Poster: P9.010
P9: Multiple Sclerosis – Clinical Trials and Therapeutics (including Safety)
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Longer-Term Safety and Efficacy of Ofatumumab in People With Relapsing Multiple Sclerosis for Up to 6 Years

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Disclosures

Heinz Wiendl declares that he has acted as a member of the Scientific Advisory Boards of Alexion, Argenx, Biocryst, Bristol Myers Squibb, Cellerys, Galapagos, Janssen, Merck, Novartis, Sandoz-Hexal, and Uniqure. He also declares that he has received speaker honoraria and travel support from Alexion, Biogen, Bristol Myers Squibb, EPG Health, Genzyme, Merck, Neurodiem, Novartis, Ology, Roche, Teva, and WebMD Global and acts as a paid consultant for AbbVie, Actelion, Argenx, Biogen, Bristol Myers Squibb, and EMD Serono. He is acting as a paid consultant for Actelion, Argenx, BD, Bristol Myers Squibb, Dianthus, EMD Serono, EPG Health, Fondazione Cariplo, Gossamer Bio, Idorsia, Immunic, Immunovant, Inmune Bio, Syneos Health, Janssen, LTS, Merck, NexGen, Novartis, Roche, Samsung, Sangamo, Sanofi, Swiss Multiple Sclerosis Society, Toleranzia, UCB, Viatris, VirBio, and Worldwide Clinical Trials. His research is funded by Alexion, Amicus Therapeutics, Argenx, Biogen, CSL Behring, F. Hoffmann-La Roche, Genzyme, Merck, Novartis, Roche, and UCB

Stephen L. Hauser currently serves on the scientific advisory board of Accure, Alector, and Annexon. He has previously consulted for BD, Moderna, NGM Bio, and Pheno Therapeutics and served on the Board of Directors of Neurona. Dr. Hauser also has received travel reimbursement and writing support from F. Hoffmann-La Roche and Novartis AG for anti-CD20 therapy–related meetings and presentations. Grants: NIH/NINDS (R35NS111644), NMSS (SI-2001-35701), and Valhalla Foundation

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Alit Bhatt, **Xixi Hu**, **Haoyi Fu**, **Valentine Jehl**, **Roseanne Sullivan**, and **Ibolya Boer** are employees of Novartis

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Introduction 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,a]
- The phase 3 ASCLEPIOS I/II trials demonstrated the **superiority of ofatumumab** (up to 30 months) compared with teriflunomide in **reducing the clinical and magnetic resonance imaging (MRI) disease activity** while maintaining a favorable safety profile in people with RMS (pwRMS)[2]
- Treatment with ofatumumab for up to **5 years**[b] showed **sustained efficacy** and a **favorable safety profile** during the ALITHIOS open-label extension study[3,4]
- Longer-term safety and efficacy assessments are important to further understand ofatumumab's benefit–risk profile in pwRMS

Objective: To assess the longer-term safety and efficacy of ofatumumab treatment for up to 6 years (data cutoff: 25-Sep-2023) in pwRMS

[a]In the United States, ofatumumab is indicated for the treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[1] [b]Data cutoff: 25-Sep-2022.
MS, multiple sclerosis; **pwRMS**, people with relapsing multiple sclerosis.
1. Kesimpta (ofatumumab). Prescribing Information. Accessed February 17, 2024. https://www.novartis.com/us-en/sites/novartis_us/files/kesimpta.pdf. **2**. Hauser SL, et al. *N Engl J Med.* 2020;383:546−557. **3**. Cohen JA, et al. P8.004. Presented at: American Academy of Neurology (AAN) Annual Meeting, Boston, MA, USA; April 22–27, 2023. **4**. Kappos L, et al. EPR-097. Presented at: European Academy of Neurology (EAN), Budapest, Hungary; July 1–4, 2023.

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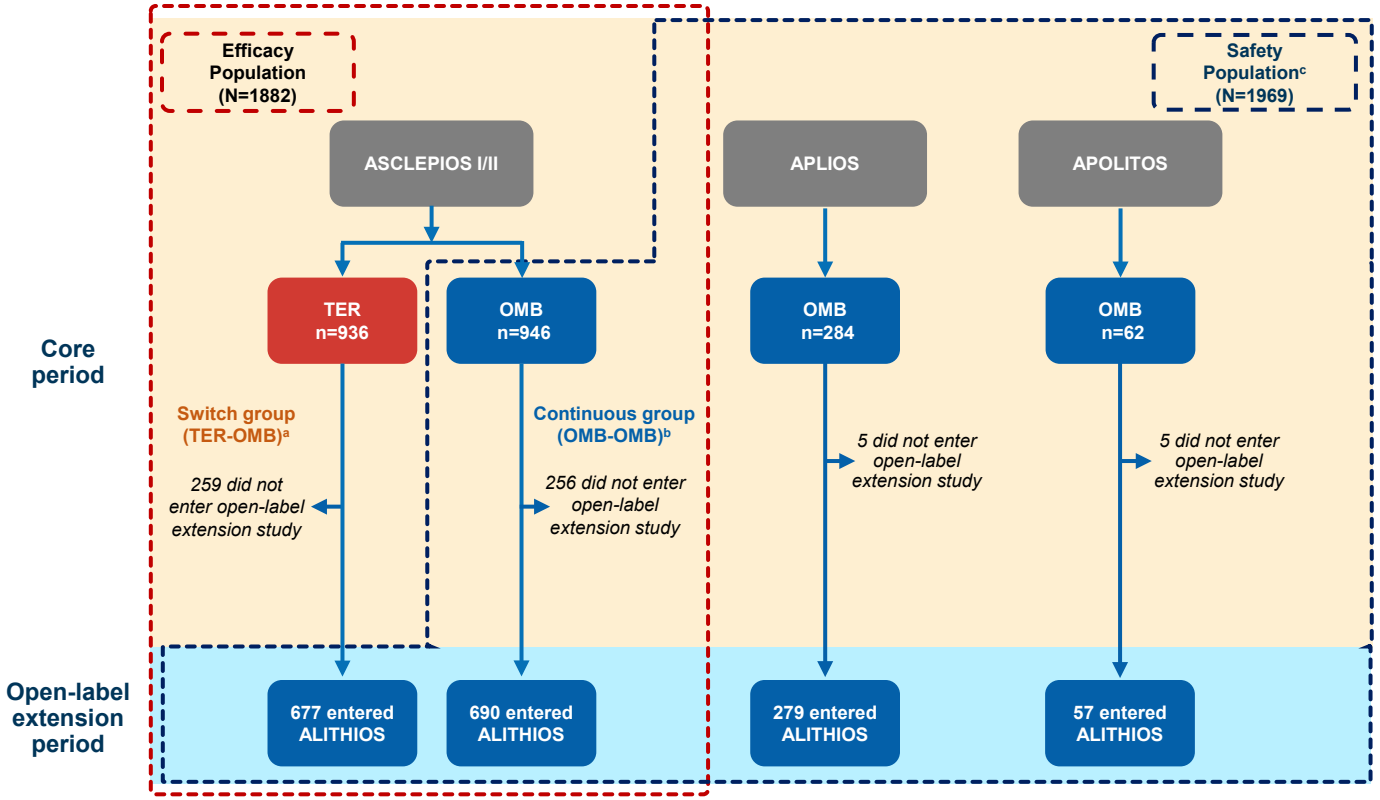
Participant disposition and key assessments



Key assessments

Efficacy[d]

- Annualized relapse rate (ARR)
- Mean number of gadolinium-enhancing (Gd+) T1 lesions per scan
- Number of new or enlarging T2 (neT2) lesions per year
- 6-month confirmed disability worsening (6mCDW)
- No evidence of disease activity (NEDA-3)[e]

