SUPPLEMENTARY MATERIAL

Five-year safety and efficacy outcomes with ofatumumab in patients with relapsing multiple sclerosis

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Key protocol amendments

During ASCLEPIOS I/II, APLIOS and APOLITOS, investigators were required to interrupt treatment if immunoglobulin M (IgM) levels fell below 10% of lower limit of normal (LLN) or IgG levels fell below 20% of LLN; treatment was not to resume until IgM or IgG levels returned to normal limits. This requirement was removed by a protocol amendment (03 June 2021) for ALITHIOS, and the decision was left to the discretion of the investigator.

Key inclusion and exclusion criteria for the ALITHIOS open-label extension

Eligibility criteria at screening included 18–55 years of age (inclusive), a diagnosis of multiple sclerosis (MS; according to the 2010 revised McDonald criteria) [1] with a relapsing-remitting course or a secondary progressive course with disease activity (according to the Lublin criteria) [2], Expanded Disability Status Scale (EDSS) score of 0–5.5, ≥1 relapse in the year before screening, or ≥2 relapses in the 2 years before screening, or ≥1 gadolinium-enhancing (Gd+) lesion detected on magnetic resonance imaging (MRI) in the year before randomisation, and neurologically stable for ≥1 month prior to randomisation. Key exclusion criteria included a diagnosis of primary progressive MS or secondary progressive MS without disease activity, neuromyelitis optica, disease duration of >10 years with an EDSS score of ≤2.0, neurological findings consistent with progressive multifocal leukoencephalopathy (PML) or confirmed PML, recipient of live or live attenuated vaccines during the 2 months prior to randomisation, or previous treatment with disease-modifying treatments [3].

Trial oversight

Prior to commencement, study protocols were approved by an institutional review board or ethics committee at each site, and all randomised patients provided written informed consent prior to receiving trial treatment. All data were collected by site investigators and then analysed by Novartis Pharmaceuticals. The trials were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice [4] and the principles of the Declaration of Helsinki [5], while US sites maintained compliance with Health Insurance Portability and Accountability Act regulations [6].

Analysis populations

Safety analysis set

Safety analyses used the data of patients who received ≥1 dose of ofatumumab in ASCLEPIOS I/II, APLIOS, APOLITOS or ALITHIOS (see **Figure S1**) from the first dose of ofatumumab in either the core or extension period.

Efficacy analysis set

Efficacy analyses used data from the full analysis set (data of patients enrolled in ASCLEPIOS I/II from the first dose of study treatment [ofatumumab or teriflunomide]). For three-parameter no evidence of disease activity

(NEDA-3), the modified efficacy analysis set excluded patients who discontinued treatment early (other than due to lack of efficacy or death) and achieved NEDA-3 prior to early discontinuation.

Analysis periods

Two analysis periods were defined: the core and the extension periods. The core period was defined as the period between the first dose of active study drug in ASCLEPIOS I/II and one day before the first dose of ofatumumab in ALITHIOS (~2 years or, if the subject did not enter ALITHIOS, to the end of the safety follow-up in ASCLEPIOS I/II). The extension period was defined as the period between the first dose of ofatumumab in ALITHIOS and the end of open-label treatment.

Endpoints: definitions and assessment criteria

Safety endpoints

IgG and IgM

IgG and IgM were measured at baseline, Week 4, Week 12 and every 12 weeks thereafter in the core studies (with an additional measure at Week 28 in APOLITOS). In the ALITHIOS study, data were collected at Week 4, Week 12, every 12 weeks up to Week 48, and every 24 weeks thereafter up to the end of the 5-year treatment. Only events (serious infections) occurred 1 month before or after the occurrence of <LLN date were counted in the analysis. The proportion of patients with ofatumumab interruptions/discontinuations due to an IgG decrease (i.e., related to preferred terms: Blood immunoglobulin G decreased, Blood Immunoglobulin G abnormal, and Immunoglobulins decreased post first IgG decline for patients with at least one episode) or IgM decrease (i.e., related to preferred terms: Blood immunoglobulin M decreased, Blood Immunoglobulin M abnormal, Immunoglobulins decreased, Selective IgM immunodeficiency, Hypogammaglobulinaemia and Hypoglobulinaemia post first IgM decline for patients with at least one episode) was analysed. Sensitivity analyses were conducted to evaluate whether ofatumumab interruption due to low IgG/IgM impacted the overall Ig trends, where IgG and IgM values after the first interruption due to either notably low IgM (10% below the LLN) or IgG (20% below the LLN) levels were imputed using the last observation carried forward (LOCF).

Lymphocyte and neutrophil levels

The assessment schedule for serum lymphocyte and neutrophil levels was the same as that of IgG and IgM levels. The mean absolute lymphocyte and neutrophil levels from baseline up to Week 264 were analysed. All assessments contributed to the calculation of the mean irrespective of whether the patient had treatment interruption or discontinuation.

Injection-related reactions (IRRs)

IRRs were reported by the investigators using the relevant case report form pages and were defined as reaction/symptoms occurring after the injection administration These were systemic IRRs (systemic reactions/generalised symptoms) occurring within 24 hours after the injection (i.e. time to onset of reaction

≤24 hours) or local-site IRRs, occurring localised to the injection administration site and reported without any time limit from the time the injection was administered.

COVID-19 outcomes

COVID-19 diagnosis

Cases were considered as confirmed COVID-19 if there was a positive laboratory test result including real-time polymerase chain reaction, antigen detection or serological evidence of infection, as reported by the investigator. Cases were considered as suspected COVID-19 in the absence of a positive SARS-CoV-2 laboratory test result but with signs and symptoms consistent with COVID-19.

COVID-19 assessments: additional information

Demographics, key baseline disease characteristics and history were summarised for patients who entered the ALITHIOS study, patients with confirmed/suspected COVID-19, and hospitalised patients with COVID-19. COVID-19 cases, seriousness, severity category, COVID-19 outcomes, reinfections, COVID-19 vaccination status, and vaccine breakthrough infection with associated outcomes were assessed. COVID-19 seriousness category was based on the regulatory reporting definition established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [7] guidelines E2A [8]. Severity assessment was provided by the reporting investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE [v5.0]) grading system [9], as described in the protocol; AEs were reported as mild (Grade 1), moderate (Grade 2), severe (Grade 3) or life-threatening (Grade 4). COVID-19 outcomes were reported by the investigator as recovered or recovering or recovered with sequelae, not recovered, or fatal. Per the Centers for Disease Control and Prevention, reinfection was defined as a second confirmed infection after 90 days from the end date of the recovered first COVID-19. Vaccine breakthrough COVID-19 was defined as confirmed COVID-19 after being fully vaccinated. Fully vaccinated means at least 14 days after receiving all recommended doses of a COVID-19 vaccine (excluding booster), and partially vaccinated means either not received all recommended doses or <14 days after receiving all recommended doses of a COVID-19 vaccine [10]. Potential risk factors of serious COVID-19 were evaluated.

Serological response to SARS-CoV-2 infection and vaccine

The serological response to SARS-CoV-2 infection and vaccine was evaluated retrospectively in patients with RMS who entered the ongoing ALITHIOS open-label extension study. Patients with blood samples available before and after infection/vaccination and with negative IgG antibodies to the receptor-binding domain (RBD) spike protein prior to infection/vaccination were included in the analysis. Antibody levels were measured (Abbott Architect SARS-CoV-2 IgG II Quant assay) in four pre-defined subgroups: COVID-19 infection only (no vaccination, n=76), fully vaccinated only (no infection; n=181), booster vaccination (fully vaccinated+booster; n=93) and breakthrough infection (SARS-CoV-2 infection after full vaccination; n=82).

Compliance to study treatment

Compliance was calculated as the duration of exposure to the study drug/duration of the on-treatment period×100%, where on-treatment period included days from the first injection date until 30 days after the last injection date. Exposure does not include the interruptions/delays in doses, whereas on-treatment period does. Measurement of compliance was based on dosing information recorded by the patient in a study treatment diary. Details captured included the time and date of each subcutaneous injection, any administration-related symptoms and records of missed doses.

Efficacy endpoints

B-cell depletion over time

Median B-cell count and proportion of patients with B-cell count ≤10 cells/μL were assessed.

Confirmed disability worsening at 3 months (3mCDW) and 6 months (6mCDW)

CDW was defined as an increase from baseline in EDSS score (≥1.5, ≥1 or ≥0.5 points for patients with a baseline EDSS score of 0, 1–5 or ≥5.5, respectively) sustained for ≥3 (3mCDW) or ≥6 (6mCDW) months. Therefore, after a scheduled or unscheduled visit at which the patient fulfils the disability worsening criterion, all EDSS assessments (scheduled or unscheduled) need to also fulfil the worsening criteria until the worsening ('the event') can be confirmed at the first scheduled visit that occurs 3 or 6 months after the onset of the worsening, or later. Censoring occurred in all patients who did not experience a 3mCDW or 6mCDW event in the study (censoring also occurred in patients who had a 'tentative' disability worsening that could not be confirmed due to an early discontinuation or any another reason). The censoring time was defined as the time from the first dose to the last available EDSS assessment.

Progression independent of relapse activity at 6 months (6mPIRA)

6mPIRA was defined as a 6mCDW event with either no prior relapse or an onset more than 90 days after the start date of the last investigator-reported relapse (irrespective of the EDSS confirmation). In addition, to qualify as a PIRA event, no relapse must have occurred within 30 days after confirmation of EDSS worsening.

Relapse-associated worsening at 6 months (6mRAW)

6mRAW was defined as a 6CDW event due to incomplete recovery from a relapse.

Confirmed disability improvement at 6 months (6mCDI)

CDI was defined as a decrease from baseline EDSS sustained for at least 6 months. For patients with a baseline EDSS score of 0 to 1.5, no improvement is deemed possible; for patients with a baseline EDSS score of ≥2 to 6 and ≥6.5 to 9.5, the criteria for improvement were a decrease of at least 1 point and a decrease of at least 0.5 points, respectively. Censoring occurred in patients who did not experience a 6mCDI event in the study. The censoring time was defined as the time from the first dose to the last EDSS assessment.

