

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

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Disclosures

Francesco Saccà served on advisory boards for Almirall, Argenx, Avexis, Biogen, Forward Pharma, Merck, Novartis, Pomona, Roche, Sanofi, Alexion, and Takeda. He received public speaking or travel honoraria from Biogen, Mylan, Novartis, Roche, Sanofi, and Teva. He received honoraria from Almirall, Novartis, and Sanofi for educational editorial work. He received consultancy fees from Argenx, Forward Pharma, Novartis, and Novatek.

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Kevin Winthrop has received honoraria and/or support for contracted research from Pfizer, AbbVie, Union ChimiqueBelge, Eli Lilly & Company, Galapagos, GlaxoSmithKline, Roche, Gilead, BMS, Regeneron, Sanofi, AstraZeneca and Novartis.

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. Heinz Wiendl 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.

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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 adults¹
- 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 patients²
- Cumulative safety data of ofatumumab treatment 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 longer-term safety of ofatumumab is important to further understand its benefit–risk profile (longer-term efficacy of ofatumumab is discussed in presentation EPR161)

Objective

To assess the longer-term safety and tolerability of ofatumumab treatment for up to 4 years in patients with RMS

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

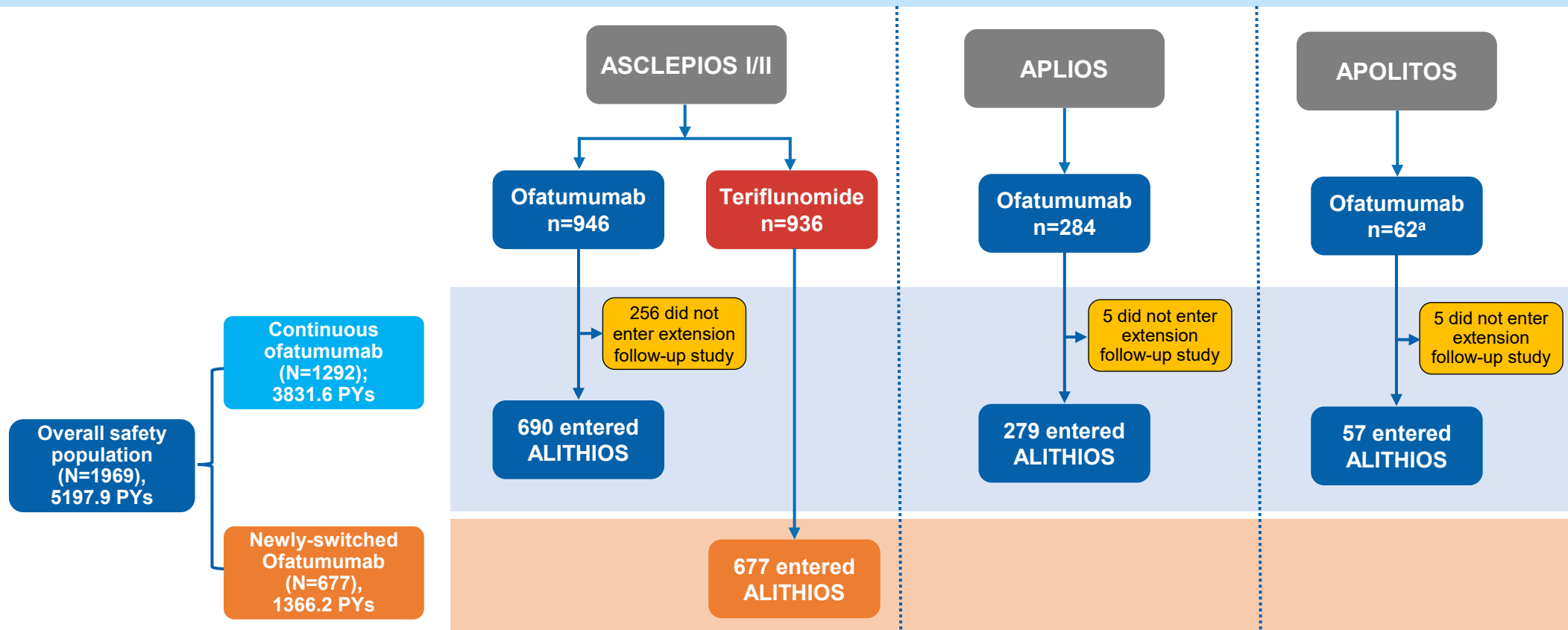
1. KESIMPTA® (ofatumumab) Prescribing Information. <https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf> (accessed February 17, 2022).

