Novartis Pharma AG.

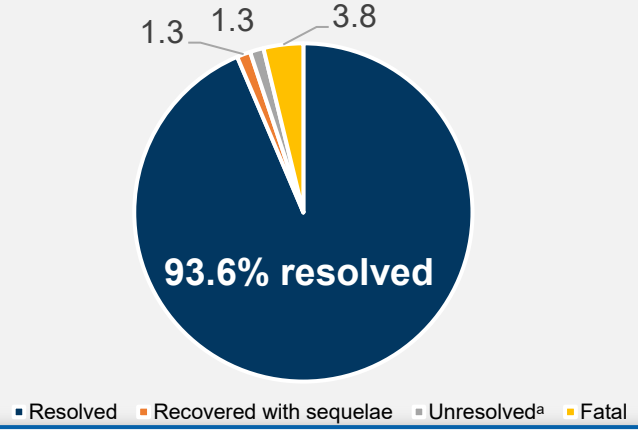
Incidence of Serious Infections Remained Stable Over Time and Did Not Increase with Long-term Use up to 4 Years

Total infections **n=1149 (58.4%);** EAIR: 40.95 [95% CI: 38.65, 43.39]

Incidence of serious infections



Outcomes of serious infections



Severity of serious infections

Grade 1 (3.85%)	Grade 2 (28.21%)	Grade 3 (60.25%)	Grade 4 (7.69%)

Treatment withdrawn: 4 patients (5.13%)

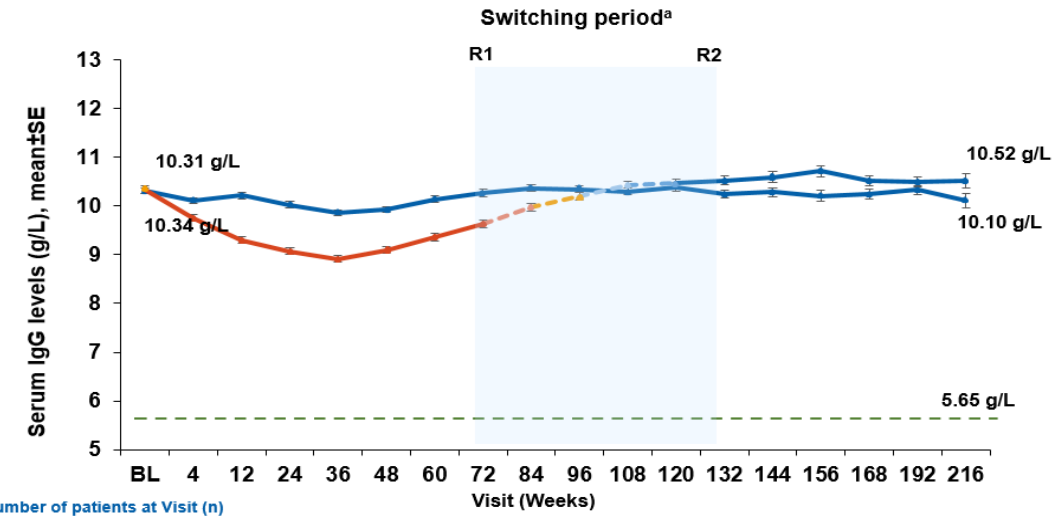
- The most common serious infections were COVID-19 pneumonia / COVID-19 (n=23)[b], appendicitis (n=13)[c]; most resolved without discontinuing ofatumumab
- Of three fatal cases due to serious infections, two were COVID-19 related and one was due to pneumonia and septic shock
- Majority of serious infections were of Grade 3 severity or below
- The overall rate of serious infections was consistent with Phase 3 ASCLEPIOS I/II trials (2.5%, EAIR: 1.44) and did not increase with treatment up to 4 years despite COVID-19 pandemic
- One case of serious opportunistic infection of pneumocystis jirovecii pneumonia[d] was reported

[a]at the cut off; [b]there are n=24 COVID-19 related SAE's in total, one of them has PT of "suspected COVID-19"; [c]includes 8 cases reported during ASCLEPIOS trial; [d]Patient was suspected to have serious, Grade 2 pneumocystis jirovecii pneumonia and was assessed by independent, external expert. The final diagnosis was not confirmed by an external adjudication panel and the clinical course was not suggestive of pneumocystis jirovecii pneumonia. No action was taken on ofatumumab therapy and patient recovered; AEs, adverse events; EAIR, exposure adjusted incidence rate.