Safety[f]

- Overall safety profile
- Serious infections
- Laboratory parameters
  - Immunoglobulin (Ig) G and IgM levels
  - Lymphocyte and neutrophil counts
- Malignancies

Baseline demographics and participant characteristics of both safety and efficacy population represent a typical phase 3 RMS population
(please refer to backup slides for additional details on baseline characteristics)

[a]Switch group: Participants who were randomized to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab during ALITHIOS. [b]Continuous ofatumumab group: Participants randomized to ofatumumab in ASCLEPIOS I/II and continuing ofatumumab in ALITHIOS. [c]Safety population: Participants who received ≥1 dose of ofatumumab in ASCLEPIOS I/II, APLIOS, APOLITOS, or ALITHIOS. [d]Efficacy outcomes were analyzed in efficacy analysis set (N=1882). [e]NEDA-3 is defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions, and no Gd+ T1 lesions. [f]Safety outcomes were analyzed in the safety analysis set (N=1969).
6mCDW, 6month confirmed disability worsening; **Gd+**, gadolinium-enhancing; **Ig**, immunoglobulin; **MS**, multiple sclerosis, **NEDA**, no evidence of disease activity; **neT2**, new or enlarging T2 lesions; **OMB**, ofatumumab; **RMS**, relapsing multiple sclerosis; **TER**, teriflunomide.

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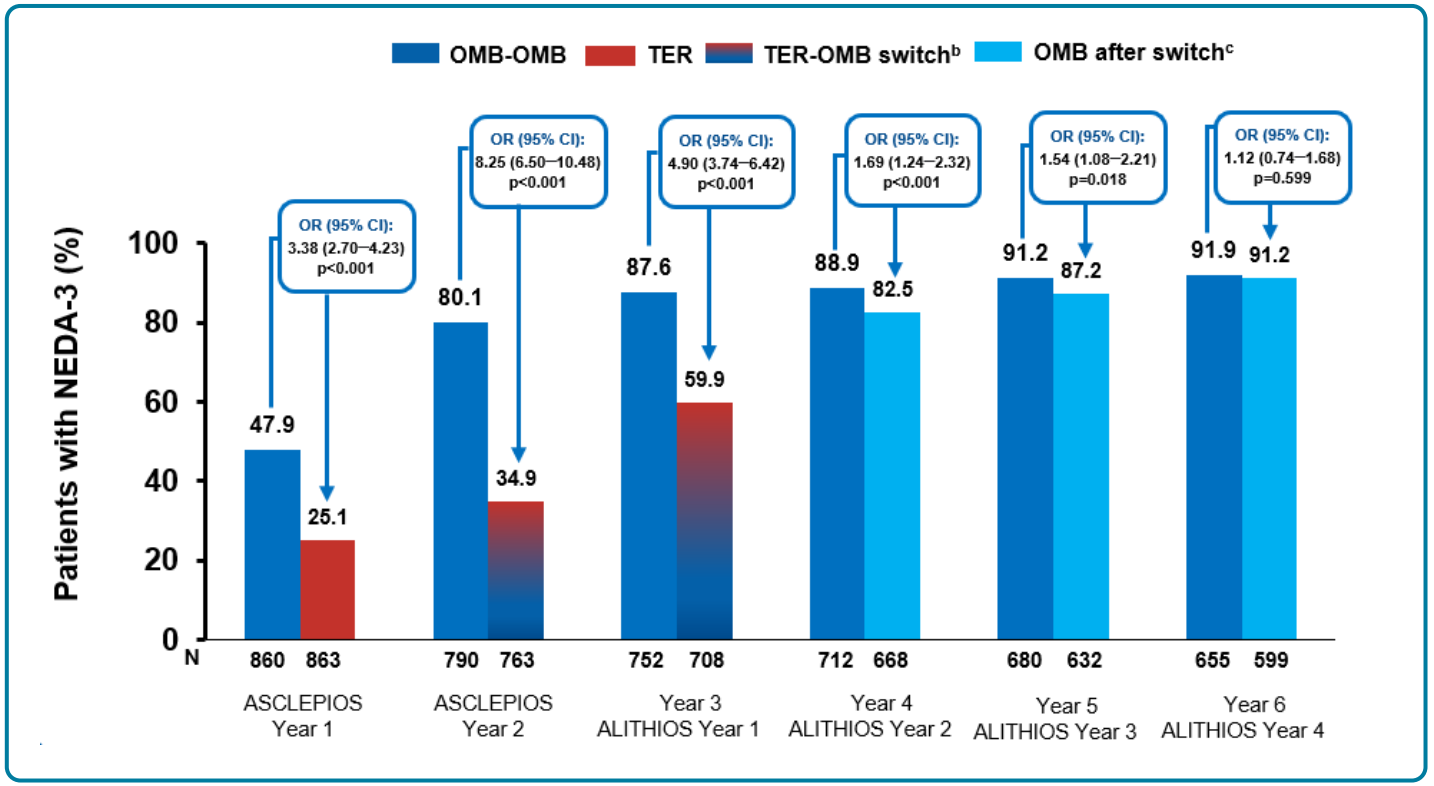
At Year 6, 9 of 10 participants were free of disease activity (NEDA-3) in the continuous and switch groups

NEDA-3[a] status up to 6 years of ofatumumab treatment



- There was a **rapid initial increase** in **NEDA-3** with **continuous ofatumumab**; **high rates of NEDA-3** was **maintained over 6 years**
- Participants who were initially on teriflunomide had significantly lower NEDA-3 rates, but a **rapid increase in NEDA-3** was observed **after switching to ofatumumab**

[a]NEDA-3 is defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions, and no Gd+ T1 lesions. [b]TER-OMB switch: Participants transitioning from teriflunomide to ofatumumab; due to event-driven core study design (flexible duration), participants transitioned at various exposure time points; i.e., the switch from teriflunomide to ofatumumab started from Year 2 and was completed by Year 3. [c]OMB after switch: Teriflunomide participants now on ofatumumab. OMB-OMB, continuous ofatumumab. N is the total number of participants in the treatment group excluding those who discontinued treatment early for reasons other than lack of efficacy or death and had NEDA before early discontinuation.
6mCDW, 6month confirmed disability worsening; **CI**, confidence interval; **Gd+**, gadolinium-enhancing; **NEDA**, no evidence of disease activity; **neT2**, new or enlarging T2 lesions; **OMB**, ofatumumab; **OR**, odds ratio; **TER**, teriflunomide.