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 atECTRIMS 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 cut-off (25-Sep-2021)

^apatients 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
 - Injection-related reactions
- AEs of Grade 3 or 4 (combined) severity
- AEs leading to ofatumumab discontinuation
- EAIRs^a 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 vaccination¹

Malignancies

- Incidence of malignancies along with year wise IR of malignancy

^aExposure-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, estimated by Poisson regression where patients were censored at time of first event; 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.

1. Habek M, et al. epresentation presented at EAN 2022. EPR169.

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/m²	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 ^a (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 ^b (0.30)	–

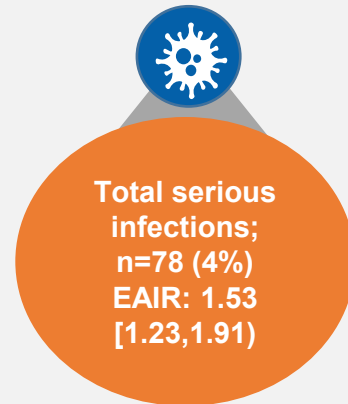
- Overall rate of AEs and SAEs remained consistent with the rates observed during the phase 3 ASCLEPIOS I/II trials
- No new safety signals were identified
- The most common AEs were infections; the most frequent infections in the overall safety population were nasopharyngitis (17.5%), upper respiratory 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; ^aAEs related to reduced IgM levels is the most common reason for treatment discontinuation (71[3.6%]); ^bPT 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).

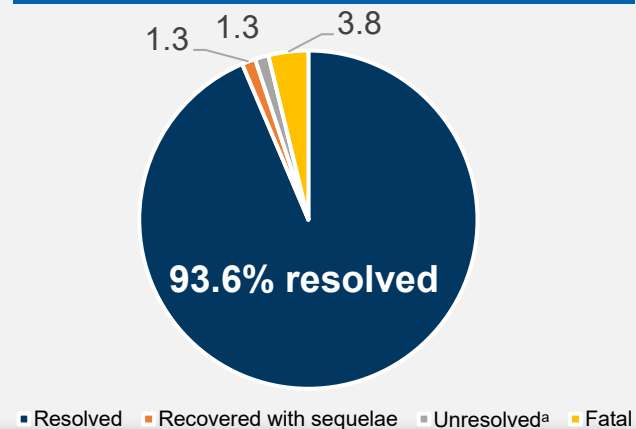
Incidence of Serious Infections Remained Stable Over Time and Did Not Increase with Longer-term Use up to 4 Years

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%)
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Discontinuation
of ofatumumab

4 patients (5.13%)

