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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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KEY FINDINGS & CONCLUSIONS

- During 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 significantly lower rates of NEDA-3, but these rates **rapidly increased after switching to ofatumumab**
- **Continuous ofatumumab treatment** was associated with **numerically fewer CDW events** up to 6 years versus switching from teriflunomide, supporting the long-term benefit of **earlier initiation of ofatumumab on disability progression**, which cannot be recovered in those initially randomised to teriflunomide
- The sustained efficacy of ofatumumab was accompanied by a **consistent safety profile**, with no new safety signals
  - The rate of AEs, SAEs, serious infections, and malignancies **remained consistent** with no increased risks over 6 years
- Mean IgG levels **remained stable**, whereas mean IgM levels decreased but **remained above the LLN**
- These results in participants treated up to 6 years support the **long-term, favourable benefit-risk profile of ofatumumab** treatment and reinforce the **benefit of early ofatumumab initiation** in pwRMS

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INTRODUCTION

- 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[1,2]
- The phase 3 ASCLEPIOS I/II trials demonstrated the superiority of ofatumumab (up to 30 months) compared with teriflunomide in reducing clinical and magnetic resonance imaging (MRI) disease activity while maintaining a favourable safety profile in people with RMS (pwRMS)[3]
- Treatment with ofatumumab for up to 5 years showed sustained efficacy and a favourable safety profile during the ALITHIOS open-label extension study[4,5]
- 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 September 2023) in pwRMS

METHODS

Key assessments

Efficacy

- Annualised 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)[a]

Safety

- Overall safety profile
- Serious infections[b]
- Laboratory parameters:
  - Immunoglobulin (Ig) G and IgM levels
  - Lymphocyte and neutrophil levels
- Malignancies

[a]NEDA-3 is defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions, and no Gd+ T1 lesions.
[b]Serious infections that occurred within 1 month prior and until 1 month after single or consecutive values of IgG (or IgM) <LLN were analysed.

Participant population and disposition (Figure 1)

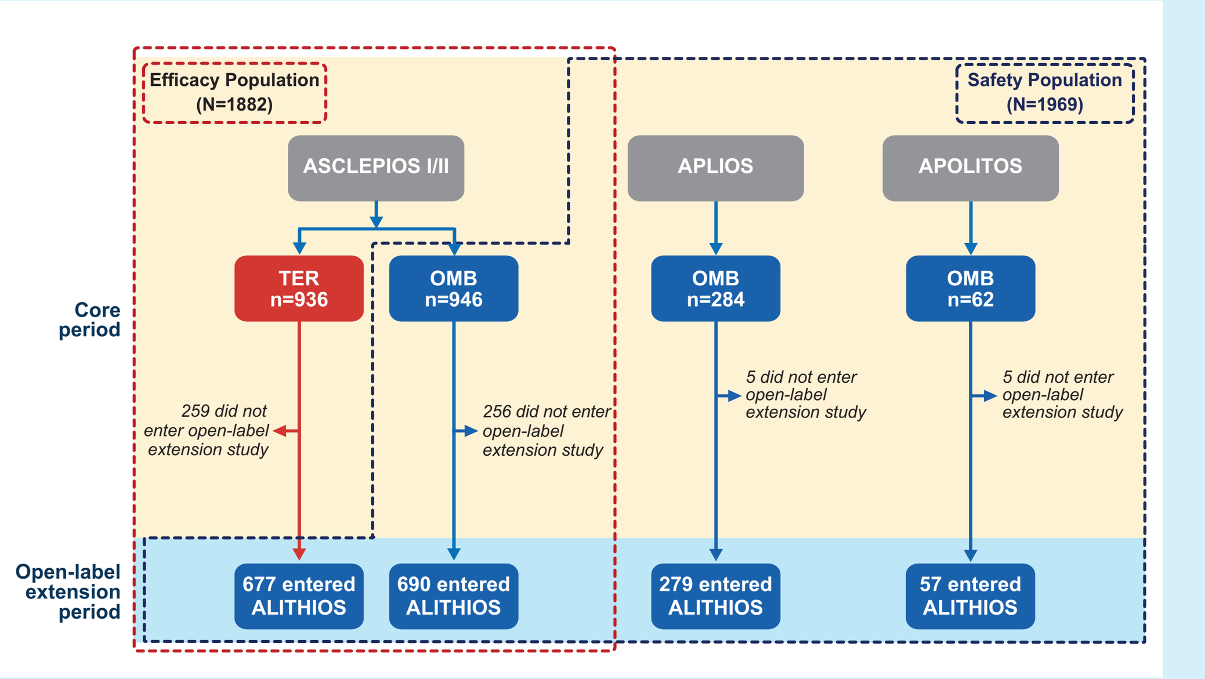
Efficacy population (N=1882)