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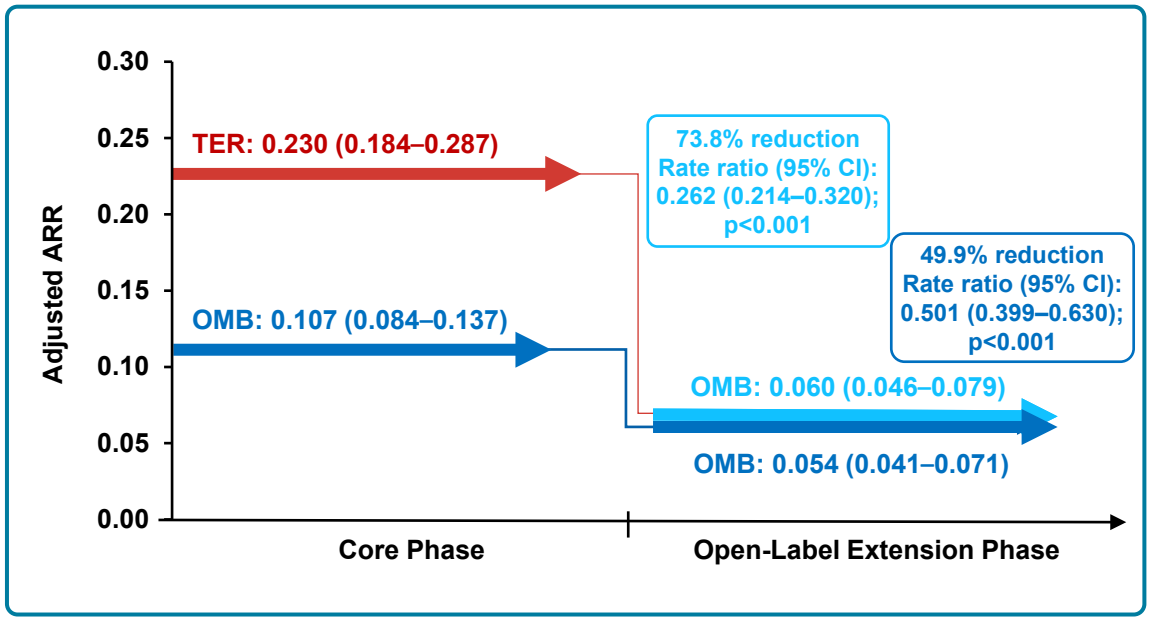
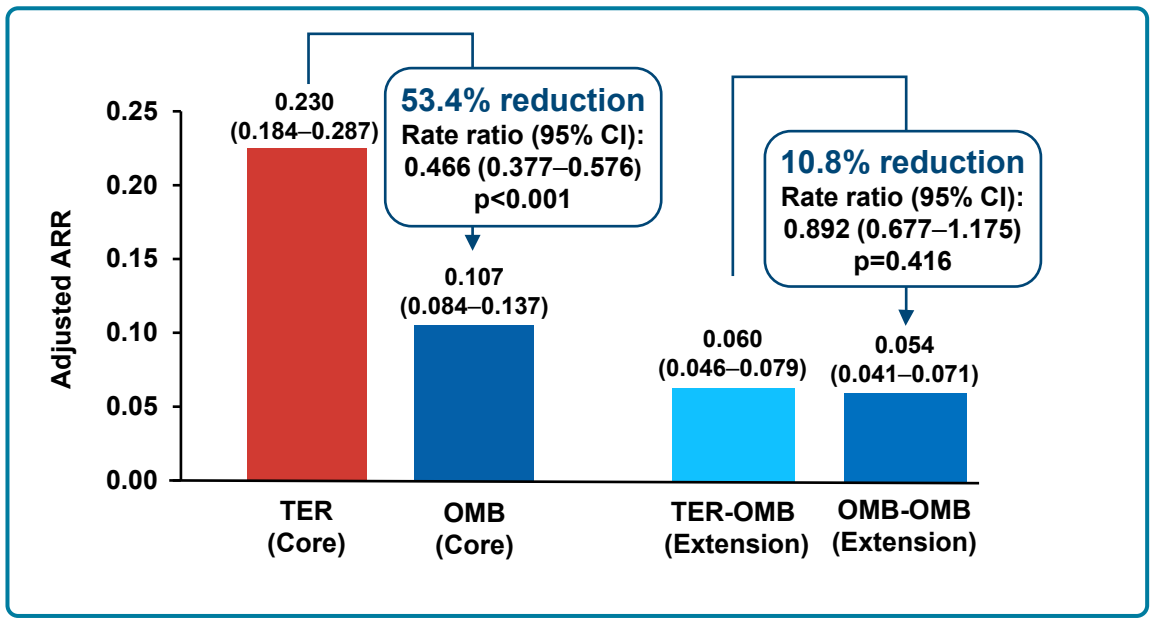
A sustained low ARR[a] was observed in participants receiving ofatumumab for up to 6 years

Within-group comparison[b] between the core and extension phase (continuous ofatumumab and switch groups)



Between-group comparison[b] between the core and extension phase (continuous ofatumumab and switch groups)



- Continuous treatment with ofatumumab up to 6 years was associated with a **significant reduction in ARR by 49.9%**
- Switch from teriflunomide to ofatumumab resulted in a **pronounced reduction in ARR (73.8%)**

- A significant reduction in the ARR was observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies, and both groups receiving ofatumumab in the extension study **maintained a low ARR**

[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS. [b]ARRs are obtained from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors and number of relapses in previous year, baseline EDSS, baseline number of Gd+ lesions, and the participant's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the relapse rate in each period. Baseline variables are from the core study baseline. All p values are nominal p values. **ARR**, annualized relapse rate, **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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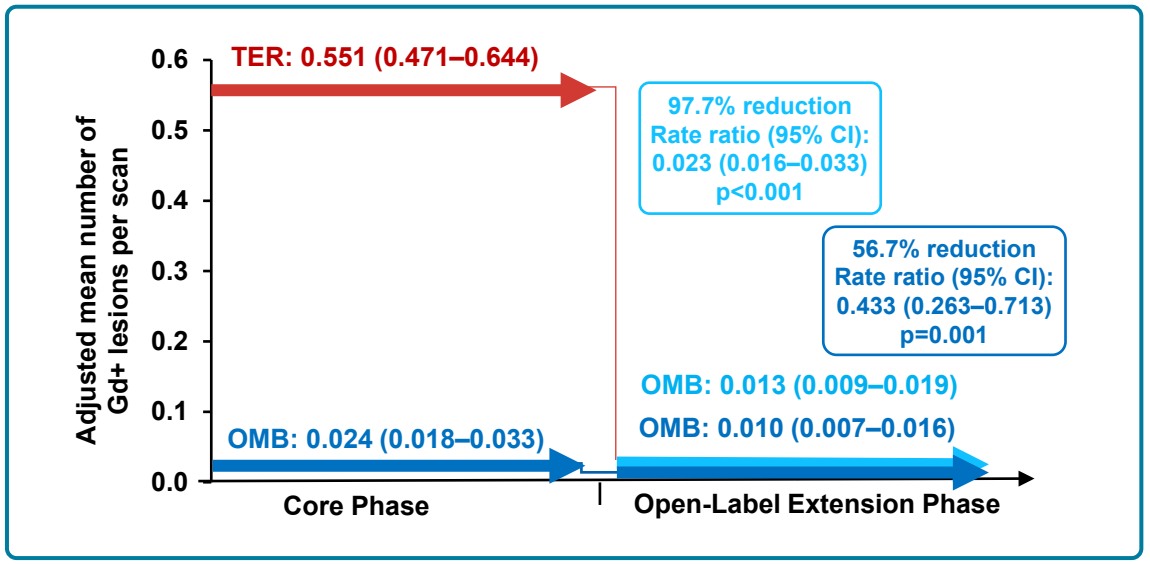
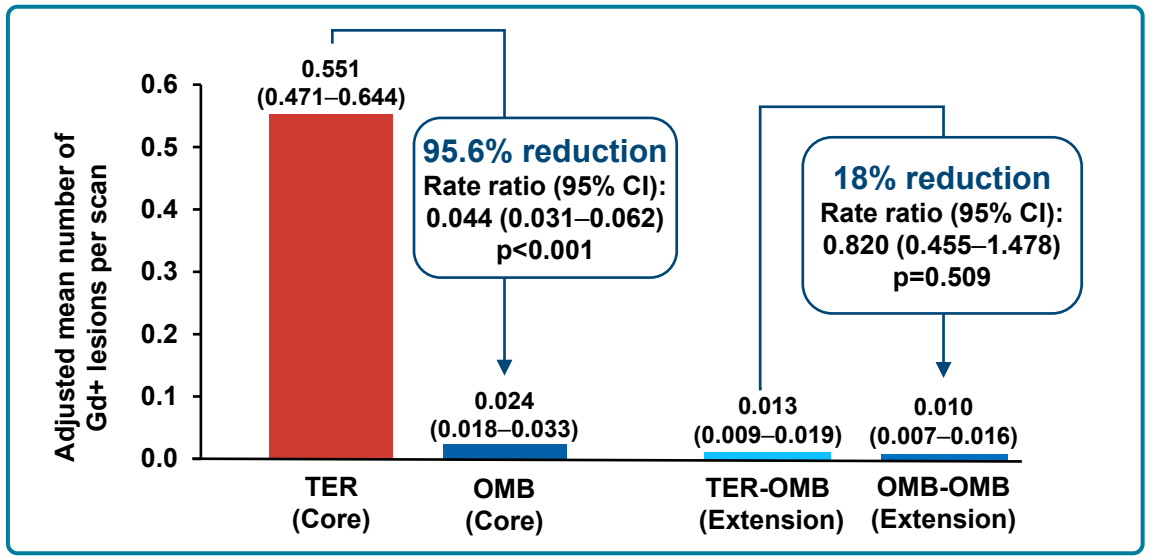
Gd+ T1 lesion activity remained almost completely suppressed in participants receiving ofatumumab for up to 6 years