Annualised relapse rate (ARR)

The ARR per study period (core and extension) was defined as the number of confirmed MS relapses per year. A relapse was defined as the appearance of a new neurological abnormality or worsening of a pre-existing neurological abnormality (persisting for ≥24 hours), separated by ≥30 days from the onset of a preceding clinical demyelinating event. The definition of a confirmed MS relapse was a relapse accompanied by a clinically relevant change in the EDSS performed by the EDSS rater, i.e. an increase of ≥0.5 points on the EDSS score, or an increase of 1 point on two functional scores (FSs) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previously available rating (the last EDSS rating that did not occur during a relapse). Confirmation of MS relapse based on these definitions was done centrally.

Acute brain MRI lesion activity

The number of Gd+ T1 lesions and number of new or enlarging T2 (neT2) lesions were assessed every year.

NEDA-3 status

NEDA-3 was defined as no 6mCDW events, no confirmed relapses and no MRI activity (new Gd+ T1 lesions or neT2 lesions) within a given year on study.

Serum neurofilament light chain (sNfL) concentration

Neurofilament light (NfL) chain is a specific biomarker of neuro-axonal injury, released into the cerebrospinal fluid and serum following neuro-axonal damage. Serum and cerebrospinal fluid concentrations of NfL are highly correlated, and sNfL concentration is higher in people with MS versus age-matched healthy controls [11]. Two assays were used to assess sNfL: for ASCLEPIOS I/II (core period), the Quanterix Simoa® NF-light™ Advantage Kit validated at Navigate BioPharma Services (Carlsbad, CA, USA), assay was used; for ALITHIOS (extension period), the Siemens Healthineers NfL laboratory developed test on the Atellica® Immunoassay system, which was validated at Siemens Healthcare Laboratory (Berkeley, CA, USA), was used. A good correlation between the two assays was observed (Pearson's correlation=0.995; average quantitation difference of 8%) [12]. To assess the long-term treatment effect on sNfL in the overall period, it was necessary to pool the core and extension data. As the two assays were not equivalent, a transformation algorithm (from the Quanterix Simoa® assay to the Siemens Atellica® assay) was established by Siemens [12]. These 'assay-transformed values' can be calculated as 2.06+0.83×original values.

Statistical methods

All baseline variables included in the model were from the core study. Statistical hypotheses were tested at the 5% significance level, and *p* values less than 0.05 were considered nominally statistically significant. All *p* values are nominal *p* values.

Serious infections

The annualised rate of serious infections for each year was estimated using a negative binomial regression model, with number of infections in each participant in the year as the response variable, year as factor and time at risk in the year as offset variable. COVID-19 incidence was evaluated based on calendar years rather than years on ofatumumab, as cases of COVID-19 occurred only during 2020–2023; a Poisson model was used to analyse the outcome.

CDW, PIRA, RAW and CDI

Cumulative 3mCDW and 6mCDW, time to first 6mPIRA, 6mRAW and 6mCDI were assessed using Kaplan–Meier estimates. Hazard ratios (HRs) in the core/extension phase obtained from a Cox regression model based on events in that time period, adjusted for treatment and region as factors and baseline EDSS as a continuous covariate; *p* values are for the log-rank test.

ARR, Gd+ T1 lesions per scan and neT2 lesions

The by-year ARR for the TER-OMB and OMB-OMB groups was estimated from a negative binomial model with a log link, adjusted for treatment, visit, region, number of relapses in previous year, baseline EDSS, baseline number of Gd+ lesions, age at baseline and a treatment by visit interaction. Log-transformed exposure time (in years) per visit is included as an offset variable to annualise the relapse rate at each visit. An unstructured within-subject correlation between periods was assumed.

By-year estimates of Gd+ T1 lesions per scan were estimated using a negative binomial model with log link, similar to the ARR. This model was adjusted for treatment, visit, baseline number of Gd+ T1 lesions, age at baseline and a treatment by visit interaction. The natural log of number of assessments per year was used as offset to annualise the lesion rate at each visit.

By-year estimates of the annualised rate of neT2 lesions was estimated using a similar approach, considering treatment, visit, baseline volume of T2 lesions, age at baseline and a treatment by visit interaction. The natural log of the time-in-study (in years) between visits was used as an offset to annualise the lesion rate at each visit.

The 'visit' included in the models in this section refers to Year of assessment i.e. Year 1, Year 2, Year 3, Year 4, and Year 5. Baseline variables were taken from the core study baseline.

NEDA-3

NEDA-3 was analysed separately per year using logistic regression models (adjusted for treatment and region as factors, and age, baseline EDSS, and number of Gd+ T1 at baseline as covariates).

sNfL concentrations

Adjusted geometric means of sNfL concentrations with 95% CIs at each time point were analysed by mixed-effect modelling of repeated measures adjusted for treatment, region and visit window as factors, age,

number of Gd+ T1 lesions at baseline, baseline T2 lesion volume and the log-transformed NfL baseline concentration as continuous covariates; and treatment-by-visit-window interaction. Geometric mean sNfL concentrations at baseline were derived as exponentiated arithmetic mean of natural logarithmic of raw values of sNfL concentrations.

Whole brain volume change

Both annualised brain volume change (ABVC) and percentage brain volume change (PBVC) outcomes are percent change from baseline. All ABVC estimates were obtained from a random coefficient model with treatment, time period (core vs. extension) and region as factors; time, baseline number of Gd+ T1 lesions, baseline T2 volume and baseline normalised brain volume as continuous covariates; and the three-way interaction (treatment group by time period by time) and all its associated two-way interactions. Estimates of mean PBVC at each visit were obtained from a mixed model for repeated measure with treatment and visit window as interacting factors, with region as a factor, and with baseline age, baseline number of Gd+ T1 lesions, baseline T2 volume and baseline normalised brain volume as continuous covariates.

Results

Additional safety assessments

Injection-related reactions

Of 1969 patients, 502 (25.5%) and 243 (12.3%) patients had an injection systemic reaction and injection site reaction, respectively. IRRs were predominantly reported after the first injection and the incidence decreased with subsequent injections. The number of reported IRRs declined between the first and the last injection; 17.5% of patients had a systemic IRR to injection 1, versus 1.3% for injection 10, whereas 3.0% of patients had an injection site reaction to injection 1, versus 1.6% for injection 10. Most systemic and site IRRs were Grade 1 (n=346 [17.6] and 208 [10.6%]) and Grade 2 (n=151 [7.7%] and 34 [1.7]) (see **Table S7**). No life-threatening IRRs were reported.

Lymphocyte and neutrophil levels

Mean lymphocyte and neutrophil levels remained stable and were above LLN (see **Figure S5A**). Neutropenia and lymphopenia occurred in 18 (0.91%) and 22 (1.11%) of 1969 patients, respectively. The exposure-adjusted incidence rates of neutropenia and lymphopenia were 0.27 (95% CI: 0.17–0.43) and 0.33 (95% CI: 0.22–0.50), respectively. During the core period, neutrophil levels were lower in the TER-OMB group but returned to baseline levels following the switch to ofatumumab (see **Figure S5B**). No serious AEs of lymphopenia or neutropenia occurred. The majority of drops in levels below LLN or respective Common Terminology Criteria for Adverse Events (CTCAE) grades were single occurrences and not sustained over time (see **TableS8**).

COVID-19 outcomes

At data cutoff (DCO), 38% (n=648/1703) of patients that entered ALITHIOS had COVID-19 (confirmed: n=603; suspected: n=45). Most COVID-19 infections were mild to moderate in severity (93.9%) and non-serious (92.3%) (see **Figure S14**). Most patients (98.6%) recovered while five had a fatal outcome (three unvaccinated and two fully vaccinated). In most patients, the severity of COVID-19 was mild to moderate irrespective of vaccination status (see **Table S9**): 97.6% of those who had received their primary vaccine recovered and 100% of those who had received one or two boosters recovered. Among those who were infected after receiving their primary vaccine (before booster), 91.6% had non-serious COVID-19.

Identified risk factors associated with serious COVID-19 were high body mass index (BMI ≥30 kg/m^2, hazard ratio [HR] 1.98 [95% CI: 1.06–3.67]; *p*=0.031) and male sex (HR 1.89 [95% CI: 1.08–3.31]; *p*=0.026) (see **Figure S15**). No relationship was identified between duration of ofatumumab treatment and risk of serious COVID-19.

Serological responses were detected after both SARS-CoV-2 infection and COVID-19 vaccination [13]. The proportion of patients seropositive for RBD antibody (geometric mean ± standard deviation [SD] of anti-RBD IgG) was 47.4% (36/76; 8.19±7.57) following COVID-19 infection and 44.2% (80/181; 6.43±7.86) of fully vaccinated patients [13]. Seropositivity rates were higher in subgroups that received a booster vaccination (60.2%; 56/93; 17.54±10.57) or had a breakthrough infection (64.6%; 53/82; 17.82±10.89; see **Table S10** and **Figure S16**).

Additional efficacy assessments

B-cell depletion over time

In the OMB-OMB group, the ofatumumab dosing regimen led to rapid B-cell depletion, from a median B-cell count of 200 cells/μL at baseline to 10 cells/μL by Week 2; this further decreased to 0 cells/μL by Week 4 and was sustained up to Week 288. In the TER-OMB patients who switched to OMB, the median B-cell count before the first dose of ofatumumab was 174 cells/μL, which reduced to 2 cells/μL by Week 4 and to 0 cells/μL by Week 72 following the switch and were sustained at 0 cells/μL thereafter. In the overall ofatumumab population, 81.9% and 97.7% of patients achieved B-cell counts ≤10 cells/μL by Week 2 and Week 12, respectively; 96.6% of participants had B-cell counts ≤10 cells/μL at Week 288.

Relapses

The adjusted ARRs in the OMB-OMB group were 0.11 (95% CI: 0.08–0.14) in the core period and were reduced by a further 47.4% (p<0.001) to 0.056 (95% CI: 0.04–0.08) in the extension period (see **Figure S9**). For the TER-OMB group, the ARR was significantly reduced in the extension versus the core period following switch to ofatumumab (72.6% reduction; p<0.001); adjusted ARRs in the TER-OMB group were 0.23 (95% CI: 0.18–0.29) in the core period and were similar to the OMB-OMB group in the extension period (0.063 [95% CI: 0.05–0.08]; see **Figure S9**).