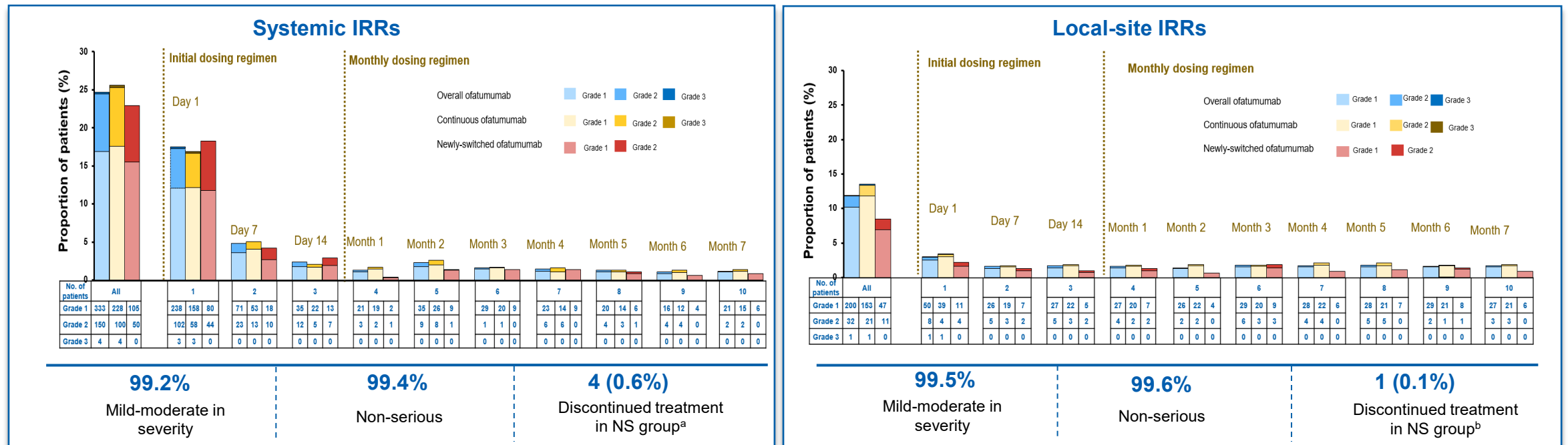
- The most common serious infections were COVID-19 pneumonia / COVID-19 (n=23)^b, appendicitis (n=13)^c; most resolved without discontinuing ofatumumab treatment
- There were three fatal cases due to serious infections, two were COVID-19 related and one was due to pneumonia and septic shock
- The majority 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; the final diagnosis was not confirmed by an external adjudication panel and the clinical course was not suggestive of pneumocystis jirovecii pneumonia

^aat the cut off; ^bthere are n=24 COVID-19 related SAE's in total, one of them has PT of "suspected COVID-19"; ^cincludes 8 cases reported during ASCLEPIOS trial; ^dPatient was suspected to have serious, Grade 2 pneumocystis jirovecii pneumonia and was assessed by independent, external expert. 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.

Injection-related Reactions Were Mostly Mild-to-moderate in Severity and Non-serious in Nature

IRRs were predominantly reported with first injection and the incidence decreased with subsequent injections¹