1. Data on file. OMB 157G Summary of clinical safety. Novartis Pharma AG.

IgG Levels Remained Stable Up to 4 Years of Treatment, While IgM Levels Decreased but Remained Above the LLN

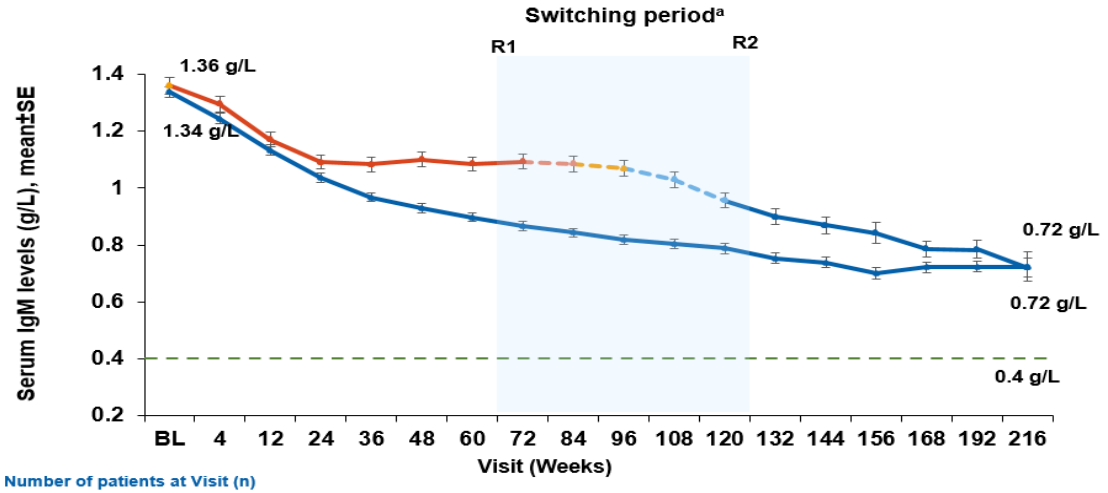
Mean IgG Levels



Number of patients at Visit (n)

	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168	192	216
Continuous OMB	1269	1233	1248	1219	1179	1129	1080	903	982	782	903	653	610	475	350	456	488	212
TER/OMB	675	672	673	666	672	669	666	670	635	633	631	564	495	439	348	448	458	186
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 320	167/ 464	72/ 492	495	439	348	448	458	186

Mean IgM Levels



Number of patients at Visit (n)

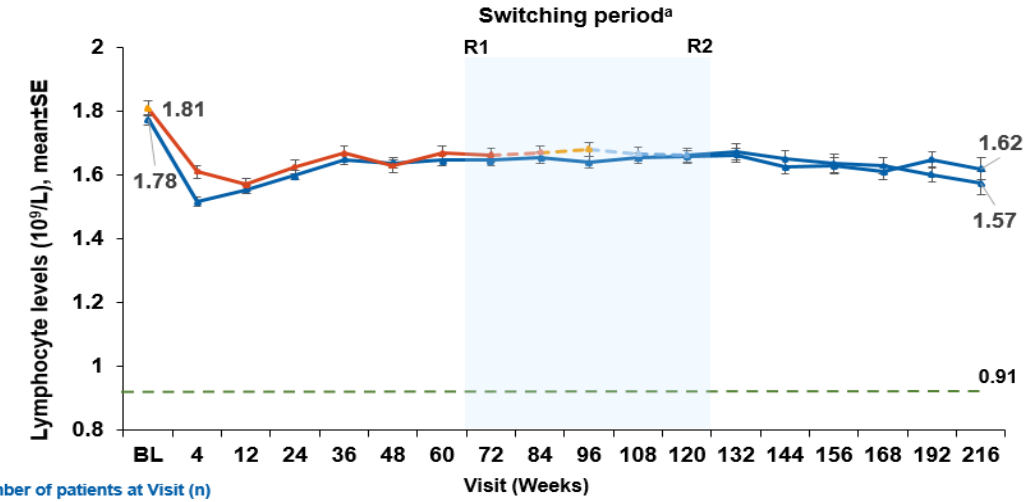
	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168	192	216
Continuous OMB	1271	1235	1250	1221	1181	1131	1085	906	986	789	906	660	612	484	356	463	490	215
TER/OMB	675	672	673	666	672	669	666	670	635	633	632	564	502	442	355	451	461	186
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 320	167/ 465	72/ 492	502	442	355	451	461	186

