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Continuous Ofatumumab Treatment Up to 7 Years Shows a Consistent Safety and Efficacy Profile in Recently Diagnosed Treatment-Naive People Living With Relapsing Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- Treatment of RDTN plwRMS with ofatumumab for up to 7 years demonstrated a consistent safety profile, with no new safety concerns
  - Exposure-adjusted incidence rates of serious adverse events of infections and malignancies remained consistent up to 7 years
  - Mean IgG levels remained stable, whereas mean IgM levels initially decreased but then stabilised and remained above the LLN
- First-line ofatumumab treatment for up to 7 years showed sustained efficacy with an adjusted rate of one relapse for every 23 years during the extension phase and a profound suppression of MRI activity
- Participants who switched from teriflunomide to ofatumumab in the extension phase also showed pronounced reductions in relapses and MRI activity
- High rates of NEDA-3 were achieved in RDTN participants (9 of 10 participants) with up to 7 years of ofatumumab treatment
- Limitations include a potential for attrition bias and the open-label nature of the extension study
- The 7-year results further confirm the long-term, favourable benefit-risk profile of ofatumumab treatment when used as first-line therapy for RDTN plwRMS

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INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosage regimen, is the only anti-CD20 approved for the treatment of relapsing multiple sclerosis (RMS) via self-administration[1,2]
- In the ASCLEPIOS I/II phase 3 trials, ofatumumab demonstrated a favourable safety profile and superior efficacy compared with teriflunomide in reducing clinical and magnetic resonance imaging (MRI) disease activity in both the overall RMS population and the recently diagnosed (≤3 years) and treatment-naive (RDTN) subgroup[3,4]
- Up to 7 years of ofatumumab treatment in the ASCLEPIOS I/II trials and ALITHIOS open-label extension study showed sustained efficacy and a favourable safety profile in the overall participant population[5]
- Furthermore, previously reported data show that the benefit of ofatumumab treatment up to 7 years on disability worsening was particularly pronounced in the RDTN subgroup of ALITHIOS (8 of 10 RDTN participants free of 6-month confirmed disease worsening [6mCDW] and nearly 9 of 10 participants free of 6-month confirmed progression independent of relapse activity), and no new safety concerns were reported[5]

OBJECTIVE

- To describe the long-term safety and efficacy outcomes (annualised relapse rate [ARR], no evidence of disease activity [NEDA-3] and MRI activity) with up to 7 years of ofatumumab treatment in RDTN people living with RMS (plwRMS; data cutoff: 25-Sep-2024)

METHODS

Safety population (N=546)

- Safety analyses included RDTN participants receiving ≥1 dose of ofatumumab in ASCLEPIOS I/II or ALITHIOS

Efficacy population (N=465)

- **Continuous ofatumumab group (OMB-OMB):** Participants randomised to ofatumumab in ASCLEPIOS I/II and continuing ofatumumab in ALITHIOS (N=233)
- **Switch group (TER-OMB):** Participants randomised to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab in ALITHIOS (N=232; switching started in Year 2 and was completed by Year 3)[a]

Assessments

- **Safety:** Overall safety profile, exposure-adjusted incidence rates (EAIRs) for serious infections, immunoglobulin G (IgG) and IgM levels, and lymphocyte and neutrophil levels
- **Efficacy:** Cumulative data up to 7 years for ARR, NEDA-3 and brain MRI outcomes (mean number of gadolinium-enhancing [Gd+] T1 lesions per scan and number of new/enlarging T2 [neT2] lesions per year)

[a]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.

RESULTS

Patient disposition and baseline characteristics

- At the time of data cut-off, 355 of the 465 RDTN participants entering ALITHIOS had completed the 5-year extension period, and 321 participants had entered a subsequent 3-year extension period
- Of the 465 RDTN participants entering ALITHIOS, 103 participants had discontinued the study and 7 were still in the 5-year extension period
- The main reasons for discontinuing the study were participant/guardian decision (46/465 [9.9%]) and occurrence of adverse events (AEs; 26/465 [5.6%])
- Baseline characteristics were typical of RDTN plwRMS and were well balanced across treatment groups

Safety profile

- The overall safety profile (based on the safety population: N=546 [RDTN]) remained consistent with the 6-year findings, with no new safety concerns reported (**Table 1**)