In between-group analyses, a significant reduction in the ARR was observed for ofatumumab versus teriflunomide in the core period (53.5%; 0.11 vs. 0.23; rate ratio: 0.47 [95% CI: 0.38–0.58]; p<0.001), and both groups receiving ofatumumab in the extension study maintained a low ARR (0.056 vs. 0.063; rate ratio: 0.89 [95% CI: 0.66–1.20]; p=0.448; see **Figure S9).** Over the combined core plus extension period, the cumulative number of confirmed relapses in the OMB-OMB group was 40% lower than in the TER-OMB group (n=304 vs. n=507; see **Figure S9**).

MRI assessments

The already low rate of Gd+ T1 lesion activity observed in the OMB-OMB group in the core period was reduced by a further 58.5% with long-term ofatumumab use (rate ratio for the core vs. extension period: 0.42; p=0.002; see **Figure S10**). Switching from teriflunomide to ofatumumab led to a rapid and almost complete (96.9%) suppression of Gd+ T1 lesion activity to closely match the OMB-OMB group (Gd+ T1 lesions per scan in the core period: 0.55 [95% CI: 0.47–0.65] and extension periods: 0.02 [95% CI: 0.01–0.03]; rate ratio 0.03; p<0.001) (see **Figure S10**). Over the core plus extension period, the cumulative number of Gd+ T1 lesions per scan in the OMB-OMB group was 94% lower than in the TER-OMB group (n=73 vs. n=1324); see **Figure S10**). For between-group comparisons, see **Figure S10**.

The already low neT2 lesion activity observed in the core period was further reduced with long-term ofatumumab use (89.4% reduction; rate ratio for core vs. extension period: 0.11; p<0.001; see **Figure S11**). Switching from teriflunomide to ofatumumab led to a suppression of neT2 lesion activity to closely match the OMB-OMB group (see **Figure S11**); in the TER-OMB group, the adjusted annualised mean rate of neT2 lesions decreased from 4.43 (95% CI: 4.00–4.90) in the core period to 0.44 (95% CI: 0.38–0.51) in the extension period, a 90% reduction (rate ratio: 0.1; p<0.001; see **Figure S11).** Over the core plus extension period, the cumulative number of neT2 lesions in the OMB-OMB group was 83% lower than that in the TER-OMB group (n=1395 vs. n=8262; p<0.001; see **Figure S11).** For between-group comparisons, see **Figure S11.**

Whole brain volume change

PBVC remained low (<1.5% loss) up to 5 years in the OMB-OMB group, with statistically significant differences between the OMB-OMB group and TER-OMB group for each year (see **Figure S13).** Overall, ABVC remained low in the OMB-OMB group with −0.27% brain volume change (BVC) per year during the

extension period. A steeper decline was noted with TER-OMB versus OMB-OMB during the core period, while the annual rate became similar to OMB-OMB during the extension indicating a slowing of brain volume loss following switch to ofatumumab (see **Table S6**). The steeper slope during the switch period can be explained through the strong anti-inflammatory effect of ofatumumab, as shown by the>95% reduction in Gd+ T1 lesion activity, and the expected associated improvement in brain oedema, which could also be observed at the initial difference between groups in brain volume in the first year. This effect has been referred to as ‘pseudo-atrophy’. Early ofatumumab initiation in the OMB-OMB group resulted in statistically significantly lower cumulative PBVC at Year 5 versus the TER-OMB group.

Supplementary Tables

Table S1. Baseline demographics and clinical characteristics (safety analysis set)

	Continuous ofatumumab group (N=1292)	Newly switched ofatumumab group† (N=677)	
		Baseline from core period	Baseline from extension period
Age, years (mean±SD)	38.0±9.06	38.2±9.22	40.1±9.21
BMI, kg/m^2	25.61±6.16	25.69±5.83	25.61±5.85
Female, n (%)	889 (68.8)	456 (67.4)	456 (67.4)
Time since MS symptom onset, years (mean±SD)	8.48±7.33	8.06±7.21	9.94±7.23
Time since diagnosis, years (mean±SD)	5.87±6.31	5.45±6.00	7.33±6.01
EDSS score at baseline, (mean±SD)	2.90±1.33	2.77±1.32	2.82±1.46
IgG levels at baseline, g/L (mean±SD)	10.31±2.24	10.35±2.09	10.23±2.14
IgM levels at baseline, g/L (mean±SD)	1.34±0.65	1.36±0.74	1.14±0.67

Data from the safety analysis set.

†Patients who completed treatment with teriflunomide in the core period were switched to ofatumumab in the open-label extension period.

BMI, body mass index; EDSS, Expanded Disability Status Scale; Ig, immunoglobulin; MS, multiple sclerosis; SD, standard deviation.

Table S2. Compliance to study treatment (safety analysis set)

Compliance to the study treatment	**Overall ofatumumab N=1969**
Summary, %	
Mean	95.97
Q1	96.13
Median	98.95
Q3	100
Categories, n (%)	
=100%	25.5
≥98%	58.3
≥95%	79.5
≥90%	88.8
≥80%	94.9
≥70%	97.8
≥60%	99.0

Data from the safety analysis set. % compliance was calculated as duration of exposure (days)/duration of time on-treatment (days) × 100. Premature discontinuation from study drug was not considered to be non-compliance. Q1: first/lower quartile; Q3: third/upper quartile.

Table S3. Safety summary of patients who completed 5 years of treatment (safety analysis set)

Adverse event	Overall ofatumumab (N=406)[†]	
	n (%)	EAIR (95% CI)
Patients with at least one AE	389 (95.8)	122.72 [111.12–135.55]
Patients with at least one SAE	73 (17.98)	3.88 [3.09–4.89]
Infections and infestations	331 (81.53)	39.44 [35.41–43.92]
Serious infections	26 (6.40)	1.28 [0.87–1.89]
Serious infections (excluding COVID-19)	17 (4.19)	0.83 [0.52–1.34]
Serious COVID-19 infections	7 (1.72)	0.34 [0.16–0.71]
Malignancies	1 (0.25)	0.05 [0.01–0.34]

Preferred terms are according to MedDRA version 25.1.

Data from the safety analysis set.

[†]Data from both the core and open-label extension periods.

AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 patient-years); SAE, serious adverse event.

Table S4. Baseline demographics and clinical characteristics (efficacy analysis set[†])

	OMB-OMB	TER-OMB[†]	
	Baseline from core study (N=946)	**Baseline from core study (N=936)**	**Baseline from extension study (N=677)**
Age, years (mean±SD)	38.4±9.04	38.0±9.22	40.1±9.21
Age group, n (%)			
18 to 30 years	223 (23.6)	219 (23.4)	116 (17.1)
31 to 40 years	306 (32.3)	345 (36.9)	239 (35.3)
41 to 55 years	414 (43.8)	371 (39.6)	288 (42.5)
>55 years	3 (0.3)	1 (0.1)	34 (5.0)
Female, n (%)	637 (67.3)	636 (67.9)	456 (67.4)
BMI, kg/m^2 (mean±SD)	25.86±6.22	25.93±6.02	25.61±5.85
Treatment-naive patients[‡] n (%)	386 (40.8)	363 (38.8)	Not applicable[§]
EDSS score at baseline (mean±SD)	2.93±1.35	2.90±1.36	2.81±1.46[‖]
Number of relapses in the last 12 months prior to screening (mean±SD)	1.2±0.69	1.3±0.71	0.2±0.49[‖]
Number of Gd+ T1 lesions (mean±SD)	1.7±4.51	1.3±3.43	0.8±2.37[‖]
Total volume of T2 lesions, cm^3 (mean±SD)	13.72±13.80	12.55±13.81	Not available
Type of MS at study entry, n (%)			
RRMS	890 (94.1)	884 (94.4)	
SPMS	56 (5.9)	52 (5.6)	
Time since first MS symptom, years (mean±SD)	8.27±7.13	8.19±7.29	9.94±7.23
Time since MS diagnosis, years (mean±SD)	5.68±6.21	5.56±6.10	7.33±6.02

Data from the efficacy analysis set.

[†]Patients who completed treatment with teriflunomide in the core period were switched to ofatumumab in the open-label extension period.

[‡]Treatment-naive patients had not received a prior MS disease-modifying therapy.

[§]Not applicable as all patients had previously received teriflunomide.

[‖]It should be noted that the values at the baseline of the open-label extension period in the newly switched ofatumumab group reflect the teriflunomide treatment effect during the core period.

BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis; OMB-OMB, continuous ofatumumab; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; TER-OMB, switch from teriflunomide to ofatumumab.

Table S5. IgG/IgM-related treatment interruptions and discontinuations in the core and extension periods and overall safety population (safety analysis set)

		Core period	**Extension period**	**Overall ofatumumab**
		N=1292 **n (%)**	**N=1703** **n (%)**	**N=1969** **n (%)**
IgG	Either interruption or discontinuation	3 (0.2)	3 (0.2)	6 (0.3)
	Interruption†	1 (0.1)	2 (0.1)	3 (0.2)
	Discontinuation†	3 (0.2)	1 (0.1)	4 (0.2)
IgM	Either interruption or discontinuation	70 (5.4)	199 (11.7)	254 (12.9)
	Interruption†	46 (3.6)	170 (10.0)	202 (10.3)
	Discontinuation†	4 (2.1)	44 (2.6)	71 (3.6)

Data from the safety analysis set.

†Patients with interruption and discontinuation have been included in both categories.

IgG, immunoglobulin G; IgM, immunoglobulin M.

Table S6. Annual rate of brain volume change (efficacy analysis set)

Whole brain volume change	Core period		Open-label extension period	
	%	*p* value‡	%	*p* value‡
OMB-OMB	−0.34	0.11	−0.27	0.64
TER-OMB†	−0.42		−0.28	

Data from the efficacy analysis set.

All ABVC estimates are obtained from a random coefficient model with treatment, time period (core vs. extension) and region as factors, time; baseline number of Gd+ T1 lesions, baseline T2 volume, and baseline normalised brain volume as continuous covariates; the three-way interaction (treatment group by time period by time); and all its associated two-way interactions. ABVC was estimated from all post-baseline MRI scans for the core and extension periods.

†Patients who completed treatment with teriflunomide in the core period were switched to ofatumumab in the open-label extension period.

‡Between-group comparison for ABVC.

ABVC, annual rate of brain volume change; Gd+, gadolinium-enhancing; OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab.