- Mean serum IgG levels remained stable and above the LLN (5.65 g/L) throughout the entire treatment period in both groups and in the majority of the patients (98.5%). Mean serum levels of IgM decreased in both groups, but in the majority of patients (76.9%), IgM levels remained above the LLN (0.40 g/L)
- Mean IgG levels were stable in each quartile from baseline to week 216. Mean IgM levels in each baseline quartile decreased over time but stayed above the LLN for all quartiles from baseline to week 216
- No association between decreased IgG/IgM levels and risk of serious infections was observed

[a]Switching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period; For TER/OMB group, data from 1st dose of TER until last dose of OMB plus 100 days/ analyses cut-off date have been used; R1: The first patient with first treatment emergent assessment in OMB period after switching to OMB (72 weeks); R2: The last patient with last treatment emergent assessment in TER period before switching to OMB (120 weeks); For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used: IgG: 5.65 g/L and IgM: 0.4 g/L
BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide.

Lymphocyte and Neutrophil Levels Remained Stable Throughout 4 Years of Treatment

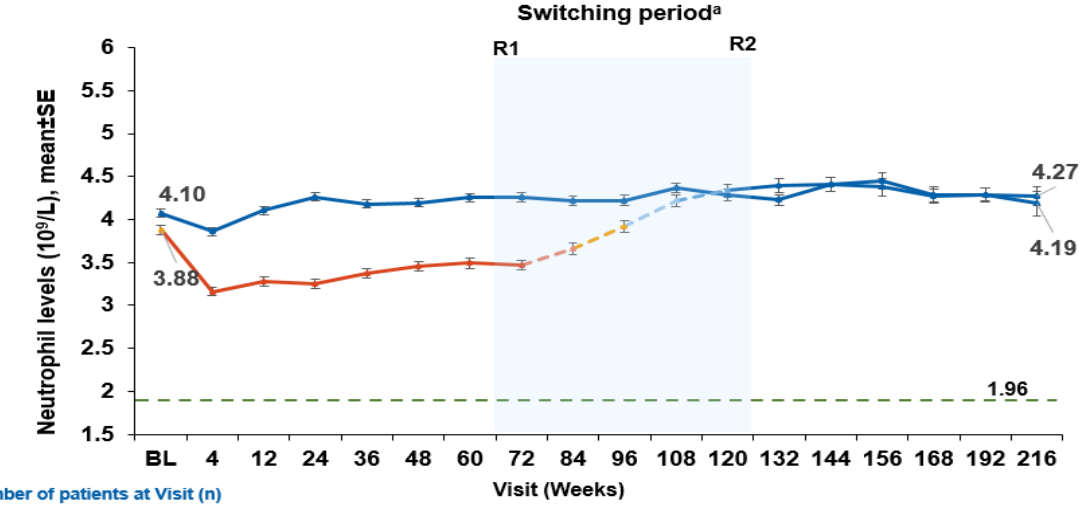
Lymphocyte Levels



Number of patients at Visit (n)

Continuous OMB	1292	1266	1264	1238	1194	1141	1086	901	982	776	915	632	595	448	341	431	475	205
TER/OMB	677	670	674	668	670	665	670	671	631	631	634	553	475	421	326	432	441	180
Before/ After switch	677	670	674	668	670	665	670	665/ 06	480/ 151	313/ 318	170/ 464	72/ 481	475	421	326	432	441	180

Neutrophil Levels



Number of patients at Visit (n)

Continuous OMB	1292	1266	1264	1238	1195	1142	1087	901	982	776	915	632	595	448	341	431	475	205
TER/OMB	677	670	674	668	670	667	670	671	631	631	634	553	475	421	326	432	441	180
Before/ After switch	677	670	674	668	670	667	670	665/ 06	480/ 151	313/ 318	170/ 464	72/ 481	475	421	326	432	441	180