Within-group comparison[a] between the core and extension phase for Gd+ T1 lesions (continuous ofatumumab and switch group)



- **Continuous ofatumumab treatment** was associated with a **significant reduction in the mean number of lesions per scan** by **56.7%** with longer-term treatment
- **Switch from teriflunomide to ofatumumab** resulted in an **almost complete suppression of Gd+ T1 lesion activity (97.7%)**

Between-group comparison[a] between the core and extension phase for Gd+ T1 lesions (continuous ofatumumab and switch group)



- A **significant reduction in the mean number of Gd+ T1 lesions** was observed for **ofatumumab versus teriflunomide** in the core ASCLEPIOS I/II studies
- Gd+T1 lesions were **almost completely suppressed during the extension phase in both the continuous ofatumumab group and the switch group**

[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment as factor and baseline number of T1 Gd+ lesions and participant's age at baseline as covariates. The natural log of the number of scans with evaluable Gd+ lesion counts by period is used as offset to obtain the lesion rate per scan in each period. Baseline variables are from the core study baseline. All p values are nominal p values.
CI, confidence interval; **Gd+**, gadolinium-enhancing; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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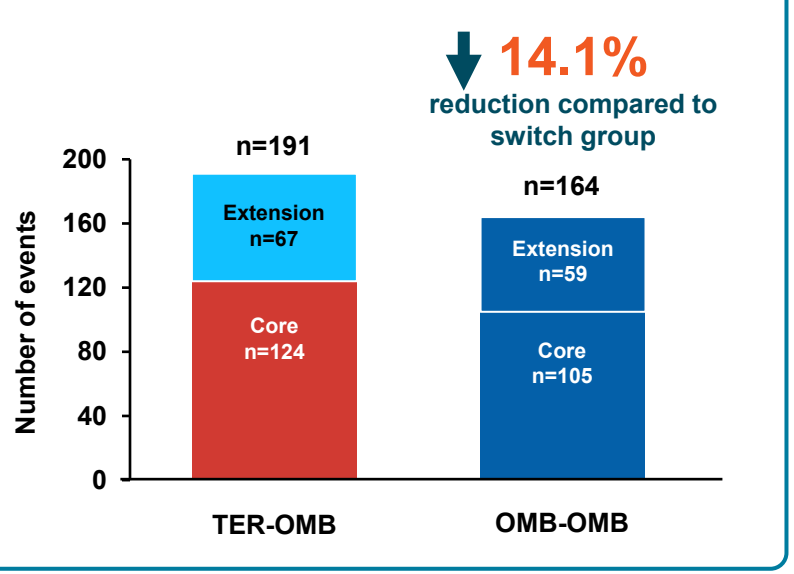
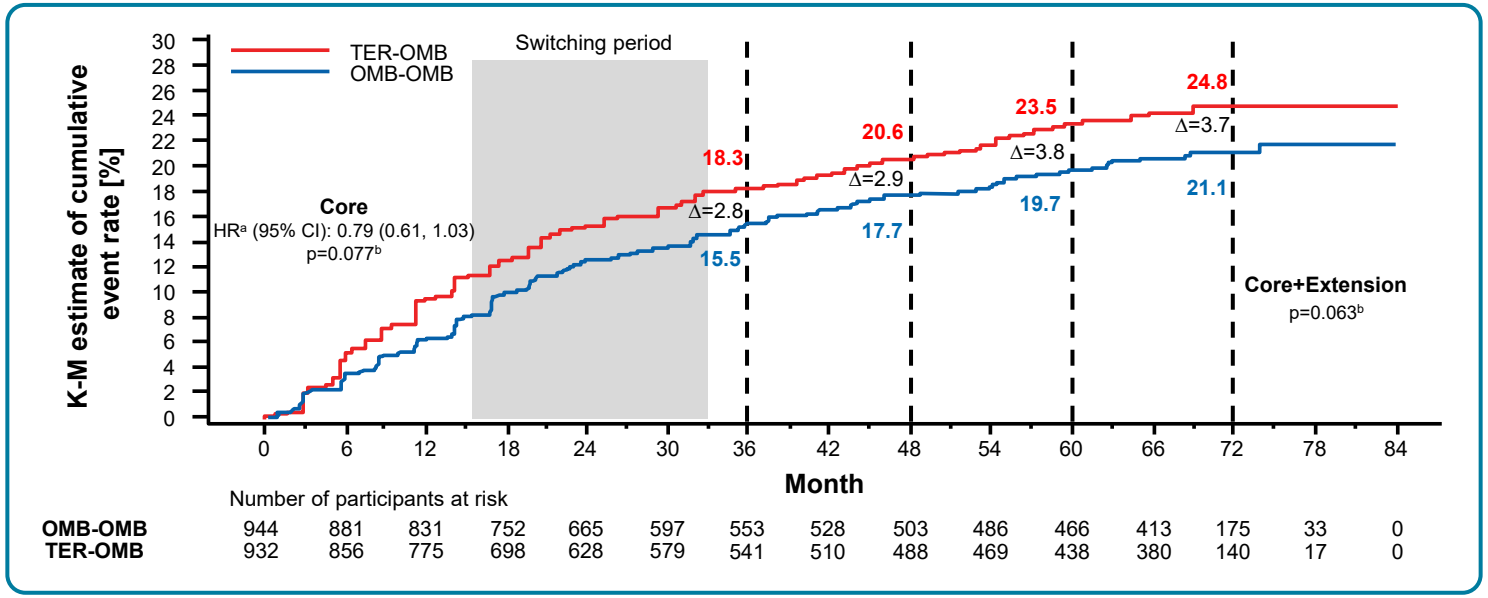
Earlier ofatumumab treatment was associated with a lower number of 6mCDW events up to 6 years

Cumulative number of first 6mCDW events



Time to first 6mCDW



- **Continuous use of ofatumumab** for up to 6 years resulted in a **sustained reduction of 6mCDW events** versus the switch group, highlighting the efficacy benefit that **cannot be recovered in those initially randomized to teriflunomide**
  - Rates of 6-month **progression independent of relapse activity (PIRA)** were **also lower at 6 years** with continuous ofatumumab versus switch from teriflunomide
- Continuous ofatumumab treatment was associated with a **significantly lower number of 3mCDW** events ($p<0.05$) up to 6 years

Cutoff for the core and extension phase refers to the first dose of ofatumumab in extension. Δ, Difference in K-M estimates (TER-OMB minus OMB-OMB). [a]HR was determined by Cox regression model. [b]p value represents log-rank test. **3mCDW**, 3-month confirmed disability worsening; **6mCDW**, 6-month confirmed disability worsening; **CI**, confidence interval; **HR**, hazard ratio; **K-M**, Kaplan-Meier; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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Safety profile of ofatumumab remained consistent with up to 6 years of treatment