- Continuous ofatumumab group (OMB-OMB; n=946): Participants randomised to ofatumumab in ASCLEPIOS I/II and continuing ofatumumab in ALITHIOS
- Switch group (TER-OMB; n=936): Participants who were randomised to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab during ALITHIOS

Safety population (N=1969)

- Participants who received ≥1 dose of ofatumumab in ASCLEPIOS I/II, APLIOS, APOLITOS or ALITHIOS
  - Continuous ofatumumab group (n=1292): Includes participants who received the first dose of ofatumumab in ASCLEPIOS I/II, APLIOS or APOLITOS
  - Newly switched ofatumumab group (n=677): Includes participants who were randomised to teriflunomide in ASCLEPIOS I/II and were switched to ofatumumab in ALITHIOS

Figure 1. Participant disposition



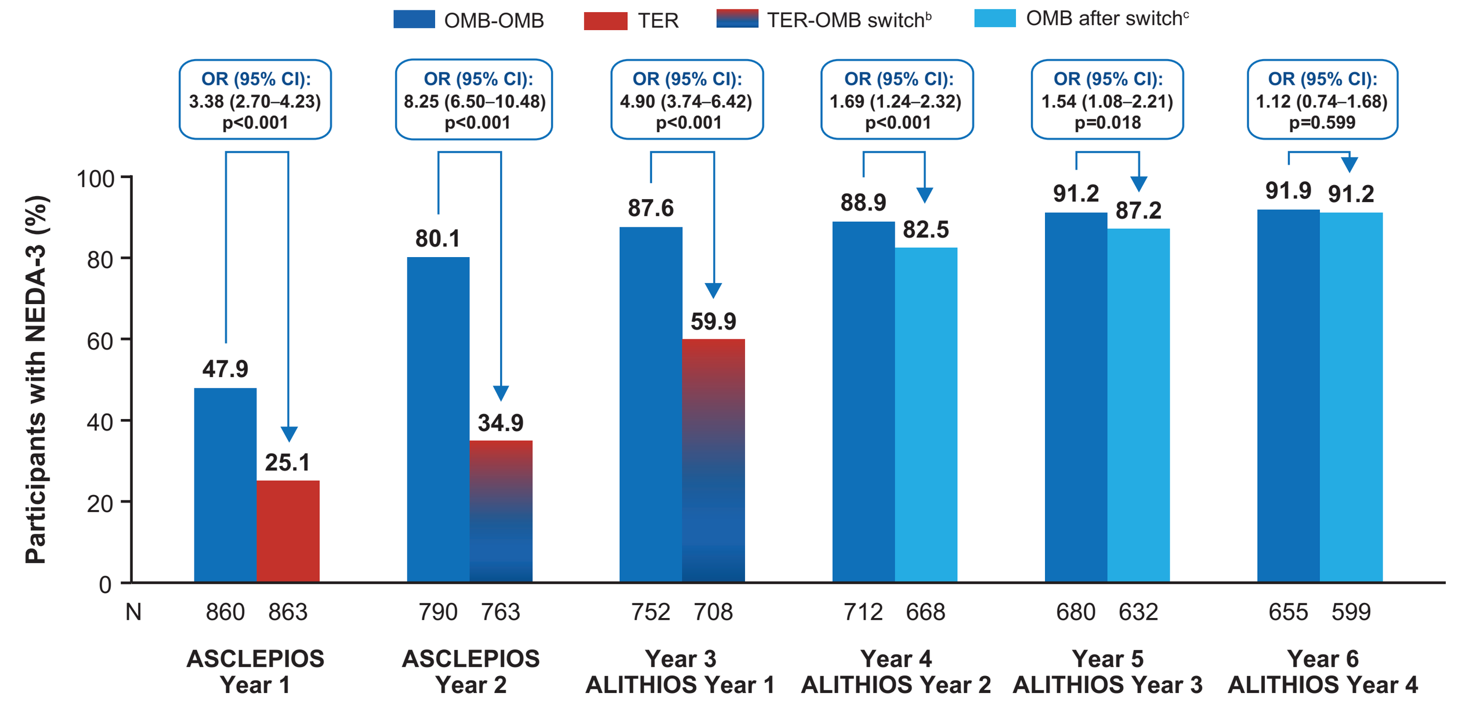
RESULTS

- Baseline demographics and participant characteristics were consistent with a typical phase 3 RMS population