Table S7. Incidence of injection systemic and injection site reactions by severity (safety analysis set)

	Continuous ofatumumab group (N=1292)	**Newly switched ofatumumab group (N=677)**	**Overall ofatumumab (N=1969)**
Injection systemic reaction, n (%)			
Grade 1	237 (18.3)	109 (16.1)	346 (17.6)
Grade 2	100 (7.7)	51 (7.5)	151 (7.7)
Grade 3	4 (0.3)	0 (0)	4 (0.2)
Missing	0	1 (0.1)	1 (0.1)
Injection site reaction, n/M (%)			
Grade 1	158 (12.2)	50 (7.4)	208 (10.6)
Grade 2	23 (1.8)	11 (1.6)	34 (1.7)
Grade 3	1 (0.1)	0 (0)	1 (0.1)

For injection systemic reactions, only reactions/symptoms within 24 hours after injections are included (i.e. time to onset of reaction was ≤24 hours).

Table S8. Summary of lymphocytes or neutrophils below different cut-off values as per CTCAE grades at least once or consecutively twice post-baseline (safety analysis set)

CTCAE Grade (Cut-off [×10^9/L])	**Time-point**	**Continuous ofatumumab N=1292 n/M (%)**	**Newly switched ofatumumab N=677 n/M (%)**	**Overall ofatumumab N=1969 n/M (%)**
Lymphocytes				
Grade ≥1 (<0.91)	At least once post-baseline	310/1290 (24.0)	85/675 (12.6)	395/1965 (20.1)
	Consecutively twice post-baseline	98/1290 (7.6)	23/675 (3.4)	121/1965 (6.2)
Grade ≥2 (<0.8)	At least once post-baseline	138/1290 (10.7)	45/675 (6.7)	183/1965 (9.3)
	Consecutively twice post-baseline	27/1290 (2.1)	7/675 (1.0)	34/1965 (1.7)
Grade ≥3 (<0.5)	At least once post-baseline	19/1290 (1.5)	5/675 (0.7)	24/1965 (1.2)
	Consecutively twice post-baseline	0	1/675 (0.1)	1/1965 (0.1)
Grade ≥4 (<0.2)	At least once post-baseline	1/1290 (0.1)	0	1/1965 (0.1)
	Consecutively twice post-baseline	0	0	0
Neutrophils				
Grade ≥1 (<1.96)	At least once post-baseline	259/1290 (20.1)	60/675 (8.9)	319/1965 (16.2)
	Consecutively twice post-baseline	64/1290 (5.0)	12/675 (1.8)	76/1965 (3.9)
Grade ≥2 (<1.5)	At least once post-baseline	78/1290 (6.0)	13/675 (1.9)	91/1965 (4.6)
	Consecutively twice post-baseline	5/1290 (0.4)	2/675 (0.3)	7/1965 (0.4)

Grade ≥3 (<1.0)	At least once post-baseline	22/1290 (1.7)	1/675 (0.1)	23/1965 (1.2)
	Consecutively twice post-baseline	0	1/675 (0.1)	1/1965 (0.1)
Grade ≥4 (<0.5)	At least once post-baseline	6/1290 (0.5)	0	6/1965 (0.3)
	Consecutively twice post-baseline	0	0	0

Assessments from the first dose of ofatumumab, up to and including last dose + 100 days are included.

CTCAE, Common Terminology Criteria for Adverse Events; N, the total number of patients in the treatment group; n. number of patients who are at the corresponding category; M, number of patients with non-missing baseline and at least one not missing post baseline value for the parameter.

Table S9. COVID-19 AEs by vaccination status (safety analysis set)

Characteristic[†]	Confirmed COVID-19 before completing the primary vaccine series N=338[‡]	Confirmed COVID-19 after completing the primary vaccine series but before booster N=167[§]	Confirmed COVID-19 after booster dose 1 but before additional boosters N=109[‖]	Confirmed COVID-19 after booster dose 2 N=12[‖]	Confirmed COVID-19 after booster dose ≥3 N=1[‖]
Covid AE serious, n (%)					
Yes	31 (9.2)	14 (8.4)	3 (2.8)	1 (8.3)	0 (0)
No	307 (90.8)	153 (91.6)	106 (97.2)	11 (91.7)	1 (100)
Covid maximum severity, n (%)					
Grade 1	151 (44.7)	75 (44.9)	68 (62.4)	5 (41.7)	1 (100)
Grade 2	162 (47.9)	84 (50.3)	39 (35.8)	6 (50.0)	0
Grade 3	22 (6.5)	5 (3.0)	2 (1.8)	1 (8.3)	0
Grade 4	3 (0.9)	3 (1.8)	0	0	0

[†]For patients with confirmed COVID-19 AEs after a given vaccination status, only COVID-19–related AEs where the onset date has that specific vaccination status are considered.

[‡]A patient is considered to have confirmed COVID-19 before completing the primary vaccine series if the patient has at least one COVID-19 AE where the vaccination status at the AE start date is either partial or not vaccinated.

[§]A patient is considered to have confirmed COVID-19 after completing the primary vaccination series but before booster if the patient has at least one confirmed COVID-19 AE where the AE start date is ≥ 14 days after completing the recommended doses in a primary COVID-19 vaccine series (e.g. two doses of Pfizer vaccine) but before any booster dose. (For patients with unknown COVID-19 vaccines, if they had at least another dose (either known or unknown), then they are considered to have completed the primary series 14 days after the second dose.

[‖]A patient is considered to have confirmed COVID-19 after booster dose if the patient has at least one confirmed COVID-19 AE where the vaccination status at the AE start date is vaccinated with booster dose.

AE, adverse event.

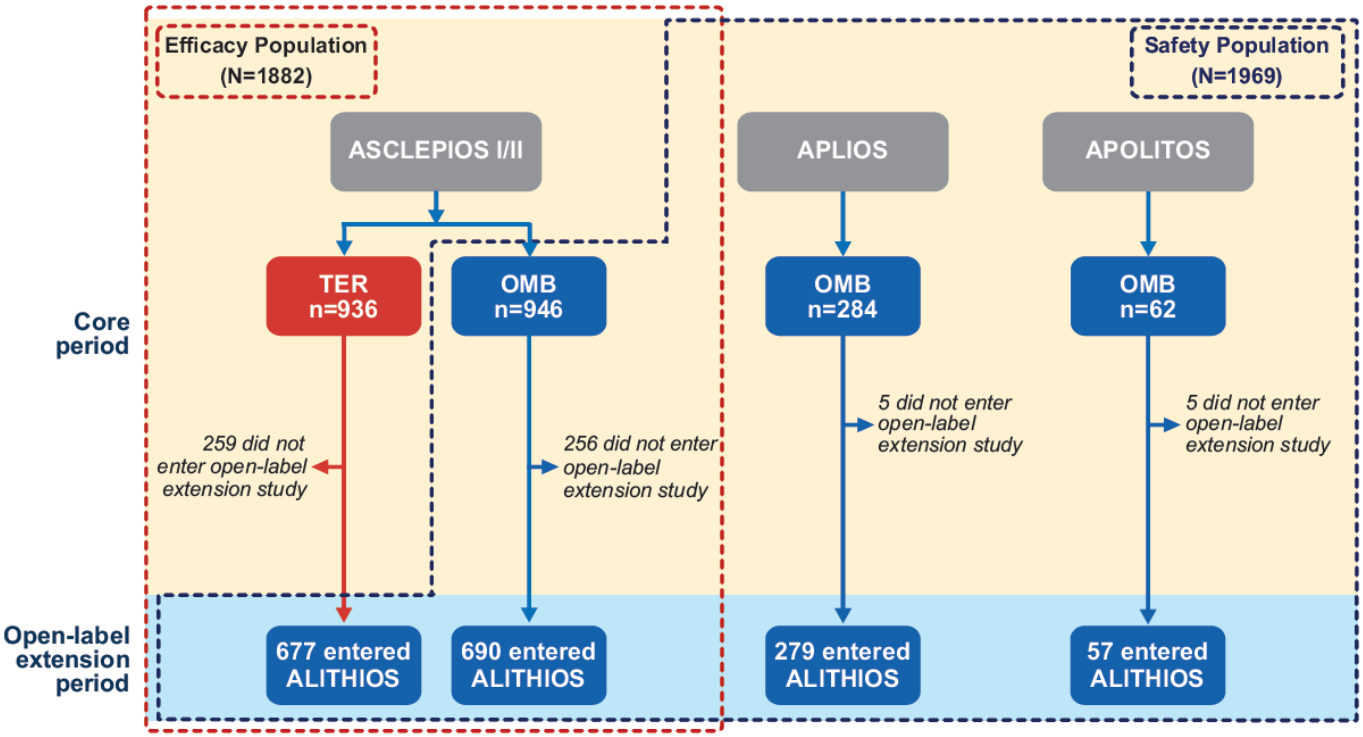
Table S10. COVID-19 anti-RBD IgG concentration across subgroups (safety analysis set)

	Anti-RBD IgG concentration (BAU/mL)	
	Geometric mean±SD	**Median (Range: min–max)**
COVID-19 infection only (n=76)	8.19±7.57	5.82 (1.0–6159.9)
Fully vaccinated only (n=181)	6.43±7.86	4.49 (1.0–1503.3)
Booster vaccination only (n=93)	17.54±10.57	23.69 (1.0–5657.6)
COVID-19 after full vaccination (n=82)	17.82±10.89	16.33 (1.0–6059.8)

BAU, binding antibody units; IgG, immunoglobulin G; RBD, receptor-binding domain; SD, standard deviation.