Adverse event	Core, ASCLEPIOS[1]				Core + extension: Overall OMB, (N=1969)	
	OMB, n (%)	OMB, EAIR (95% CI)	TER, n (%)	TER, EAIR (95% CI)	n (%)	EAIR (95% CI)
Participants with at least one AE	791 (83.61)	188.55 (175.86–202.16)	788 (84.2)	188.92 (176.18–202.58)	1796 (91.2)	116.71 (111.44–122.24)
Participants with at least one SAE	83 (8.77)	5.56 (4.48–6.89)	73 (7.8)	4.94 (3.93–6.21)	323 (16.4)	4.40 (3.94–4.91)
AEs leading to ofatumumab discontinuation	54 (5.70)	–	49 (5.2)	--	148[a] (7.5)	–
Infections and infestations	488 (51.58)	51.14 (46.80–55.88)	493 (52.7)	52.59 (48.14–57.44)	1385 (70.3)	38.86 (36.87–40.97)
Serious infections	24 (2.54)	1.55 (1.04–2.31)	17 (1.8)	1.12 (0.69–1.80)	115 (5.8)	1.48 (1.23–1.77)
Serious infections (excluding COVID-19)	24 (2.54)	1.55 (1.04–2.31)	17 (1.8)	1.12 (0.69–1.80)	71 (3.6)	0.90 (0.72–1.14)
Serious COVID-19 infections	0	0	0	0	49 (2.5)	0.62 (0.47–0.81)
Injection-related systemic reactions	195 (20.61)	15.49 (13.46–17.83)	143 (15.3)	10.90 (9.25–12.84)	514 (26.1)	8.50 (7.79–9.26)
Injection-site reactions	103 (10.88)	7.21 (5.94–8.74)	52 (5.55)	3.54 (2.70–4.65)	256 (13.0)	3.58 (3.17–4.05)
Malignancies	5 (0.53)	0.32 (0.13–0.77)	4 (0.4)[b]	0.26 (0.10–0.69)	27 (1.4)	0.34 (0.23–0.49)
Deaths	0	--	1[c]	--	10[d] (0.5)	–

- Exposure-adjusted incidence rate (EAIR) per 100 patient-years (PYs) of adverse events (AEs) and serious adverse events (SAEs) with up to 6 years of ofatumumab treatment **remained consistent** with that in the ASCLEPIOS I/II trials, with **no unexpected safety signals** identified
- The **most common AEs** were infections (COVID-19 [34.3%], nasopharyngitis [20.6%], upper respiratory tract infection [14.9%], and urinary tract infection [14.4%])
- EAIRs for malignancies **did not increase** over time in the overall safety population

EAIR per 100 PYs is defined as the expected number of patients with the given event over 100 years of exposure to a treatment, assuming the event rate is constant over time. This is estimated by Poisson regression where participants' time is taken until first event occurrence or the last day the patient was at risk for those who did not have the event. [a]AEs related to decreased IgM levels are the most common reason for treatment discontinuation (n=64 [3.3%]). [b]One case of basal cell carcinoma was not listed as an SAE. [c]Death was due to aortic dissection. [d]PTs for these 10 cases include: sudden death (n=1), completed suicide (n=1), COVID-19 and COVID-19 pneumonia (n=1), COVID-19 (n=2), intestinal metastasis (n=1), gastric ulcer perforation (n=1), pneumonia and septic shock (n=1), and pneumothorax and COVID-19 pneumonia (n=1). **AE**, adverse event; **CI**, confidence interval; **EAIR per 100 PYs**, exposure-adjusted incidence rate per 100 patient-years; **Ig**, immunoglobulin; **OMB**, ofatumumab; **PT**, preferred term; **PY**, patient-years; **SAE**, serious adverse event; **TER**, teriflunomide. **1.** Hauser SL, et al. *N Engl J Med* 2020;383:546−557.

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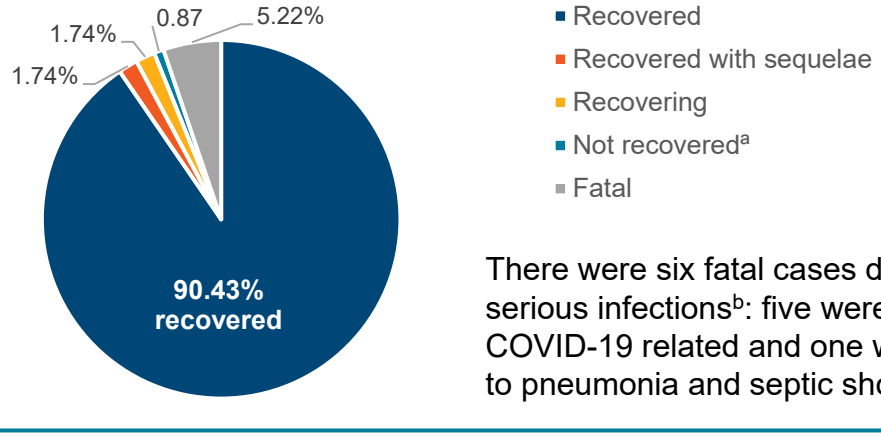
Incidence of serious infections remained stable over time and did not increase with ofatumumab treatment up to 6 years

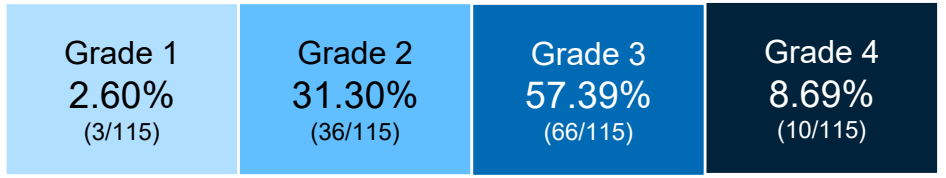
Total infections	n=1385; EAIR: 38.86 (95% CI: 36.87–40.97)
Serious infections	n=115; EAIR: 1.48 (95% CI: 1.23–1.77)

Outcomes of serious infections



There were six fatal cases due to serious infections[b]: five were COVID-19 related and one was due to pneumonia and septic shock

Severity of serious infections[c]



Discontinuation of OMB: 8 (6.95%)

- The overall **EAIR per 100 PYs of serious infections** was **consistent** with that in the phase 3 ASCLEPIOS I/II trials (EAIR: 1.55) and **did not increase** with treatment up to 6 years despite the COVID-19 pandemic; the most common serious infections were COVID-19 (1.4%)/COVID-19 pneumonia (1.3%)[d] and appendicitis (0.8%)[e]
- One case of **serious opportunistic infection** of *Pneumocystis jirovecii*[f] was reported; the final diagnosis was not confirmed by an external adjudication panel, and the clinical course was not suggestive of *P. jirovecii* pneumonia; the participant had no change in dosage or interruption of ofatumumab therapy, and fully recovered

[a]At the cutoff: 25-Sep-2023. [b]Five fatal cases were related to COVID-19 and the remaining case involved pneumonia and septic shock [n=1, unrelated to study drug; had medical history of kyphosis; treatment was discontinued due to pneumonia and septic shock]. [c]Severity grading is done by the investigator based on CTCAE version 5.0. [d]There were 49 COVID-19–related SAEs in total; one of them has PT of "suspected COVID-19," and a majority (85.71%) of the cases recovered. [e]All cases of appendicitis recovered, and a majority of them were not related to ofatumumab treatment. [f]Participant was suspected to have serious Grade 2 *P. jirovecii* pneumonia and was assessed by an independent external expert. **CI**, confidence interval; **EAIR per 100 PYs**, exposure-adjusted incidence rate per 100 patient-years; **n**, number of patients with at least one event; **OMB**, ofatumumab; **PT**, preferred term