No evidence of disease activity

- During Year 6, **9 of 10 participants were free of disease activity** in the continuous and switch groups
- A **rapid initial increase** in **NEDA-3** was observed with **continuous ofatumumab; high rates of NEDA-3** were **maintained over 6 years** (**Figure 2**)
  - **~90%** of participants on **continuous ofatumumab achieved NEDA-3 within 3 years** of starting treatment
- 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** with >80% of participants achieving NEDA-3 within 1 year of the switching period being completed

Figure 2. NEDA-3[a] status up to 6 years of ofatumumab treatment



[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.

Annualised relapse rate

- A **sustained low ARR** was observed in participants receiving ofatumumab for up to 6 years
- Continuous treatment with ofatumumab up to 6 years was associated with a **significant reduction in ARR by 49.9%** (0.107 to 0.054; p<0.001) compared to the core phase
- Switch from teriflunomide to ofatumumab resulted in a **significant reduction in ARR (73.8%**; 0.230 to 0.060; p<0.001)

MRI lesion activity

- In participants receiving ofatumumab for up to 6 years, **Gd+ T1 lesion activity** remained **almost completely suppressed** and a **profound and sustained reduction** in **neT2 lesions** was observed
- **Continuous ofatumumab treatment** was associated with a **significant reduction in the mean number of Gd+ T1 lesions** and **neT2 lesions** by **56.7%** (0.024 to 0.010) and **89.3%** (0.667 to 0.072), respectively, compared to the core phase
- Switch from teriflunomide to ofatumumab resulted in **almost complete suppression of Gd+ T1 lesion activity (97.7%** reduction; 0.551 to 0.013) and **pronounced reduction** in the number of **neT2 lesions (91.8%**; 4.281 to 0.351)

6-month confirmed disability worsening

- **Continuous use of ofatumumab** for up to 6 years resulted in a **sustained reduction of 6mCDW events** versus the switch group, highlighting an efficacy **benefit that cannot be recovered in those initially randomised to teriflunomide** (**Figures 3A** and **3B**)