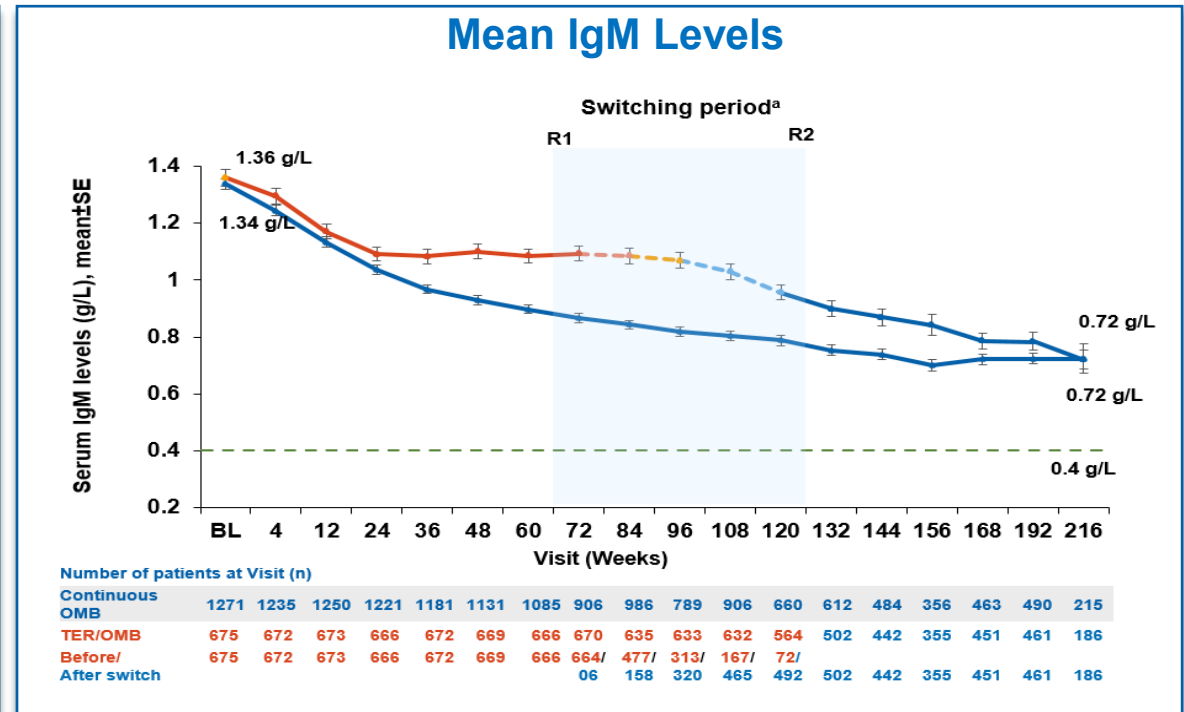
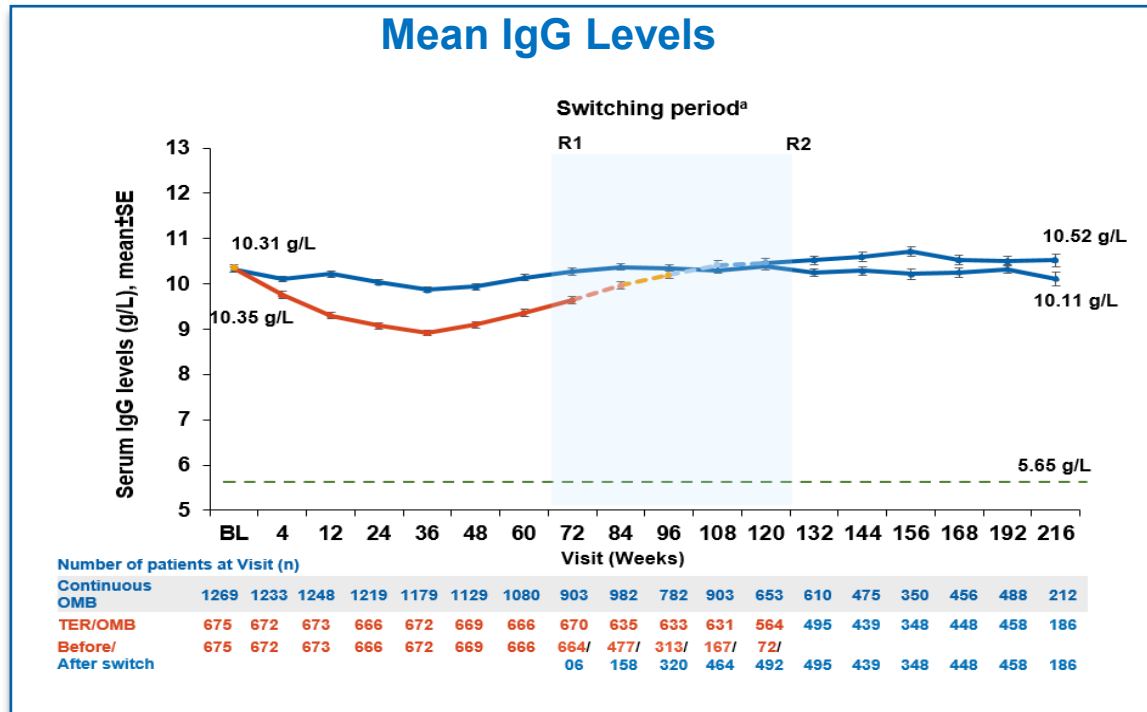
- Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in RMS clinical trials; if injection-related reactions occur, symptomatic treatment is recommended²
- Most common ($\geq 5\%$) systemic IRR symptoms observed during all injections across all groups include fever, headache, chills, other systemic reactions and fatigue; local-site IRR symptoms ($\geq 2\%$) include erythema/redness, other site reactions, pain, itching, and induration/swelling