Supplementary Figures

Figure S1. Analysis sets and time periods

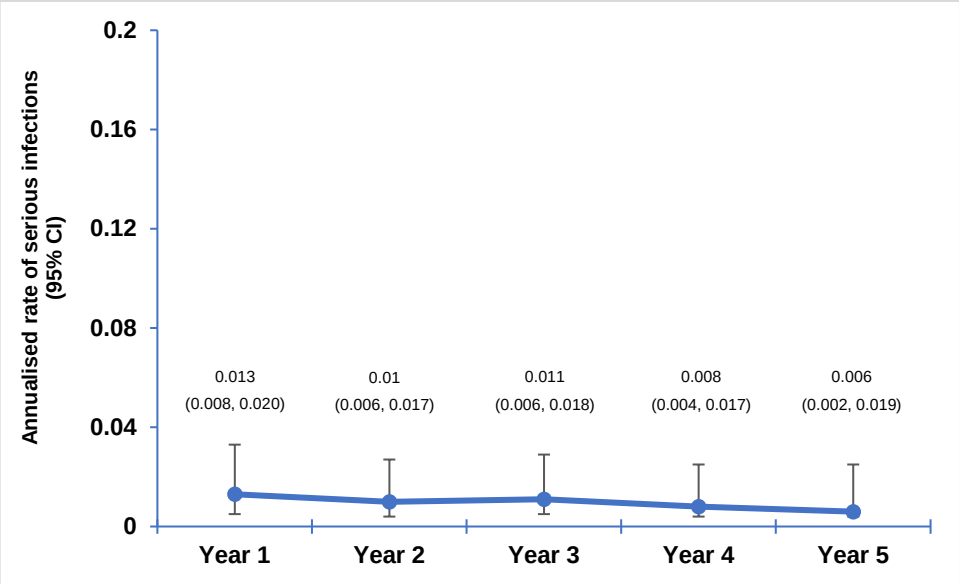


All patients who completed study treatment in the core period were eligible to enter ALITHIOS but could withdraw prior to treatment. For efficacy analyses, the OMB-OMB group included patients randomised to receive ofatumumab in ASCLEPIOS I/II, and the TER-OMB group consisted of patients randomised to receive teriflunomide in ASCLEPIOS I/II, regardless of whether or not they entered ALITHIOS. The safety analyses included patients who received at least one dose of ofatumumab in ASCLEPIOS I/II, APLIOS, APOLITOS or ALITHIOS including those who completed or discontinued ofatumumab during these trials: the continuous ofatumumab group includes those who received the first dose of ofatumumab in ASCLEPIOS I/II, APLIOS or APOLITOS and the newly switched ofatumumab group includes those who were randomised to teriflunomide in ASCLEPIOS I/II and were switched to ofatumumab in ALITHIOS.

OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

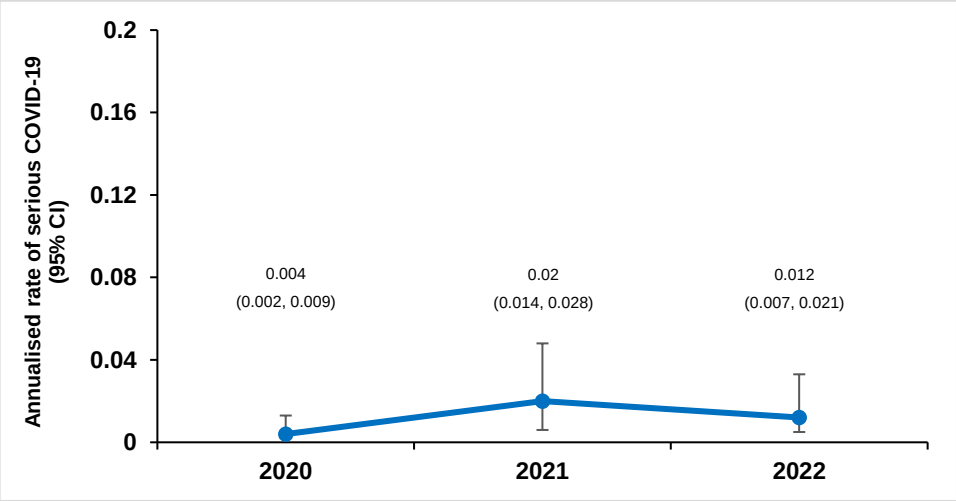
Figure S2. (A) Annualised rates of serious infections (excluding COVID-19); (B) Annualised rate of serious COVID-19 cases (safety analysis set)

(A)



Number of participants	1969	1812	1618	1381	615

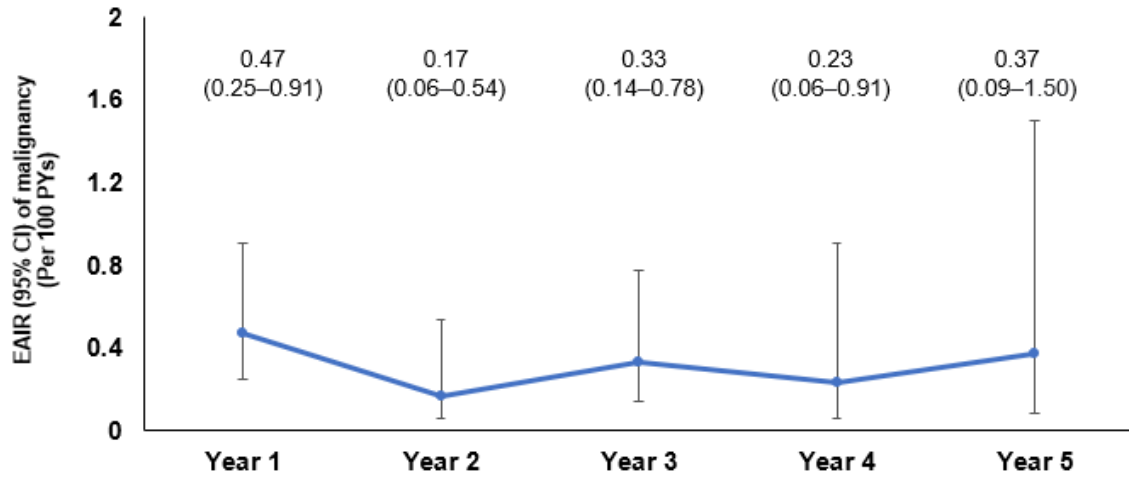
(B)



Number of participants	1669	1562	1472

CI, confidence interval

Figure S3. EAIR of malignancy over time (safety analysis set)



Patients (N)	**1969**	**1812**	**1618**	**1381**	**615**
PYs	**1901**	**1719**	**1531**	**877**	**535**
No. of events	**9**	**3**	**5**	**2**	**2**

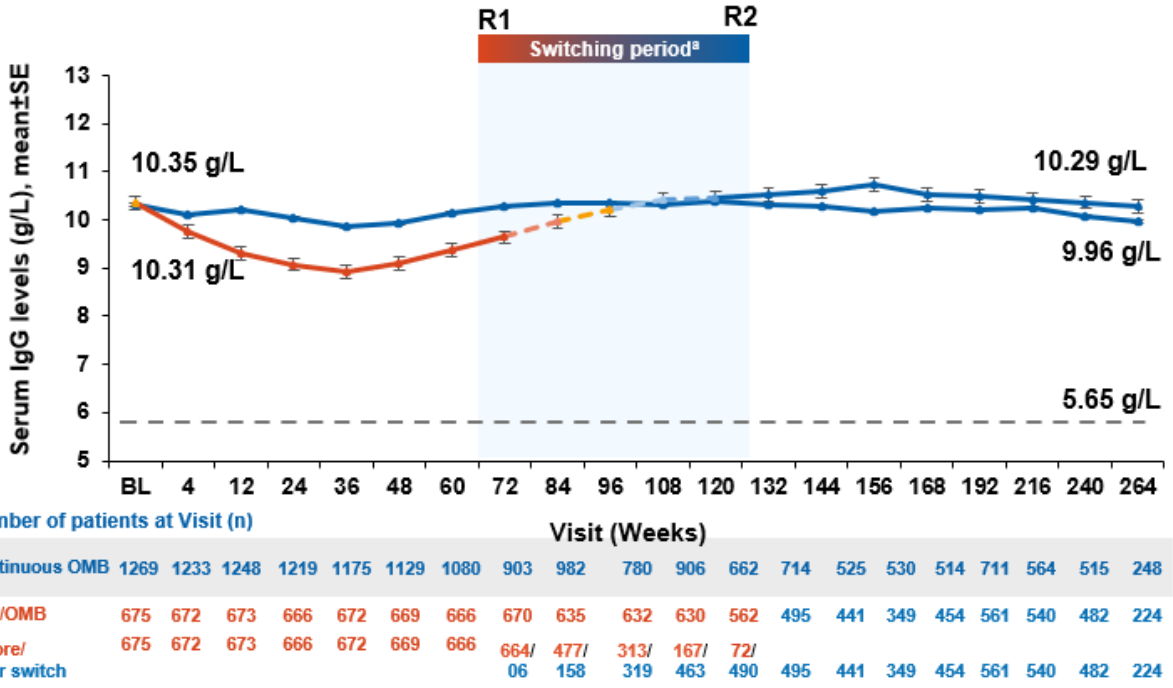
Twenty-one malignancies include breast and nipple neoplasms malignant (n=9); colorectal neoplasms malignant (n=1); metastases to specified sites (n=1); oesophageal neoplasms malignant (n=1); neoplasms malignant site unspecified NEC (n=1); non-Hodgkin's lymphomas NEC (n=1); ovarian neoplasms malignant (excluding germ cell) (n=1); renal neoplasms malignant (n=2); skin melanomas (excl. ocular) (n=1); skin neoplasms malignant and unspecified (excluding melanoma) (n=4). n, is the number of patients, and a patient can have >1 malignancy at a time.

CI, confidence interval; EAIR, exposure-adjusted incidence rate; N, number of patients; NEC, not elsewhere classifiable; PY, patient-year.