Figure 3A. Cumulative number of first 6mCDW events

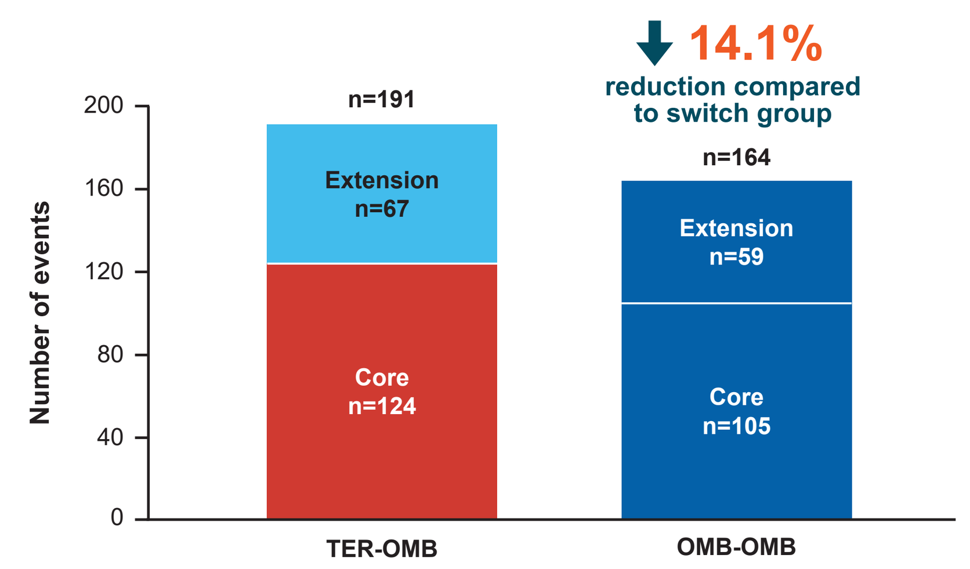
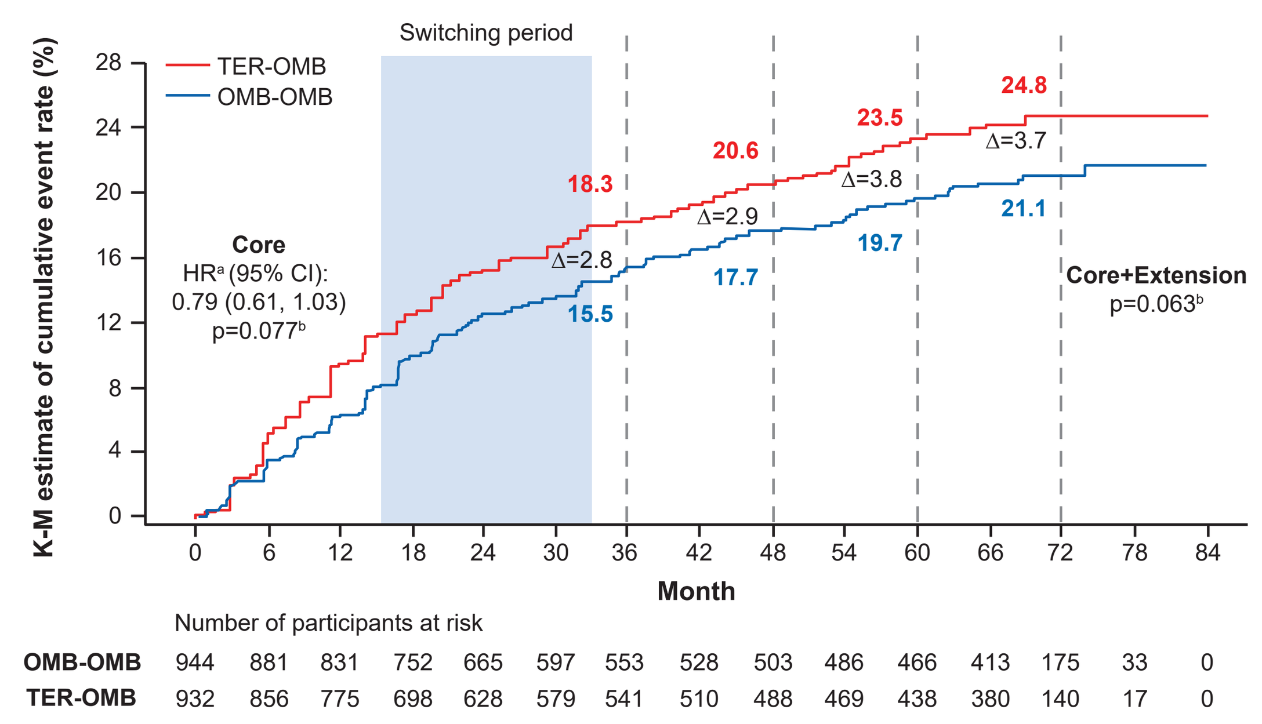


Figure 3B. Time to first 6mCDW



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.

Overall safety profile

- 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 those in the ASCLEPIOS I/II trials, with **no new safety signals** identified (**Table 1**)
- 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 infections and malignancies **did not increase** over time in the overall safety population

Serious infections

- The overall **EAIR per 100 PYs of serious infections** (EAIR: 1.48) 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/COVID-19 pneumonia (1.4%/1.3%; 85.7% cases recovered) and appendicitis (0.8%, all cases recovered)

Table 1. Overall safety profile over 6 years of treatment

Adverse event	Core, ASCLEPIOS[3]				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 treatment 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[e]	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[e]	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)	–

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=2), 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). [e]During the core phase, teriflunomide patients received placebo injections.

- **90.4% of patients** treated with ofatumumab who had serious infections **recovered**; most serious infections were **Grade 3 or below** in severity
- One case of **serious opportunistic infection** of *Pneumocystis jirovecii* was reported; the final diagnosis was not confirmed by an external adjudication panel, and the clinical course was not suggestive of *P. jirovecii* pneumonia

Mean IgG/IgM levels

- Mean IgG levels **remained stable** up to 6 years of treatment; mean IgM levels decreased but **remained above the lower limit of normal** (LLN)
- **97.2%** and **65.9%** of participants had IgG and IgM levels **above LLN**, respectively (**Figures 4A** and **4B**)
- Serious infections were reported in **3/55 (5.5%)** participants with **IgG levels <LLN** and **11/671 (1.6%)** participants with **IgM levels <LLN**, all resolved
- **Treatment interruption/discontinuation** was reported in **3 (0.2%)/4 (0.2%)** participants due to **low IgG**, and in **203 (10.3%)/71 (3.6%)** participants due to **low IgM**