^amild-moderate in severity and got resolved without concomitant medication; ^bmild-moderate in severity and got resolved without concomitant medication.

IRR, injection-related reaction; NS, newly-switched.

1. Kramer J et al. Poster presented at CMSC 2022; 2. KESIMPTA® (ofatumumab) Prescribing Information. <https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf> (accessed February 17, 2022)

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



- Mean serum IgG levels remained stable and above the LLN (5.65 g/L). Mean serum IgM levels decreased over time but remained above the LLN (0.40 g/L). Majority of patients had Ig levels above LLN (98.4% in IgG and 73.4% in IgM)
- For each baseline quartile, mean IgG levels were stable; whereas mean IgM levels in each baseline quartile decreased over time but stayed above the LLN for all quartiles from baseline to week 216.
- Treatment interruption/discontinuation^b was reported in 2 (0.1%)/4 (0.2%) patients due to low IgG; and 193 (9.8%)/71 (3.6%) patients due to low IgM

^aSwitching period refers to the patients started with terifunomide 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; ^bPer core and extension study protocols, investigators were required to interrupt study treatment if IgM levels fell below 10% LLN or IgG levels fell below 20% LLN. The requirement to interrupt treatment due to low IgM or IgG levels was removed with protocol amendment 2 for study COMB157G2399 and is left to the discretion of the investigator; Treatment interruption PT due to low IgM include blood immunoglobulin M decreased, immunoglobulins decreased, hypogammaglobulinaemia and hypoglobulinaemia while for discontinuation include blood immunoglobulin M decreased, immunoglobulins decreased, blood immunoglobulin M abnormal and hypogammaglobulinaemia while treatment interruption PT due to low IgG include blood immunoglobulin G decreased and for discontinuation include immunoglobulins decreased, blood immunoglobulin G abnormal, blood immunoglobulin G decreased; BL, baseline; Ig, immunoglobulin; LLN, lower limit of normal; OMB, ofatumumab; SE, standard error of the mean; TER, terifunomide.