Figure S4. Serum Ig levels over time with up to 5 years of ofatumumab treatment:

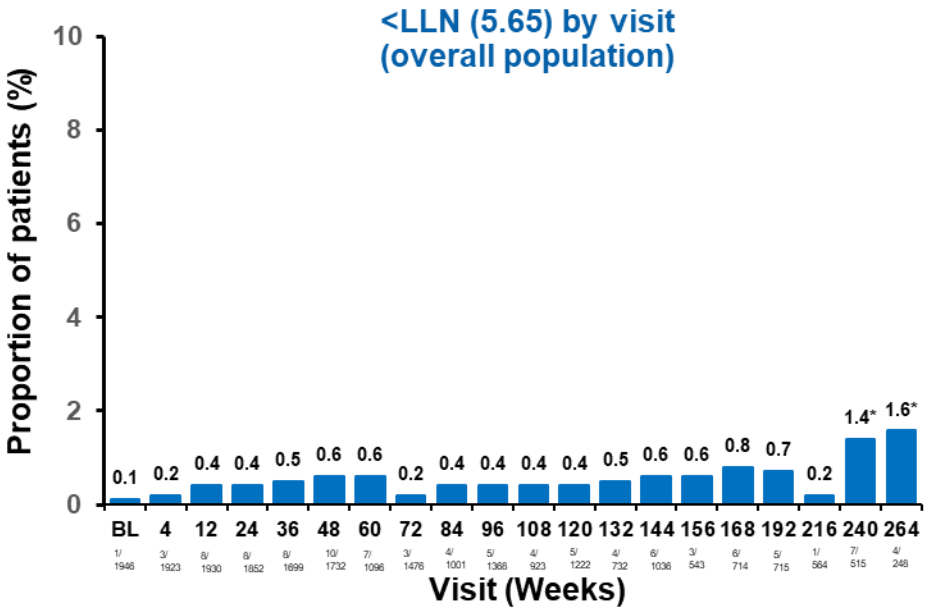
A) Mean IgG levels with ofatumumab treatment; B) Proportion of patients with IgG below the LLN by visit; C) IgG levels by sensitivity analysis (± LOCF imputation) for treatment interruption; D) Mean IgM levels with ofatumumab treatment; E) Proportion of patients with IgM below the LLN by visit; F) IgM levels by sensitivity analysis (± LOCF imputation) for treatment interruption (safety analysis set)

(A)

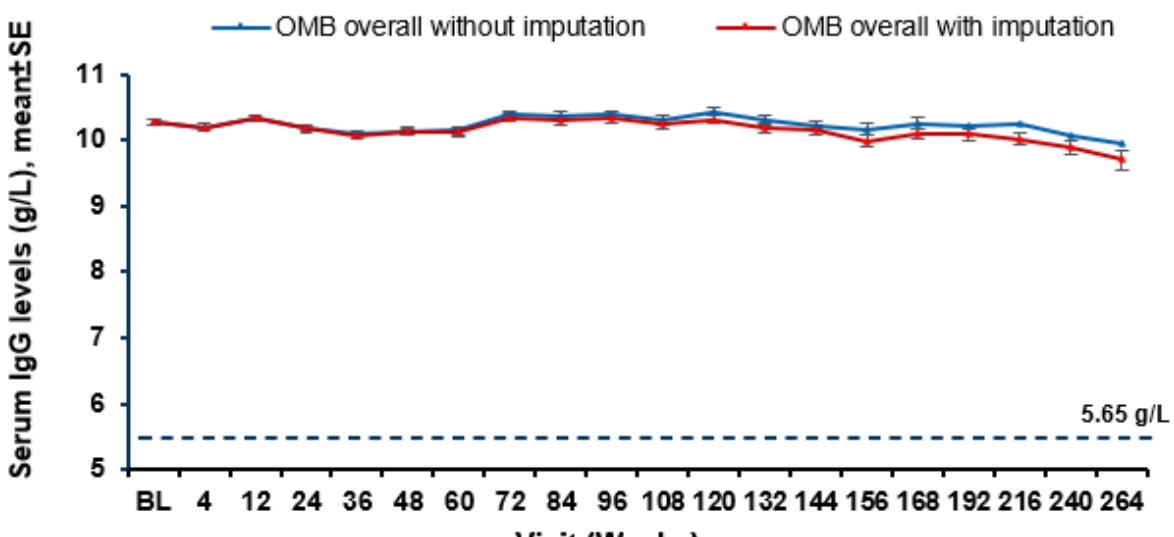


Number of patients at Visit (n)	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168	192	216	240	264
Continuous OMB	1269	1233	1248	1219	1175	1129	1080	903	982	780	906	662	714	525	530	514	711	564	515	248
TER/OMB	675	672	673	666	672	669	666	670	635	632	630	562	495	441	349	454	561	540	482	224
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 319	167/ 463	72/ 490	495	441	349	454	561	540	482	224

(B)



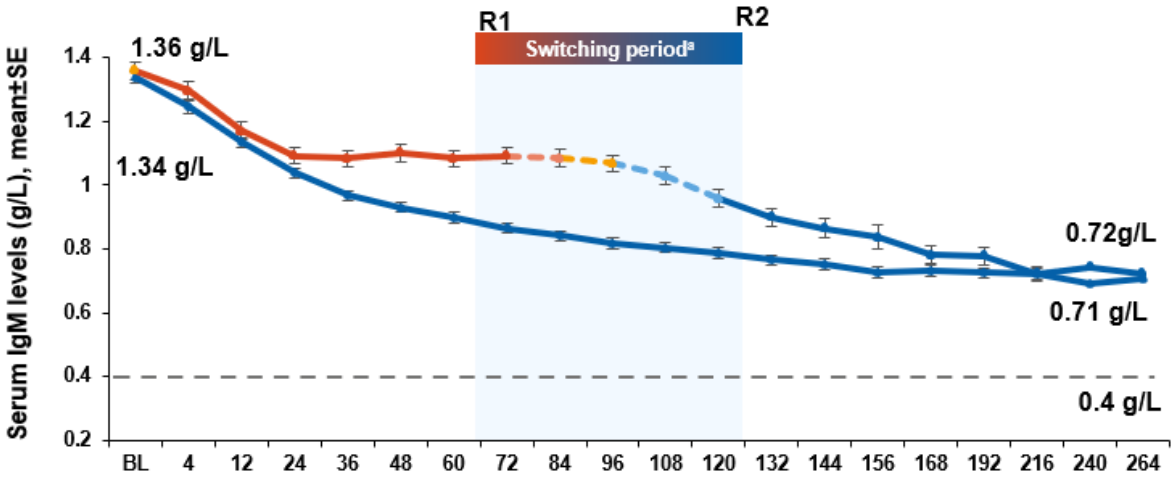
(C)



Number of patients at visit (n)

No imputation	1946	1901	1907	1828	1679	1716	1080	1466	982	1364	906	1218	714	1032	530	712	711	564	515	248
With imputation	1946	1901	1907	1828	1679	1716	1080	1467	983	1365	907	1221	717	1035	533	715	714	567	518	251

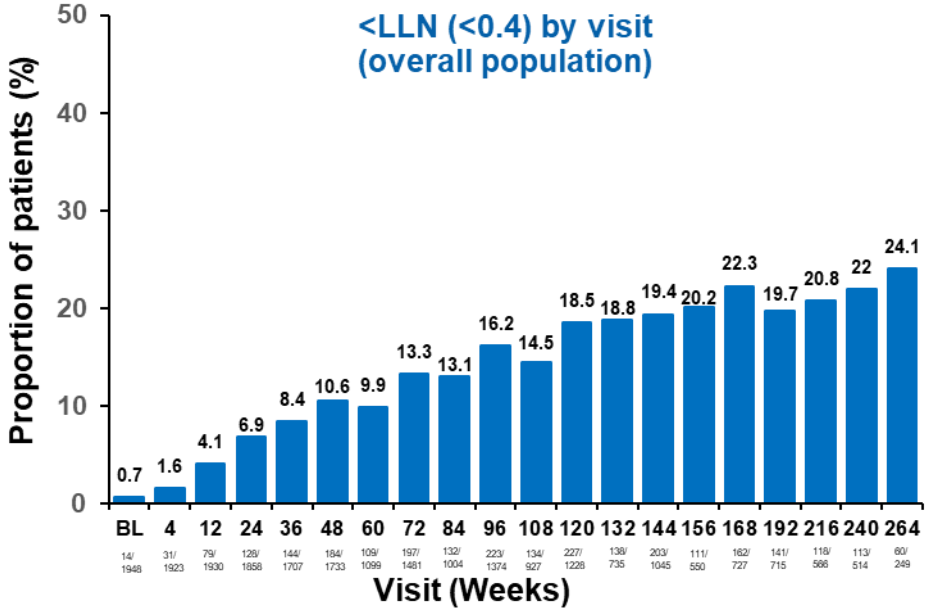
(D)



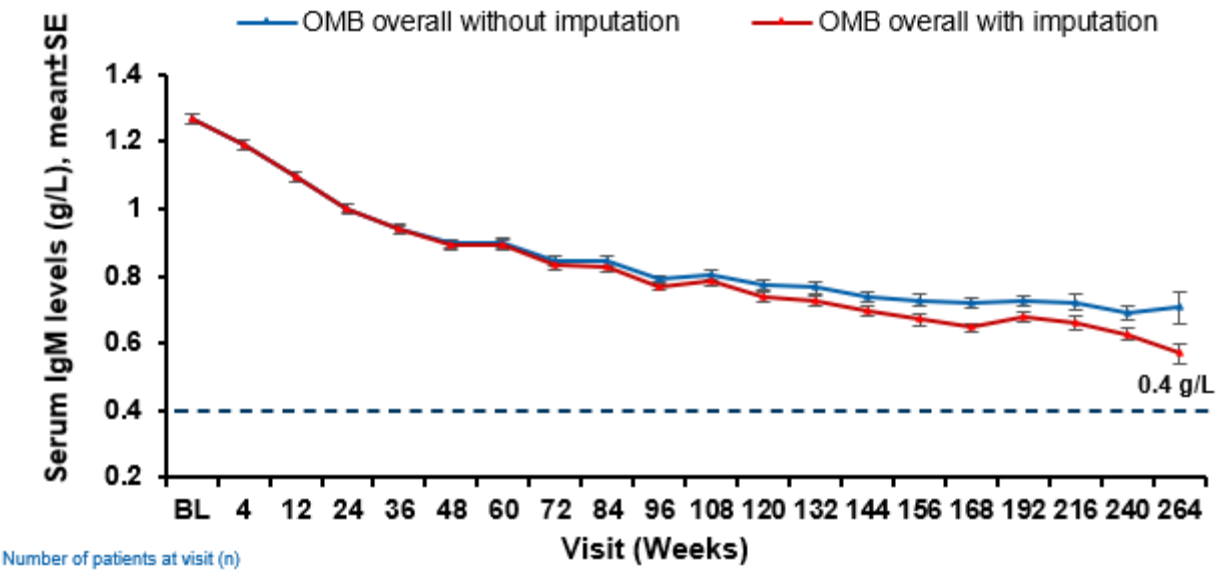
Number of patients at Visit (n)

Continuous OMB	1271	1235	1250	1221	1181	1131	1085	906	986	789	910	669	719	534	538	525	711	566	514	249
TER/OMB	675	672	673	666	672	669	666	670	635	633	632	563	502	445	358	456	563	539	483	225
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 320	167/ 465	72/ 491	502	445	358	456	563	539	483	225

(E)



(F)



Number of patients at visit (n)

No imputation	1948	1903	1909	1835	1686	1719	1085	1469	986	1372	910	1225	719	1041	538	725	711	566	514	249
With imputation	1948	1903	1909	1837	1692	1727	1095	1502	1015	1428	947	1307	785	1151	625	881	796	669	622	395

Data are from the safety analysis set.