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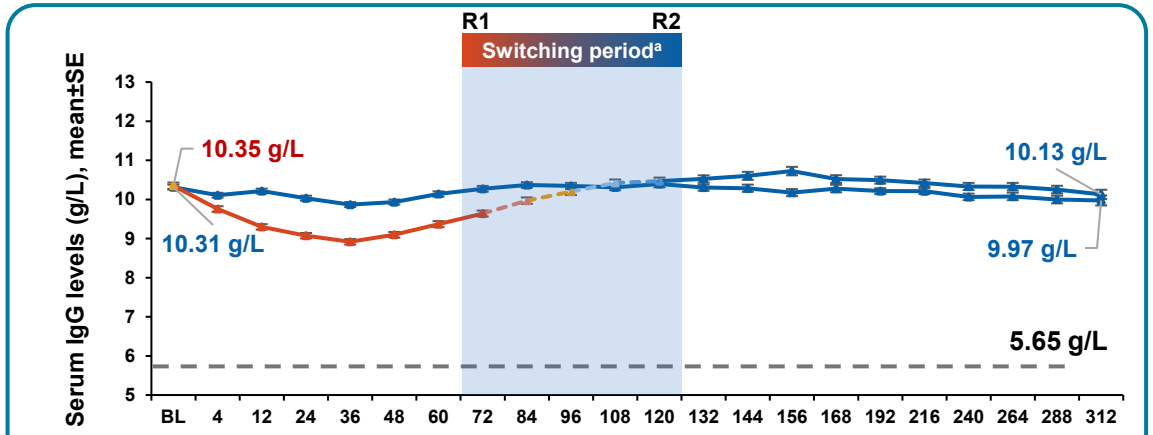
Mean IgG levels remained stable up to 6 years of treatment; mean IgM levels decreased but remained above the LLN

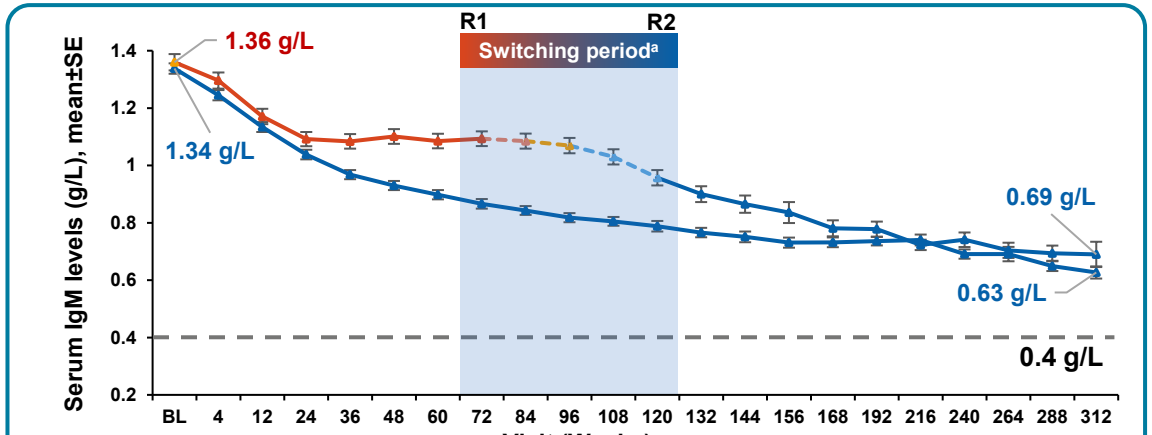
Mean IgG levels



Number of patients at visit (n)

	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168	192	216	240	264	288	312
Continuous OMB	1269	1233	1248	1219	1179	1129	1080	903	982	783	908	662	715	525	534	524	817	794	688	548	539	304
TER/OMB Before/	675	672	673	666	672	669	666	670	635	633	631	564	495	442	350	454	562	541	539	518	507	290
After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 320	167/ 464	72/ 492	495	442	350	454	562	541	539	518	507	290

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	240	264	288	312
Continuous OMB	1271	1235	1250	1221	1181	1131	1085	906	986	790	911	669	719	534	542	535	819	798	687	548	539	305
TER/OMB Before/	675	672	673	666	672	669	666	670	635	633	632	564	502	445	359	456	563	540	539	519	507	290
After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 320	167/ 465	72/ 492	502	445	359	456	563	540	539	519	507	290

- The **majority of the participants** had Ig levels **above the lower limit of normal** (LLN): **97.2%** for IgG and **65.9%** for IgM
- **Treatment interruption/discontinuation** was reported in **3 (0.2%)/4 (0.2%)** participants due to **low IgG**, and **203 (10.3%)/71 (3.6%)** participants due to **low IgM**
  - In ASCLEPIOS I/II, the investigators were required to interrupt study treatment if IgM levels fell 10% <LLN or IgG levels fell 20% <LLN; due to a protocol amendment at the beginning of ALITHIOS (June 3, 2021), the requirement to interrupt treatment based on a specific threshold due to low IgG/IgM was removed, and the decision was left to the discretion of the investigator
- **No clinically meaningful association** was observed between IgG/IgM levels <LLN and risk of serious infections

[a]Switching period refers to the participants started on teriflunomide and not applicable to the participants on ofatumumab in the core period. For the teriflunomide/ofatumumab group, data from the first dose of teriflunomide until the last dose of ofatumumab plus 100 days or analysis cutoff date has been used. R1: The first participant with first treatment-emergent assessment in ofatumumab period after switching to ofatumumab (72 weeks); R2: The last participant with last treatment-emergent assessment in teriflunomide period before switching to ofatumumab (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; **PT,** preferred term; **SE**, standard error of the mean; **TER**, teriflunomide.

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Conclusions

- At Year 6, **9 of 10 participants** were **free of disease activity (NEDA-3)** in both the continuous and switch groups
  - Participants who were initially treated with teriflunomide had initially significantly lower rates of **NEDA-3,** but these rates **rapidly increased after switching to ofatumumab**
- **Continuous ofatumumab treatment** was associated with **fewer confirmed disability worsening events up to 6 years** versus switching from teriflunomide, supporting the long-term benefit of **earlier initiation of ofatumumab,** which cannot be recovered in those initially randomized to teriflunomide
- The sustained efficacy of ofatumumab for up to 6 years was accompanied by a **consistent safety profile**, with no unexpected safety signals
  - The rate of AEs, SAEs, serious infections, and malignancies **remained stable** with no increased risks over 6 years
- Mean IgG levels **remained stable**, whereas mean IgM levels decreased but **remained above the LLN; no clinically meaningful association** between reductions in Ig levels and risk of serious infections was observed

These results support the long-term, favorable benefit–risk profile of ofatumumab treatment (up to 6 years) and reinforce the benefit of early ofatumumab initiation in pwRMS

AE, adverse event; **Ig**, immunoglobulin; **LLN**, lower limit of normal; **NEDA**, no evidence of disease activity; **pwRMS**, people with relapsing multiple sclerosis; **SAE**, serious adverse event.