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

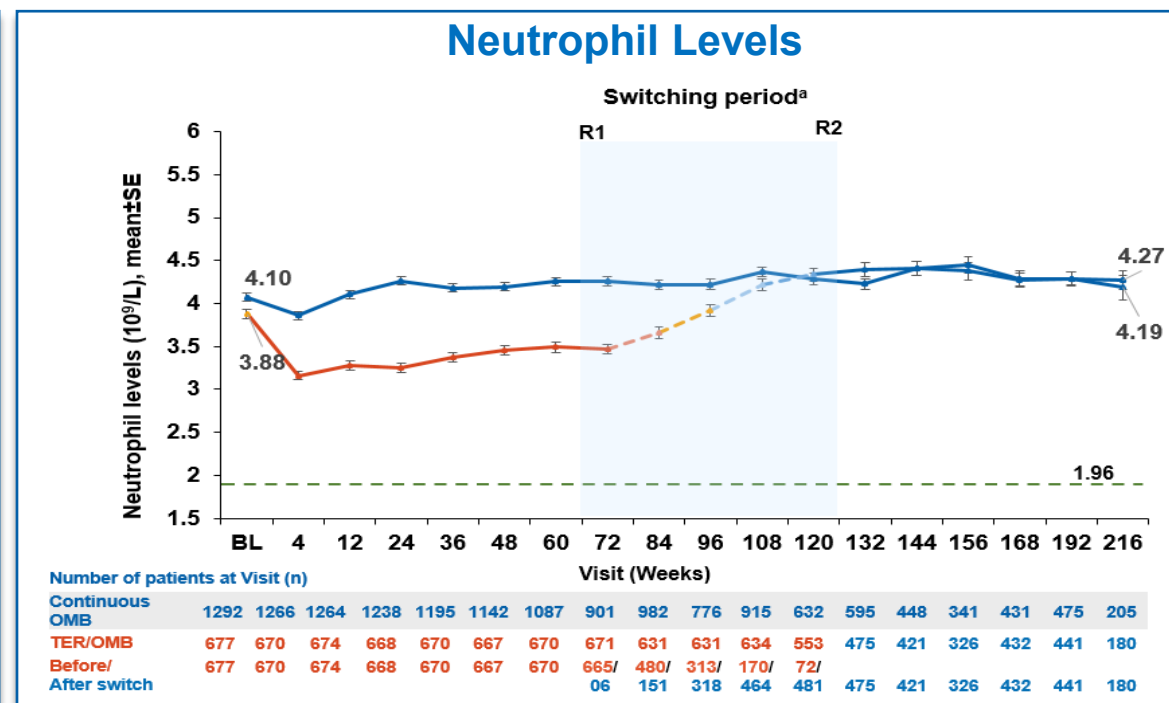
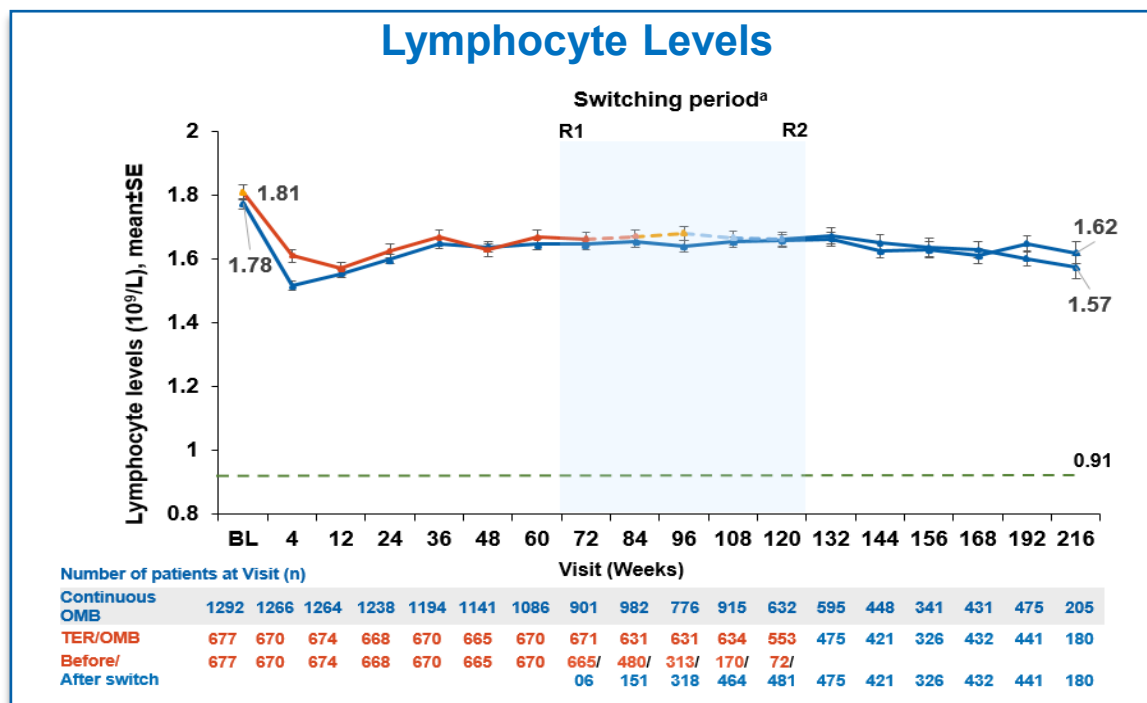
Patients with ≥ 1 serious infection within 1 month prior and until 1 month after any series of drops in IgG/IgM $<LLN$

	IgM				IgG				Overall	
	$<LLN$ (N=523 [†])		$\geq LLN$ (N=1443 [‡])		$<LLN$ (N=31 [†])		$\geq LLN$ (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.