Figures show mean level; error bars represent ± standard error of the mean.

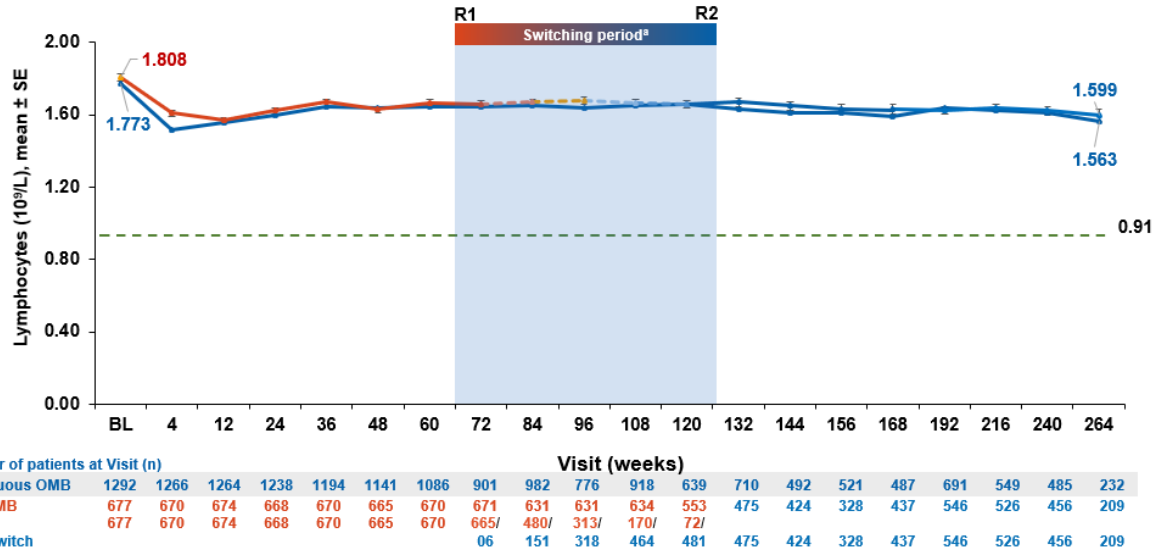
[a]Switching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period. For teriflunomide-ofatumumab switch group, data from first dose of teriflunomide until last dose of ofatumumab plus 100 days/analyses cut-off date have been used; R1: The first patient with first treatment-emergent assessment in ofatumumab period after switching to ofatumumab (72 weeks); R2: The last patient 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.

*Data based on the overall safety population with only data from the first dose of ofatumumab included.

BL, baseline; IgG, immunoglobulin; IgM, immunoglobulin M; OMB, ofatumumab; LLN, lower limit of normal; LOCF, last observation carried forward; SE, standard error of the mean.

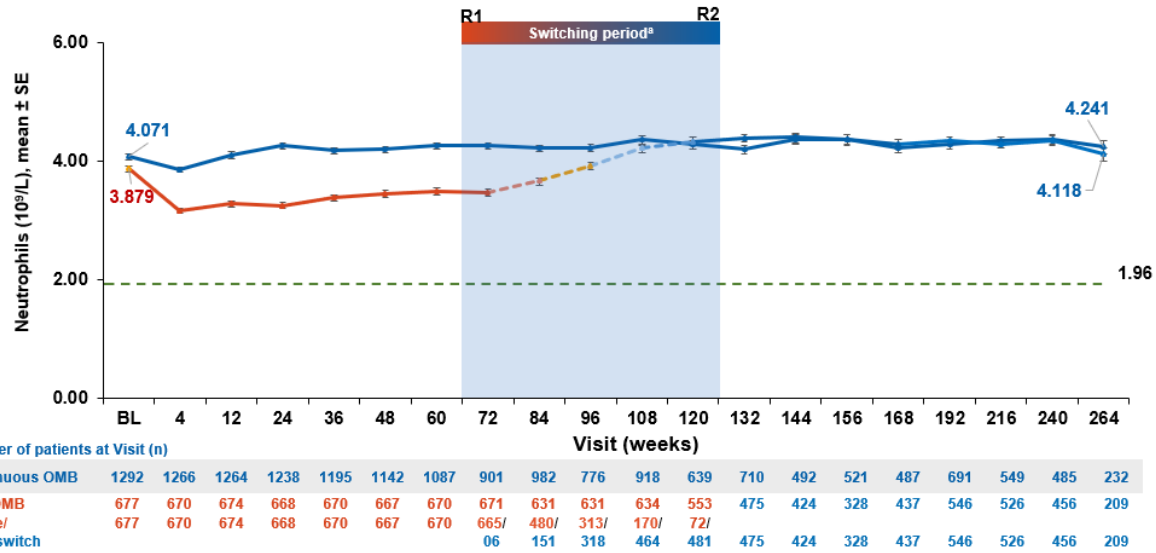
Figure S5. (A) Lymphocyte levels over time with up to 5 years of ofatumumab treatment; (B) Neutrophil levels over time with up to 5 years of ofatumumab treatment (safety analysis set)

(A)



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
Continuous OMB	1292	1266	1264	1238	1194	1141	1086	901	982	776	918	639	710	492	521	487	691	549	485	232
TER/OMB	677	670	674	668	670	665	670	671	631	631	634	553	475	424	328	437	546	526	456	209
Before/	677	670	674	668	670	665	670	665/	480/	313/	170/	72/								
After switch								06	151	318	464	481	475	424	328	437	546	526	456	209

(B)

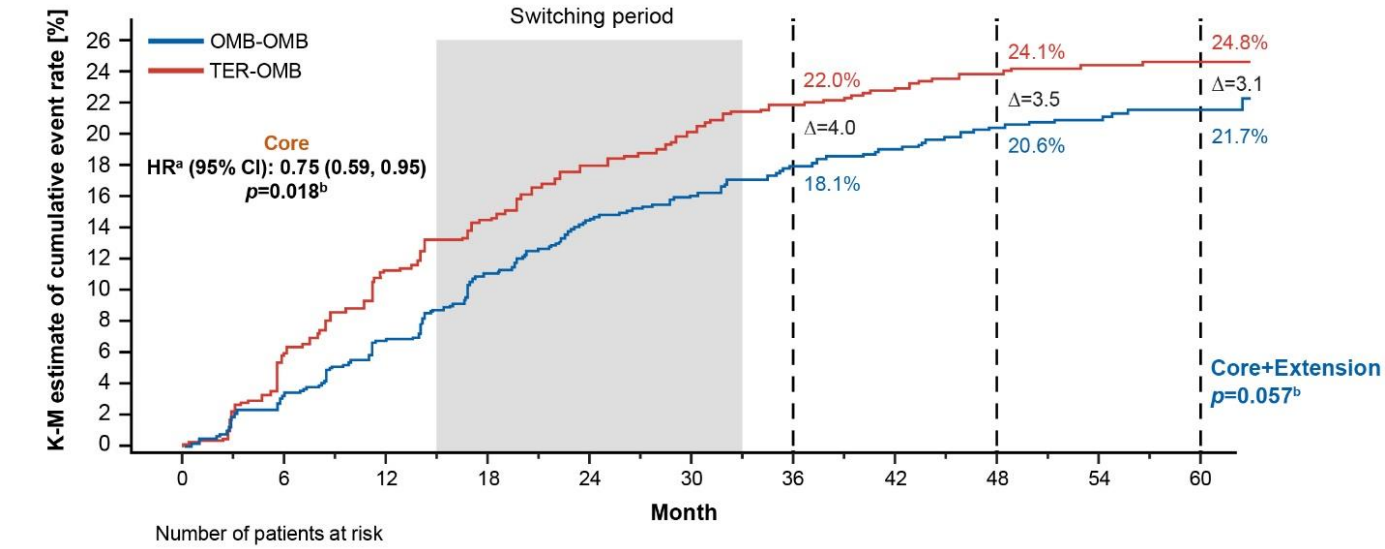


Number of patients at Visit (n)	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168	192	216	240	264
Continuous OMB	1292	1266	1264	1238	1195	1142	1087	901	982	776	918	639	710	492	521	487	691	549	485	232
TER/OMB	677	670	674	668	670	667	670	671	631	631	634	553	475	424	328	437	546	526	456	209
Before/	677	670	674	668	670	667	670	665/	480/	313/	170/	72/								
After switch								06	151	318	464	481	475	424	328	437	546	526	456	209

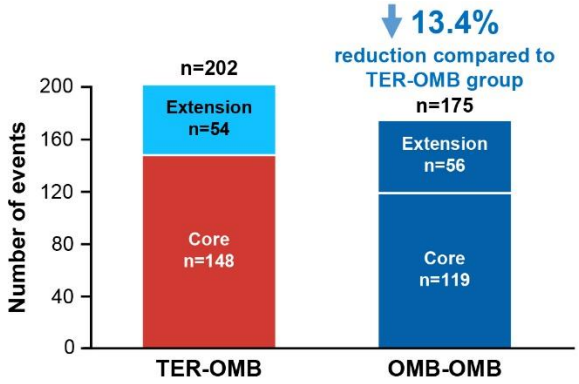
[a]Switching period refers to the participants started on teriflunomide and not applicable to the participants on ofatumumab in the core phase. For the teriflunomide-ofatumumab switch group, data from the first dose of teriflunomide until the last dose of ofatumumab plus 100 days or analysis cutoff date 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.