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Backup slides

Baseline demographics and disease characteristics of the safety population[a]

	Continuous OMB (N=1292)	Newly switched OMB (N=677)		Overall OMB (N=1969)
		Baseline from core study	Baseline from extension study	
Age, years	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	8.48±7.33	8.06±7.21	9.94±7.23	8.98±7.33
Time since diagnosis, years	5.87±6.31	5.45±6.00	7.33±6.01	6.37±6.25
EDSS score at baseline	2.90±1.33	2.77±1.32	2.82±1.46	2.88±1.38
IgG levels at baseline, g/L	10.31± 2.24[b]	10.35±2.09[c]	10.23±2.14[c]	10.28±2.21
IgM levels at baseline, g/L	1.34± 0.65[d]	1.36±0.74[e]	1.14±0.67[e]	1.27±0.66
Median duration of time at risk, years	4.7	4.1	4.1	4.3
Total time at risk, PYs	5535.5	2507.2	2507.2	8042.7

Data presented as mean±SD, unless otherwise mentioned.
[a]Participants who received ≥1 dose of ofatumumab in ASCLEPIOS I/II, APLIOS, APOLITOS, or ALITHIOS from the first dose of ofatumumab in either the core or extension period. [b]Number of participants at baseline, n=1269.
[c]Number of participants at baseline, n=675. [d]Number of participants at baseline, n=1271. [e]Number of participants at baseline, n=675.
For newly switched OMB participants, their baseline values from extension study contribute to the overall ofatumumab baseline values.
BMI, body mass index; **EDSS**, Expanded Disability Status Scale; **Ig**, immunoglobulin; **MS**, multiple sclerosis; **OMB**, ofatumumab; **PY**, patient-year; **SD**, standard deviation.

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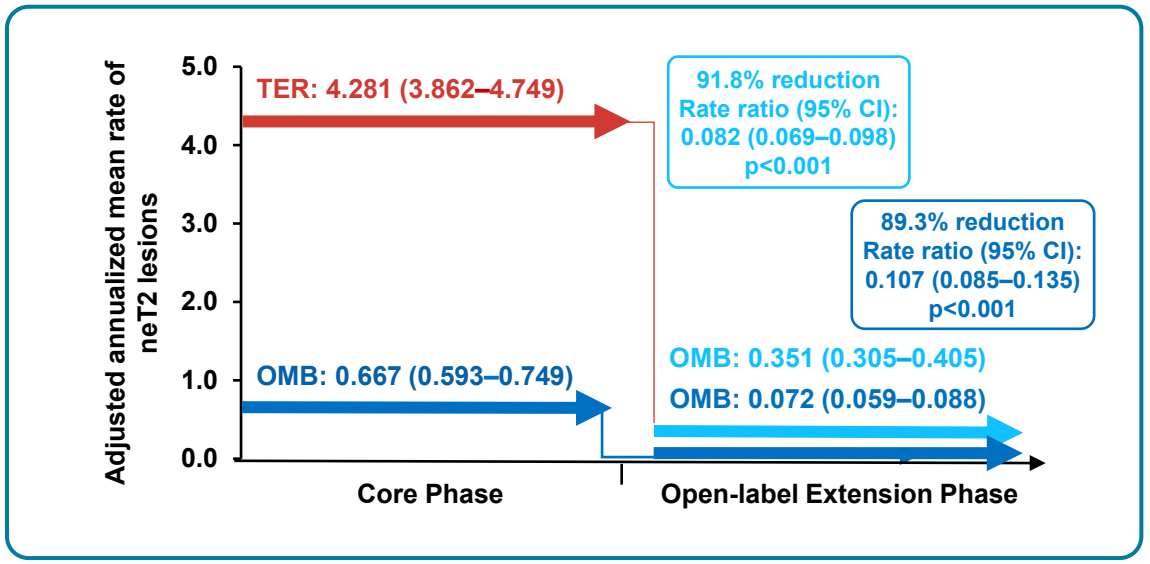
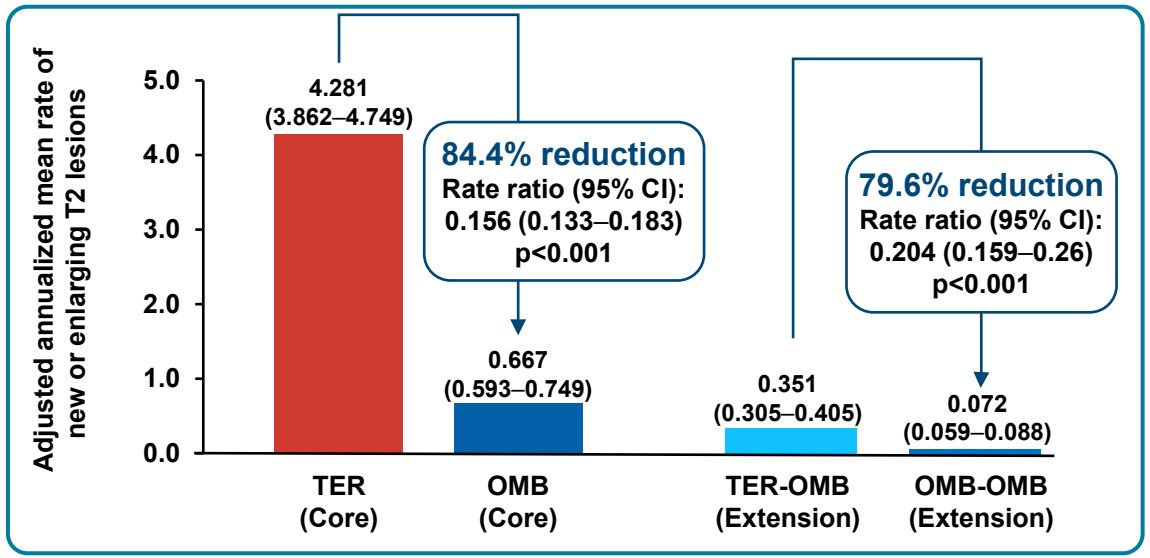
A profound and sustained reduction in neT2 lesions was observed in participants receiving ofatumumab for up to 6 years

Within-group comparison[a] between the core and extension phase for neT2 lesions (continuous ofatumumab and switch group)



Between-group comparison[a] between the core and extension phase for neT2 lesions (continuous ofatumumab and switch group)



- The within-group analysis showed that **continuous use of ofatumumab** was associated with a reduction in the neT2 lesions by **89.3%** with longer-term treatment
- **Switch from teriflunomide to ofatumumab** resulted in a **pronounced reduction** in the number of neT2 lesions **(91.8%)**

- The significant relative reduction in the mean rate of neT2 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was also seen in the extension phase, despite the overall reduced number of lesions, reflecting the known “carry over” effect on this outcome

[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment as factor, baseline volume of T2 lesions and participant’s age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the lesion rate in each period. Baseline variables are from the core study baseline. All p values are nominal p values.
CI, confidence interval; **neT2**, new or enlarging T2; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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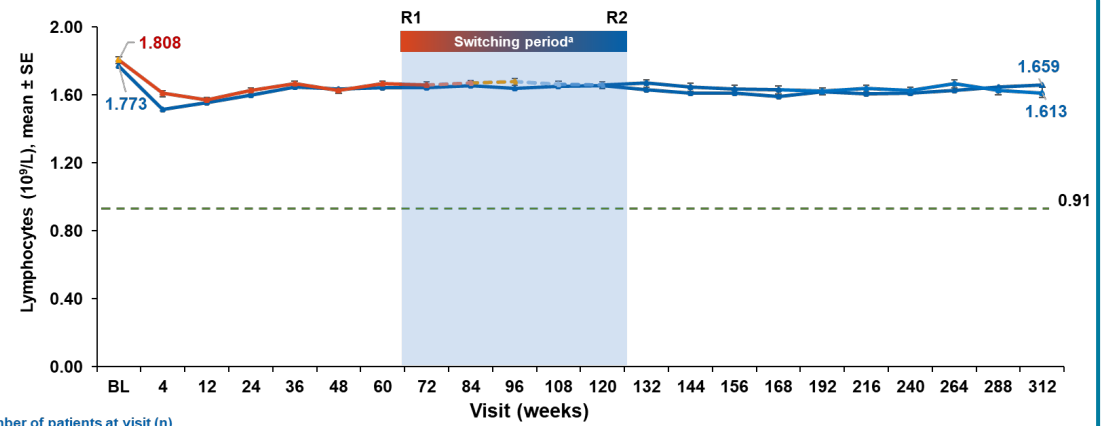
Lymphocyte and neutrophils level remained stable throughout 6 years of treatment