Lymphocyte and Neutrophil Levels Remained Stable Throughout 4 Years of Treatment



- A slight and transient decline (which was not $<LLN$) in the mean lymphocytes was observed up to W4 (%change: continuous, -11.9% ; switch, -8.2%), followed by a reversal and then stabilized up to W216, in the continuous and switch groups
- Mean neutrophil levels remained stable and above baseline for all visits up to Week 216 in continuous group while in the switch group, mean neutrophil levels decreased up to Week 4 and then stabilized while still receiving teriflunomide^b
- EAIR of lymphopenia and neutropenia^c remained low [0.31 (95% CI: 0.19, 0.51)]; no apparent association was observed between low lymphocytes/neutrophil levels and risk of serious infections

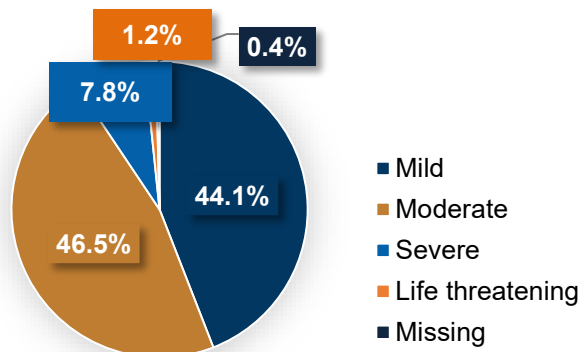
^aSwitching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period; For TER/OMB group, data from 1st dose of TER until last dose of OMB plus 100 days/ analyses cut-off date have been used; R1: The first patient with first treatment emergent 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); ^b An increase in the mean neutrophil levels reaching baseline values was observed after switching from teriflunomide to ofatumumab; ^cmost events of lymphopenia and neutropenia were Grade 1/2 in severity; Effect of ofatumumab on lymphocytes and neutrophils are reported in separate poster: DMT11 presented at CMSC 2022.

BL, baseline; LLN, lower limit of normal; IR, incidence rate; OMB, ofatumumab; SE, standard error of the mean; TER, teriflunomide.

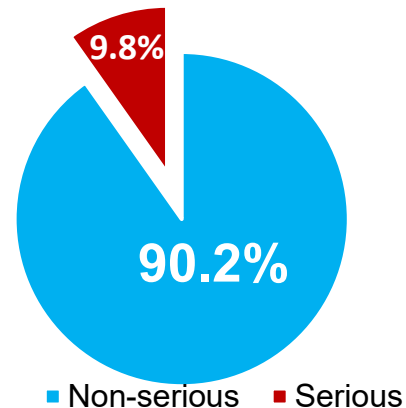
Most COVID-19 Cases were Non-serious, Mild to Moderate in Severity and the Majority of Patients Recovered^{1,2}