Figure 4A. Mean IgG levels over 6 years

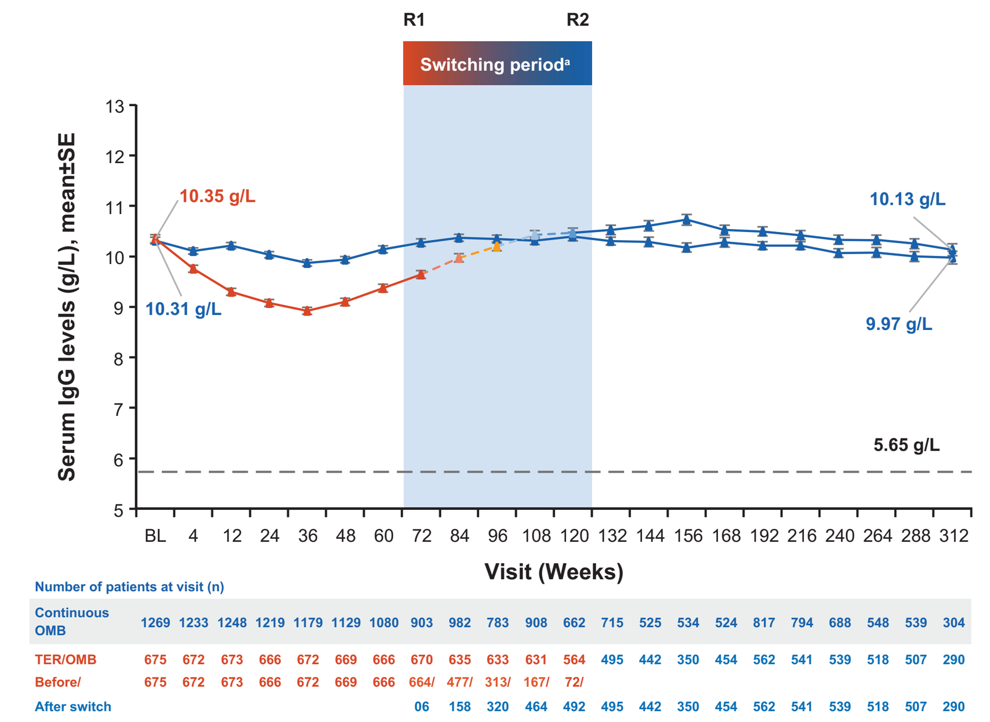
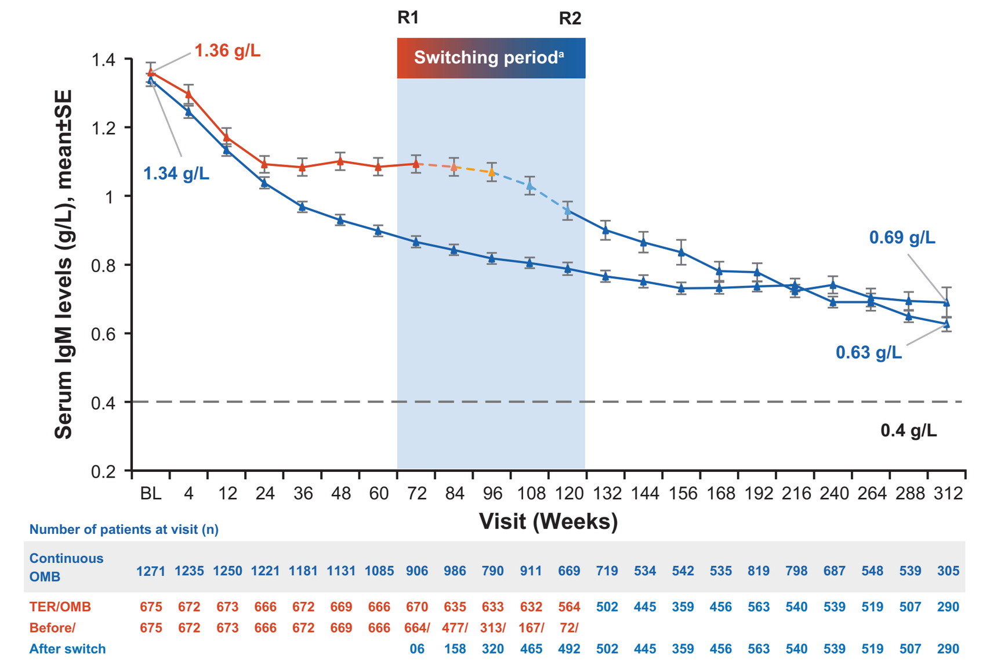


Figure 4B. Mean IgM levels over 6 years



[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.
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 (3 June 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.