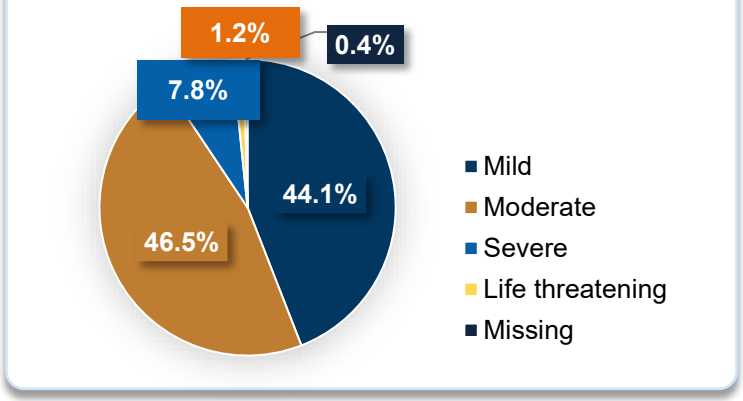
- A transient mean decline in lymphocytes was observed up to Week 4 (% change: continuous, −11.9%; newly-switched, −8.2%), followed by a reversal and increasing trend close to baseline in continuous and newly-switched groups up to Week 216
- Mean neutrophil levels remained stable and above baseline for all visits up to Week 216 (% change: continuous, 17.8%; newly-switched, 18.0%) with a rapid increase in levels for those switching from teriflunomide to ofatumumab
- EAIR of lymphopenia and neutropenia[c] remained low [0.31 (95% CI: 0.19, 0.51)] and no association was observed between decreased lymphocytes/neutrophil levels and incidence of serious infections

[a]Switching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period; For TER/OMB group, data from 1st dose of TER until last dose of OMB plus 100 days/ analyses cut-off date have been used; R1: The first patient with first treatment emergent assessment in OMB period after switching to OMB (72 weeks); R2: The last patient with last treatment emergent assessment in TER period before switching to OMB (120 weeks); [c]most events of lymphopenia and neutropenia were Grade 1/2 in severity.
BL, baseline; LLN, lower limit of normal; IR, incidence rate; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide.

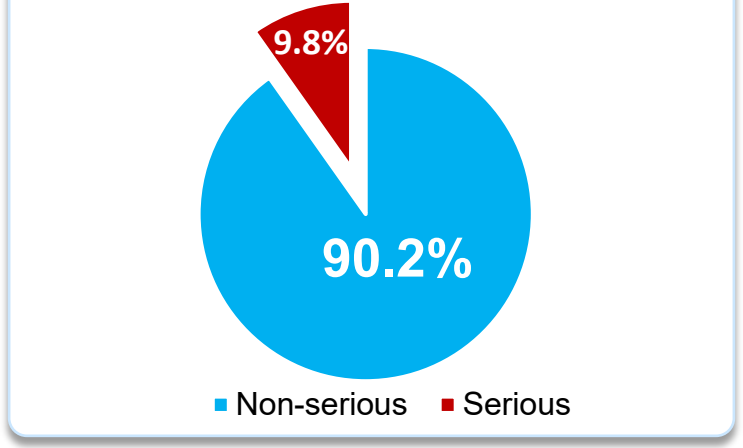
Most COVID-19 Cases were Non-serious, Mild to Moderate in Severity and the Majority of Patients Recovered

As of 25 Sep 2021, 245/1703 patients in ALITHIOS reported confirmed/suspected COVID-19