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

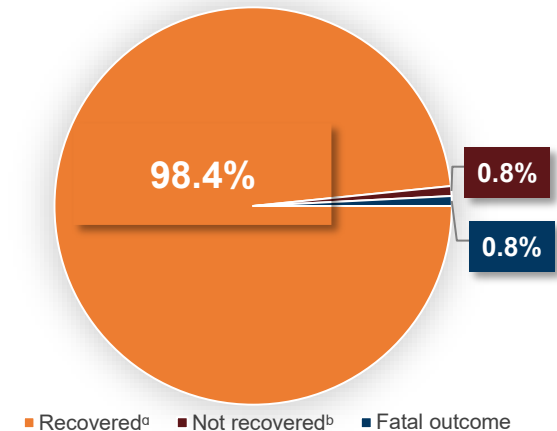
90.6% were mild to moderate



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 sequelae, 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
- Majority (84.1%) of patients with COVID-19 did not experience treatment interruption with ofatumumab
- No patients had COVID-19 reinfection
- As of 25-Sep-2021 data cutoff, few COVID-19 cases (1.5%) after full vaccination were observed and mostly were mild to moderate and all recovered

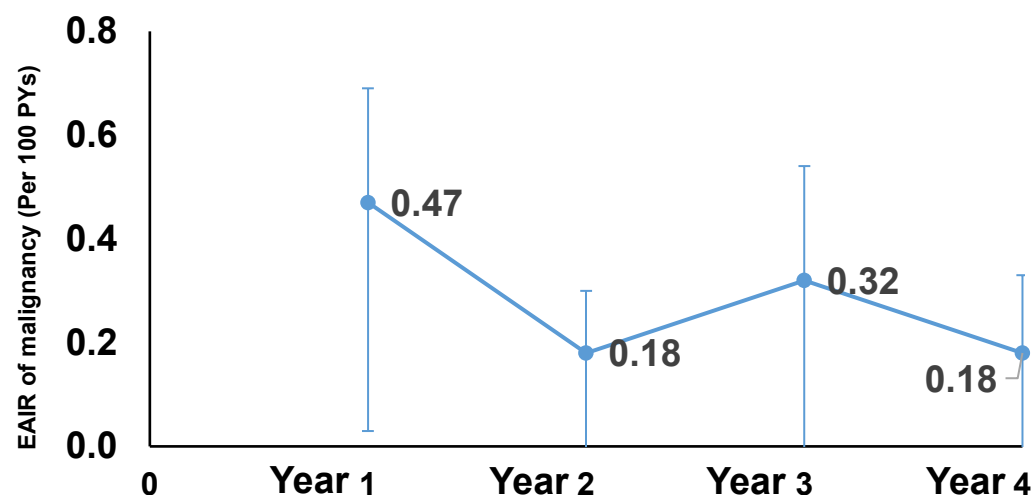
*N=1703 represents the enrolled population in the ALITHIOS study.

^arecovered includes recovered or recovered with sequelae or recovering at the time of data cutoff; ^bat the time of data cutoff; ^cfirst patient: 31/Male, 16.88 kg/m²; second patient: 47/Female, 25.77 kg/m² (overweight as it's > 25); COVID-19 outcomes are reported in separate poster: DMT36 presented at CMSC 2022.

1. Cross AH et al. Neurol Ther. 2022 Mar 13:1–18. doi: 10.1007/s40120-022-00341-z. Epub ahead of print; 2.Habek M, et al. epresentation presented at EAN 2022. EPR169.

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. ^aone 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 indicates that extended treatment with ofatumumab is well-tolerated in patients with RMS, with no new safety risks identified
 - AEs and SAEs rates remain consistent with observations in the Phase 3 trials
 - IRRs were mostly mild-moderate in severity and non-serious in nature
 - Rate of serious infections remained stable
 - Mean IgG levels remained stable
 - No association between Ig levels and risk of serious infections
 - Most reported cases of COVID-19 were non-serious and the majority of patients recovered
 - No increase in risk of malignancies over time
- Combined with its sustained effectiveness (up to 4 years; **presentation EPR161**), these findings support the favorable benefit–risk profile for ofatumumab in RMS patients

AE, adverse event; Ig, immunoglobulin; RMS, relapsing multiple sclerosis; SAE, serious adverse event.

1. Cross AH et al. *Neurol Ther*. 2022 Mar 13:1–18. doi: 10.1007/s40120-022-00341-z. Epub ahead of print