Lymphocyte and neutrophil levels

- Lymphocyte and neutrophil levels **remained stable** throughout 6 years of treatment
- 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
- In the continuous ofatumumab group, the mean **neutrophil levels** remained **stable and above baseline levels** for all visits up to Week 312; whereas in the newly switched group, mean neutrophil levels **decreased up to Week 4** and **remained low during the pre-switch period** followed by a reversal and **stabilisation** (reaching baseline levels) post-switch

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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 Unique. 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. **Jacqueline Nicholas** has received research grants from Biogen, Novartis, PCORI, Genentech and University of Buffalo. He has received consulting fees from Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Greenwich Biosciences, Novartis and TG therapeutics. He also received speaking honoraria from Alexion, Bristol Myers Squibb, EMD Seono and Viela Bio. **Jérôme de Seze** received personal compensation from Alexion, Biogen, F. Hoffmann-La Roche Ltd, Sanofi, LFB, Merck, Novartis, Horizon-Amgen, Argenx and UCB. **Sven G. Meuth** has received honoraria for consulting from Alexion, Almirall, Amicus Therapeutics Germany, Bayer Healthcare, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva. He received a research grant from German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology and Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche and Teva. **Paul S. Giacomini** has received honoraria for consulting, speaking, and advisory board participation from Actelion, Alexion, Biogen Idec, Bristol Myers Squibb-Celgene, EMD Serono, Genzyme-Sanofi, Innodem Neurosciences, Novartis, Pendopharm, Roche and Teva Neuroscience. **Derrick Robertson** has received fees for consulting, contract research, and speaker bureau from Biogen, Celgene, EMD Serono, Genentech, Sanofi Genzyme, Janssen and TG therapeutics; consulting and speaker bureau from Bristol Myers Squibb, Horizon and Alexion; consulting and contract research from Novartis; consulting from Greenwich Biosciences; and contract research from GW Pharmaceuticals, PCORI, Atara Biotherapeutics and CorEvitas. **Sibyl Wray** received fees for consulting and advisory boards for Biogen, Celgene and EMO Serano; speaker bureaus from Biogen, Celgene, EMO Serano, Genentech-Roche and Sanofi-Genzyme and research support from Biogen, Celgene, EMO Sereno, Genentech-Roche, Novartis, Receptos, Sanofi-Genzyme and TG Therapeutics. **Jeffrey A. Cohen** received personal compensation for consulting for Astoria, Bristol Myers Squibb, Convelo, EMD Serono, FiND Therapeutics, INMune and Sandoz; and serving as an Editor of Multiple Sclerosis Journal. **Ludwig Kappos'** institution (University Hospital Basel) has received the following exclusively for research support: Steering committee, advisory board and/or consultancy fees from Biogen, EMD Serono Research and Development, Genentech, Janssen, Novartis, Clene Nanomedicine Inc., Bayer, Bristol Myers Squibb, Celltrion Inc, Eli Lilly (Suisse) SA, Galapagos NV, Kiniksa Pharmaceuticals, Merck Healthcare AG, Minoryx and Santhera, Neurostatus UHB AG, Roche, Sanofi, Santhera Pharmaceuticals, Shionogi BV, Wellmera AG and Zai Lab; speaker fees from Bristol Myers Squibb, Janssen, Novartis, Roche, and Sanofi; grants from the European Union, Innosuisse, Merck Healthcare AG, Novartis and Roche and testimony. **Alit Bhatt**, **Xixi Hu**, **Haoyi Fu**, **Valentine Jehl**, **Roseanne Sullivan** and **Ibolya Boer** are employees of Novartis.

Abbreviations

3m/6mCDW, 3-month/6-month confirmed disability worsening; **AE**, adverse event, **ARR**, annualised relapse rate; **CI**, confidence interval; **EAIR**, exposure adjusted incidence rate; **Gd+**, gadolinium-enhancing; **HR**, hazard ratio; **Ig**, immunoglobulin; **K-M**, Kaplan Meier; **LLN**, lower limit of normal; **MS**, multiple sclerosis; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **neT2**, new or enlarging T2 lesions; **OMB**, ofatumumab; **OR**, odds ratio; **PT**, preferred term; **pwRMS**, people with relapsing multiple sclerosis; **PY**, patient year; **SAE**, serious adverse event; **SE**, standard error; **TER**, teriflunomide.