Table 1. Overall safety profiles up to 7 years

	Core + Extension	
	RDTN subgroup (N=546)	
Adverse events	**n (%)**	**EAIR (95% CI)**
Participants with at least one AE	509 (93.2)	124.96 (114.56–136.30)
Participants with at least one SAE	87 (15.9)	3.70 (3.00–4.57)
AEs leading to ofatumumab discontinuation	52 (9.5)	–
Infections and infestations	411 (75.3)	42.31 (38.41–46.60)
Serious infections		
Serious infections (excluding COVID-19)	16 (2.9)	0.63 (0.39–1.03)
Serious COVID-19 infections	18 (3.3)	0.70 (0.44–1.12)
Blood Ig level		
IgG decrease	2 (0.4)	0.08 (0.02–0.31)
IgM decrease	79 (14.4)	3.28 (2.63–4.09)
Injection-related reactions	142 (26.0)	7.16 (6.08–8.44)
Injection-site reactions	87 (15.9)	3.86 (3.13–4.76)
Deaths	7[a] (1.3)	–
Malignancy	10 (1.8)	0.38 (0.21–0.72)

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]Including the following: Sudden death, (n=1), oesophageal adenocarcinoma (n=1), completed suicide (n=1), aortic dissection (n=1), COVID-19/ COVID-19 pneumonia (n=1) and COVID-19 (n=2).

Mean IgG/IgM levels

- Mean IgG levels remained stable up to 7 years of treatment; mean IgM levels initially decreased but then stabilised and remained above the lower limit of normal (LLN; **Figure 1A** and **Figure 1B**)
  - 97.6% and 62.4% of participants had IgG and IgM levels above LLN at all assessments, respectively
- Treatment interruption/discontinuation was reported in 0.0%/0.2% of RDTN participants due to low IgG and in 9.7%/4.2% of participants due to low IgM
- EAIR of serious infections did not vary in participants with IgM levels <LLN versus ≥LLN: 1.18 (95% CI: 0.44–3.14) versus 1.07 (95% CI: 0.67–1.73)

Figure 1A. Mean IgG levels over 7 years among RDTN participants

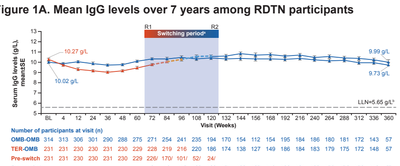
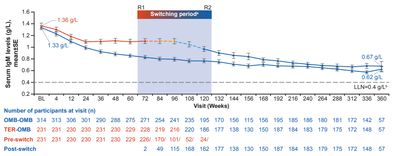


Figure 1B. Mean IgM levels over 7 years among RDTN participants



[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 cut-off date has been used. R1: The first participant with the first IgG/IgM assessment after switching to ofatumumab (72 weeks); R2: last participant with last IgG/IgM assessment in teriflunomide period before switching to ofatumumab (120 weeks). [b]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.

Serious infections and malignancy

- EAIRs per 100 patient-years (PYs) of serious AEs, including infections and malignancies, remained consistent up to 7 years (**Table 2**)

Table 2. Exposure-adjusted incidence of serious infections and malignancy TEAEs by year

Risk name IR (95% CI)	Year 1 N=546	Year 2 N=506	Year 3 N=446	Year 4 N=412	Year 5 N=385	Year 6 N=319	Year 7 N=182
Serious infections (excluding COVID-19)	0.76 (0.29–2.03)	1.47 (0.70–3.09)	2.41 (1.30–4.48)	1.85 (0.88–3.89)	0.58 (0.14–2.31)	0	0.59 (0.08–4.19)
COVID-19 infections	0	0.83 (0.31–2.22)	0.71 (0.23–2.20)	1.80 (0.86–3.78)	1.12 (0.42–2.98)	0	0
Malignancy	0.38 (0.09–1.52)	0.21 (0.03–1.48)	0.47 (0.12–1.87)	0.76 (0.24–2.35)	0.54 (0.14–2.17)	0	0

The IRs per 100 PYs were estimated via a Poisson regression model with only treatment as factor and the log-link and natural logarithm of time as the offset variable.

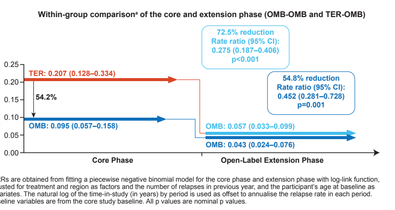
Lymphocyte and neutrophil levels

- Mean lymphocyte and neutrophil levels remained stable and similar to baseline levels with up to 7 years of ofatumumab treatment, in line with previous results[7]

Annualised relapse rate

- Treatment with ofatumumab was associated with a significant 54.2% reduction in ARR versus teriflunomide in the core phase and an even lower ARR was sustained in the extension up to 7 years (**Figure 2**)
- Switch from teriflunomide to ofatumumab resulted in a significant 72.5% reduction in ARR, which was also sustained up to 7 years (**Figure 2**)

Figure 2. ARR with up to 7 years ofatumumab treatment

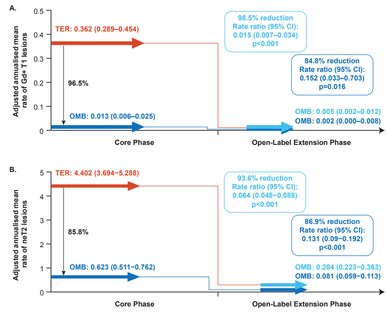


[a]ARRs are obtained from fitting a piecewise negative binomial model for the core phase and extension phase with log-link function, adjusted for treatment and region as factors and the number of relapses in previous year, and the participant's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualise the relapse rate in each period. Baseline variables are from the core study baseline. All p values are nominal p values.