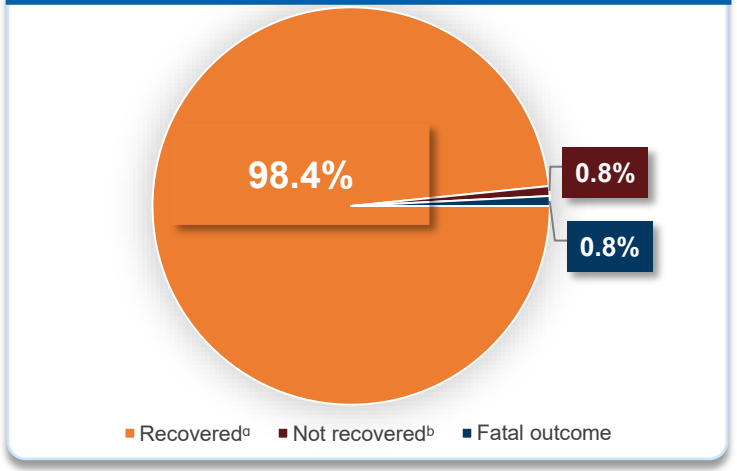
91.0% were mild to moderate



90.2% were non-serious



98.4% patients recovered



- 91% of COVID-19 cases were mild or moderate in severity and characterized as non-serious (90.2%)
- 98.4% of patients treated with ofatumumab recovered, recovered with sequalae, or were recovering from COVID-19
- Two patients[c] had a fatal outcome, both were unvaccinated, and had co-morbidities of overweight, diabetes, and hypertension
- Of patients with COVID-19, the majority (83%) did not have interruption in ofatumumab treatment
- No patients had COVID-19 reinfection

*N=1703 represents the enrolled population in the ALITHIOS study.

[a]recovered includes recovered or recovered with sequalae or recovering at the time of data cutoff; [b]at the time of data cutoff; [c]first patient: 31/Male, 16.88 kg/m^2; second patient: 47/Female, 25.77 kg/m^2 (overweight as it's > 25) .

Confirmed COVID-19 Cases After Vaccination

COVID-19 after full vaccination

7 of 476 (1.5%) patients fully vaccinated had confirmed COVID-19

- Most cases were non-serious or mild to moderate (n=5) in severity
- All 7 patients recovered as of data cutoff

COVID-19 after partial vaccination

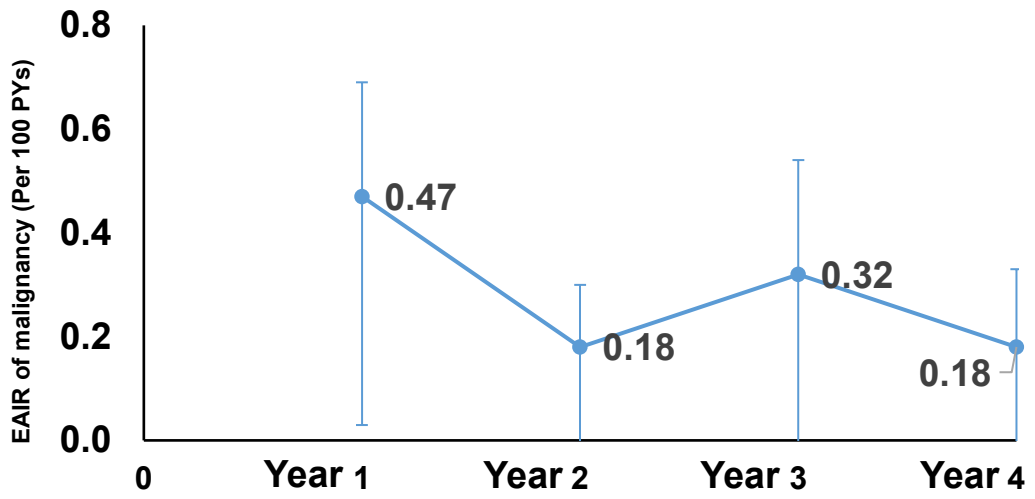
11 of 559 (2%) patients partially vaccinated had confirmed COVID-19

- Most cases were non-serious or mild to moderate (n=9) in severity
- All 11 patients recovered as of data cutoff

Fully vaccinated means at least 14 days after receiving all recommended doses of a COVID-19 vaccine (excluding booster), and partially vaccinated means at least 1 dose is taken, but either not received all recommended doses or it was less than 14 days after receiving all recommended doses of a COVID-19 vaccine.