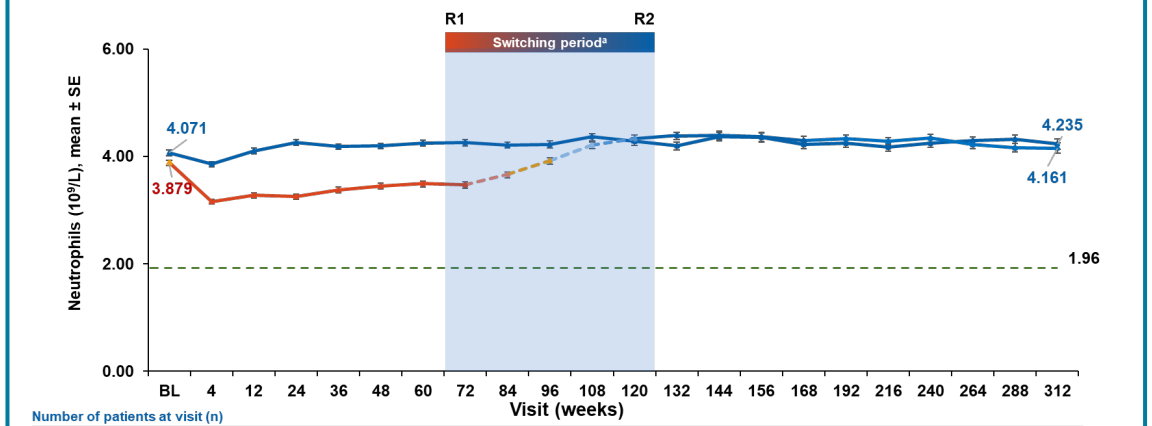
Lymphocyte levels



Number of patients at visit (n)

Continuous OMB	1292	1266	1264	1238	1194	1141	1086	901	983	777	918	639	711	492	524	494	802	782	654	518	499	287
TER/OMB	677	670	674	668	670	665	670	671	631	631	634	554	475	424	329	437	547	527	508	482	482	275
Before/ After switch	677	670	674	668	670	665	670	665/ 06	480/ 151	313/ 318	170/ 464	72/ 482	475	424	329	437	547	527	508	482	482	275

Neutrophil levels



Number of patients at visit (n)

Continuous OMB	1292	1266	1264	1238	1195	1142	1087	901	983	777	918	639	711	492	524	494	802	782	654	518	499	287
TER/OMB	677	670	674	668	670	667	670	671	631	631	634	554	475	424	329	437	547	527	508	482	482	275
Before/ After switch	677	670	674	668	670	667	670	665/ 06	480/ 151	313/ 318	170/ 464	72/ 482	475	424	329	437	547	527	508	482	482	275

- A **transient decline** in the mean **lymphocyte levels** was observed up to Week 4 (% change: continuous, −11.9%; switch, −8.2%), followed by **an increase back** to **close to baseline levels** in continuous and newly switched groups through Week 312
- The mean **neutrophil levels** remained **stable and above baseline** for all visits up to Week 312 (% change: continuous, 17.3%; switch, 15.7%), with **rapid increase** in levels **after switching** from teriflunomide to ofatumumab

[a]Switching period refers to the participants started on teriflunomide and not applicable to the participants on ofatumumab in the core phase. For the teriflunomide/ofatumumab group, data from the first dose of teriflunomide until the last dose of ofatumumab plus 100 days or analysis cutoff date has been used. R1: The first participant with first treatment-emergent assessment in ofatumumab period after switching to ofatumumab (72 weeks); R2: The last participant with last treatment-emergent assessment in teriflunomide period before switching to ofatumumab (120 weeks). For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used: lymphocytes: 0.91 10^9/L and neutrophils: 1.96 10^9/L.
BL, baseline; **LLN**, lower limit of normal; **OMB**, ofatumumab; **SE**, standard error of the mean; **TER**, teriflunomide.

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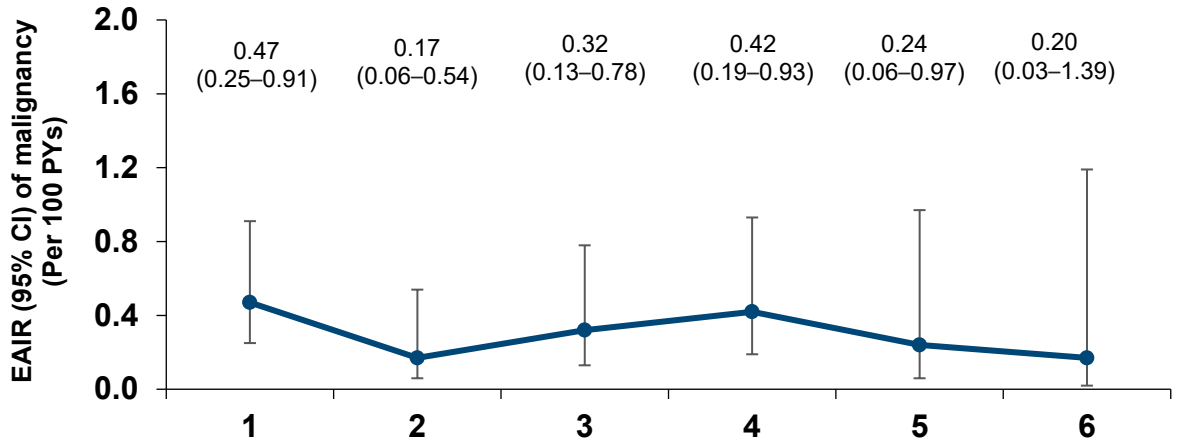
Incidence of malignancies did not increase over time

EAIR of malignancy by year in overall safety population



Participants (N)	**1969**	**1812**	**1619**	**1500**	**1291**	**589**
PYs	**1900.9**	**1719.4**	**1546.6**	**1435.0**	**821.7**	**511.5**
No. of events	**9**	**3**	**5**	**6**	**2**	**1**

- EAIRs for **malignancies did not increase over time**
- Cumulatively (core+extension), malignancies were reported in 26 participants[a] (1.32%; EAIR [95% CI]: 0.32 [0.22–0.48])
- Median (range) onset time since the first dose of ofatumumab was 843.5 days (31[b]–1931 days)

[a]Another case of non-serious malignancy (squamous cell carcinoma) was reported. [b]One event with time-to-onset of 31 days was Non-Hodgkin's lymphoma recurrent.
The 27 malignancies cases include breast and nipple neoplasms malignant (n=11), cervix neoplasm malignant (n=1), colorectal neoplasms malignant (n=1), metastases to specified sites (n=2), esophageal neoplasms malignant (n=2), neoplasms malignant site unspecified NEC (n=2), non-Hodgkin's lymphomas NEC (n=1), ovarian neoplasms malignant (excluding germ cell) (n=1), renal neoplasms malignant (n=2), skin melanomas (excluding ocular) (n=1), skin neoplasms malignant and unspecified (excluding melanoma) (n=5); n is the number of participants, and a participant can have >1 malignancy at a time.
CI, confidence interval; **EAIR per 100 PYs**, exposure-adjusted incidence rate per 100 patient-years; **OMB**, ofatumumab.

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