MRI activity

- The almost-complete suppression of Gd+ T1 activity in the core phase (96.5% for OMB vs. TER) was sustained with OMB-OMB in the extension phase and was observed in the TER-OMB group after switch (98.5%; **Figure 3A**)
- A profound reduction in neT2 lesions in the core phase (85.8% for OMB vs. TER) was sustained with OMB-OMB in the extension phase, and a similar reduction was observed in the TER-OMB group after switch (93.6%; **Figure 3B**)

Figure 3. Within-group[a] comparison[b] for Gd+ T1 and neT2 lesions

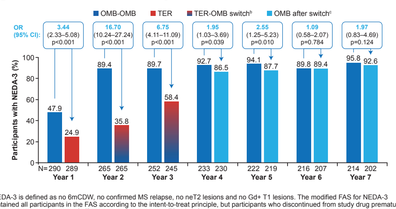


[a]Between the core and extension phase: OMB-OMB and TER-OMB. [b]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment as factor and baseline number of Gd+ T1 lesions and participant's age at baseline as covariates. 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.

No evidence of disease activity

- High rates of NEDA-3 at Year 7, observed in more than 9 of 10 participants in both treatment groups, were in line with previous results (**Figure 4**)

Figure 4. NEDA-3[a] status over 7 years



[a]NEDA-3 is defined as no 6mCDW, no confirmed MS relapse, no neT2 lesions and no Gd+ T1 lesions. The modified FAS for NEDA-3 contained all participants in the FAS according to the intent-to-treat principle, but participants who discontinued from study drug prematurely for reasons other than 'lack of efficacy' or 'death' and had NEDA-3 before early discontinuations were excluded. Statistical model used logistic regression adjusting for treatment and region as factors, and age, baseline EDSS and number of Gd+ lesions at baseline as covariates. Both scheduled and unscheduled MRI assessments are considered in the analysis. As some participants may have completed the 5-year extension prior to completing a full seventh year of ofatumumab treatment, there is a possibility that the NEDA-3 rates during Year 7 are overestimated. [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.

Please also refer to the related posters being presented at the congress:

P804: Continuous Ofatumumab Treatment for Up to 7 Years Shows a Favourable Safety and Efficacy Profile in People With Relapsing Multiple Sclerosis

P812: Over 7 Years, the Risk of Serious Infections Remained Low With Long-Term Ofatumumab Treatment in People With Relapsing Multiple Sclerosis

P932: Immunoglobulin G Levels in Ofatumumab-Treated Participants With Episodes of Low Immunoglobulin M: An Analysis of 7-Year Data From the ALITHIOS Extension Study

References

1. Kesimpta (ofatumumab). Prescribing Information. Novartis; April 2024. Accessed 24 July 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125326s079lbl.pdf.
2. Kesimpta (ofatumumab). Summary of product characteristics. Novartis; February 2025. Accessed 24 July 2025. https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf.
3. Hauser SL, et al. *N Engl J Med*. 2020;383:546–557.
4. Gärtner, et al. *Mult Scler*. 2022;28:1562–1575.
5. Gold R, et al. Presented at: European Academy of Neurology (EAN), Helsinki, 29 June–2 July 2024.
6. Pardo G, et al. Presented at: American Academy of Neurology (AAN) Meeting, San Diego, CA, USA; 5–9 April 2025.
7. Bar Or, et al. Presented at: Consortium of Multiple Sclerosis Centers (CMSC), National Harbor, Maryland, 1–4 June 2022.

Abbreviations

6mCDW, 6-month confirmed disability worsening; **AE**, adverse event; **ARR**, annualised relapse rate; **BL**, baseline; **CI**, confidence interval; **EAIR**, exposure-adjusted incidence rate; **EDSS**, Expanded Disability Status Scale; **FAS**, full analysis set; **Gd+**, gadolinium enhancing; **Ig**, immunoglobulin;
IR, incidence rate; **LLN**, lower limit of normal; **MRI,** magnetic resonance imaging; **MS**, multiple sclerosis; **NEDA**, no evidence of disease activity; **neT2**, new/enlarging T2; **OMB**, ofatumumab; **OMB-OMB**, continuous ofatumumab; **OR**, odds ratio;
PY, patient-year; **RDTN**, recently diagnosed treatment-naive; **SAE**, serious adverse event; **SE**, standard error; **TEAE**, treatment-emergent adverse event; **TER**, teriflunomide; **TER-OMB**, switch from teriflunomide to ofatumumab.

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