Incidence Rates of Malignancy Did Not Increase Over Time in the Overall Patient Population

EAIR of malignancy by year in overall safety population



Malignancies	Overall ofatumumab, N=1969 n (EAIR), [95% CI]
All malignancies	17 (0.33), [0.20, 0.53]
Basal cell carcinoma	4 (0.08), [0.03, 0.21]
Invasive breast carcinoma	2 (0.04), [0.01, 0.15]
Other[a] (1 patient each)	1 (0.02), [0.00, 0.14]

- Malignancies were reported in 17 patients (0.86%) with EAIRs of 0.33 (95% CI: 0.20, 0.53)
- EAIRs for malignancies did not increase over time in the overall ofatumumab population
- Median onset time since the first dose of ofatumumab was 301 days

CI, confidence interval; CIF, cumulative incidence function; EAIR, exposure adjusted incidence rate; PY, patient years. [a]one patient each for breast cancer, intestinal metastasis, invasive ductal breast carcinoma, invasive lobular breast carcinoma, malignant melanoma in situ, non-Hodgkin's lymphoma recurrent, esophageal squamous cell carcinoma, ovarian cancer, papillary renal cell carcinoma, renal cell carcinoma, and triple negative breast cancer.

Conclusions

- Cumulative safety data for up to 4 years indicated that extended treatment with ofatumumab is well-tolerated in patients with RMS with no new safety risks identified
  - Rates of AEs and SAEs remained consistent with those previously reported in the Phase 3 ASCLEPIOS I/II trials
  - Rate of serious infections remained stable over time and did not increase with long-term use up to 4 years despite the COVID-19 pandemic
  - Mean IgG levels remained stable for up to 4 years. For most patients, IgM levels remained within the normal reference range. No association between Ig levels and risk of serious infections was observed
  - Lymphocyte and neutrophil levels remained stable throughout 4 years of treatment
  - Most COVID-19 cases were non-serious (90.2%), mild or moderate (91.0%) in severity, and most patients recovered (98.4%)
  - The few COVID-19 cases (1.5%) observed after full vaccination were mostly mild to moderate as of data cutoff 25-Sep-2021, and all patients have recovered
  - EAIRs for malignancies did not increase over time in the overall ofatumumab population
- Combined with its sustained effectiveness (up to 4 years; Poster: P004), these findings support a favorable benefit–risk profile for ofatumumab in patients with RMS

AE, adverse event; EAIR, exposure adjusted incidence rate; Ig, immunoglobulin; RMS, relapsing multiple sclerosis; SAE, serious adverse event.

No Association Between Decreased IgG/IgM Levels and Risk of Serious Infections

Patients with ≥1 serious infection within 1 month prior and until 1 month after any series of drops in IgG/IgM <LLN

	IgM				IgG				Overall	
	<LLN (N=523†)		≥LLN (N=1443‡)		<LLN (N=31†)		≥LLN (N=1935‡)		N=1969	
	n (%)	EAIR§	n (%)	EAIR§	n (%)	EAIR§	n (%)	EAIR§	n (%)	EAIR§
Patients with ≥1 serious infection	6 (1.15)	1.32	55 (3.8)	1.45	1 (3.23)	6.29	75 (3.9)	1.49	78 (3.96)	1.53
Herpes zoster (PT)	1 (0.2)	0.22	0	0	0	0	1 (0.05)	0.02	1 (0.05)	0.02
URTI (PT)	1 (0.2)	0.22	0	0	0	0	1 (0.05)	0.02	1 (0.05)	0.02
UTI (PT)	2 (0.4)	0.44	3 (0.21)	0.08	0	0	6 (0.31)	0.12	6 (0.31)	0.12
Bronchitis	1 (0.2)	0.22	0	0	0	0	1 (0.05)	0.02	1 (0.05)	0.02
Pneumonia	0	0	8 (0.55)	0.21	1 (3.23)	6.29	8 (0.41)	0.16	9 (0.46)	0.17
COVID-19	1 (0.2)	0.22	11 (0.76)	0.29	0	0	13 (0.7)	0.25	13 (0.66)	0.25

- No association between decreased IgG/IgM levels and risk of serious infections was observed

† Number of patients with IgM/IgG <LLN at least once at any time during the post-baseline visits; ‡ Number of patients with no occurrence of IgM/IgG <LLN at least once at any time during the post-baseline visit; § IR per 100 PYs estimated via a Poisson regression model with only treatment as the factor and with the log-link and natural logarithm of time as the offset variable.
Ig, immunoglobulin; EAIR, exposure adjusted incidence rate; LLN, lower limit of normal; PT, preferred term; PY, patient year.