Figure S6. 3-month confirmed disability worsening (3mCDW): (A) Kaplan–Meier estimates of cumulative 3mCDW event rates; (B) cumulative number of 3mCDW events (efficacy analysis set)

(A)



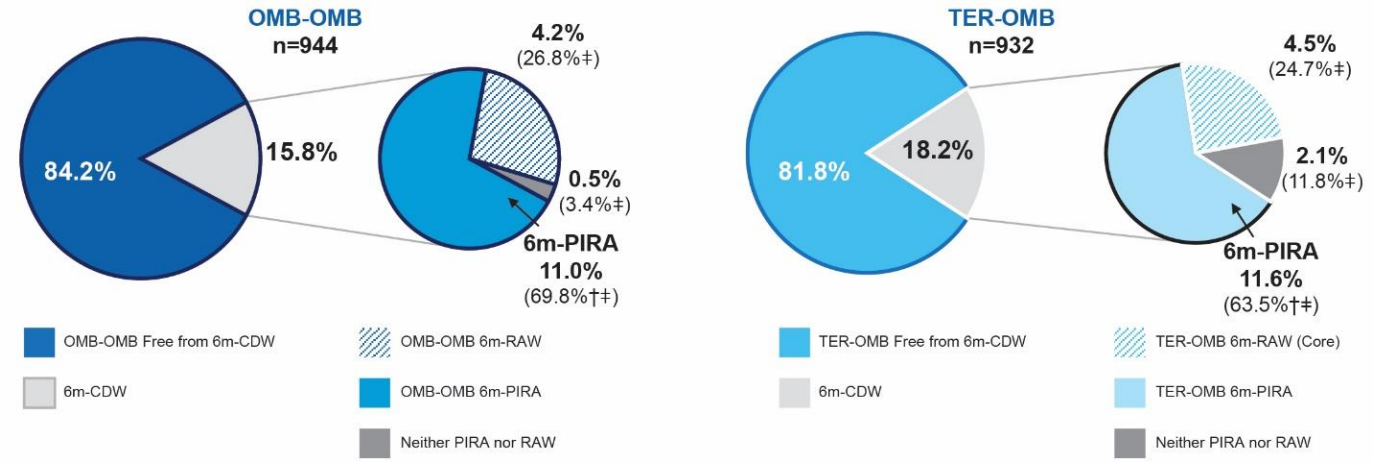
(B)



Data are from the efficacy analysis set. Superior efficacy of ofatumumab in the core period was established previously versus teriflunomide (for more information, refer to Hauser, et al.[11]). Cutoff for the core and open-label extension periods was based on the first dose of ofatumumab in the open-label extension period. 'Difference' refers to the difference in KM estimates (TER-OMB group minus OMB-OMB group). [a]HR determined by Cox regression model. [b]*p* value is a log-rank test.

3mCDW, 3-month confirmed disability worsening; HR, hazard ratio; KM, Kaplan–Meier; OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab.

Figure S7. Proportion of 6m-CDW: 6mPIRA and 6mRAW (overall)



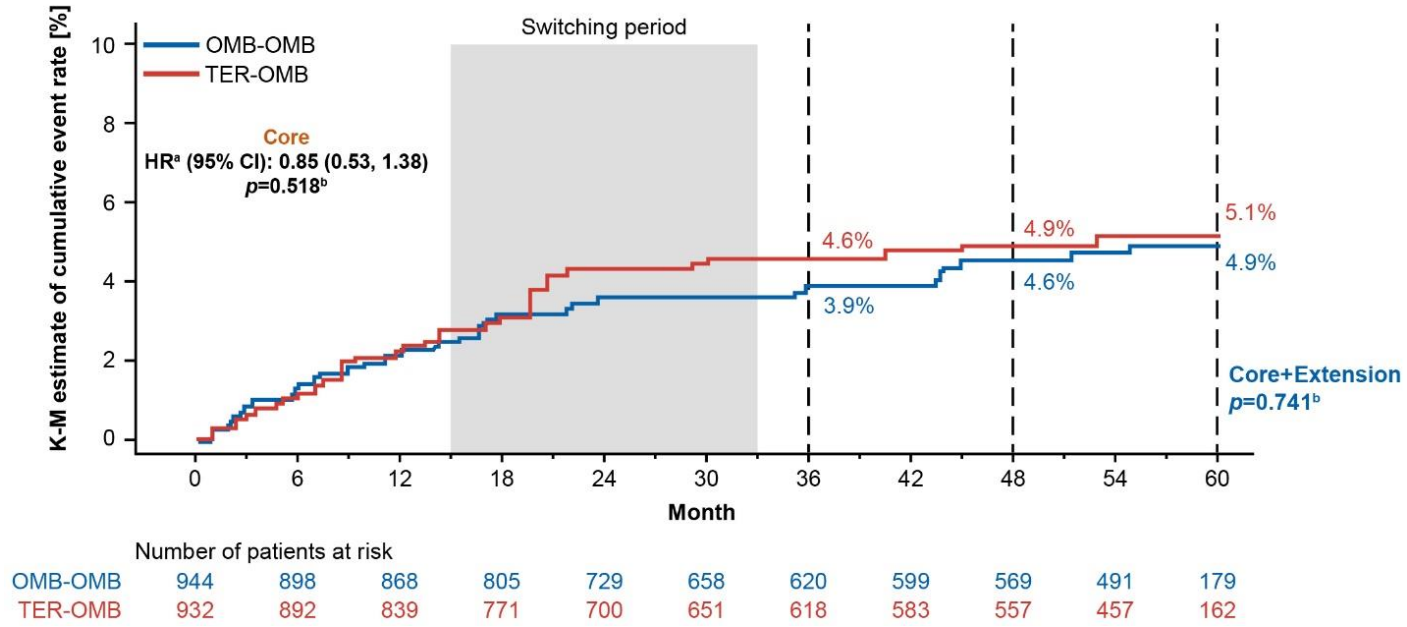
Primary pie chart details the proportion free from 6mCDW and proportion of 6mCDW events. Expanded pie chart details the proportion of 6mCDW events, 6mPIRA, and 6mRAW shown as a proportion of total number of 6m-CDW events. Neither refers to events not attributed to 6m-PIRA or 6m-RAW.

†The inset patterned segments represent the proportion classified as sustained 6mPIRA and form subsegment of the PIRA segments.

‡Values in brackets are the proportion of events relative to all 6mCDW.

6mCDW, 6-month confirmed disability worsening; 6mPIRA, 6-month confirmed progression independent of relapse activity; 6mRAW, 6-month confirmed relapse-associated worsening; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Figure S8. 6-month confirmed relapse-associated disability worsening (6m-RAW): Kaplan–Meier estimates of cumulative 6mRAW event rates (efficacy analysis set)

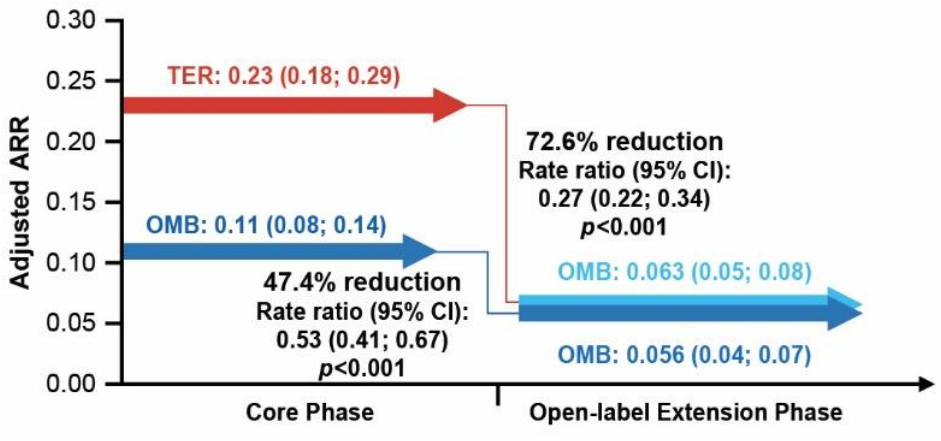


Switching period starts at the minimum switch-day and ends at the maximum switch-day among subjects in the TER-OMB group, where for each subject, switch-day is the day of the first dose of ofatumumab relative to treatment start date of the core studies. Patients with baseline Total EDSS scores 0, 1, and 1.5 are excluded from analyses as no disability improvement is possible for these patients. [a]HR determined by Cox regression model. [b]*p* value is a log-rank test.

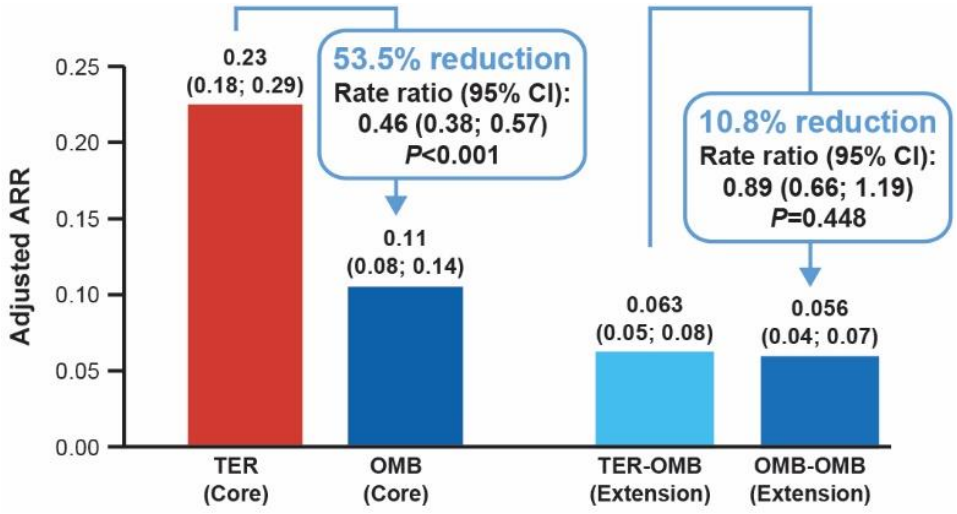
6mRAW, 6-month confirmed relapse-associated worsening; EDSS, Expanded Disability Status Scale; HR, hazard ratio; KM, Kaplan–Meier; OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab.

Figure S9. Annualised relapse rate (A) within-group comparison between the core and extension phase (OMB-OMB and TER-OMB groups); (B) ARR between-group comparison between the core and extension periods; (C) comparison of total confirmed relapses up to 5 years in the TER-OMB group and OMB-OMB group (efficacy analysis set)

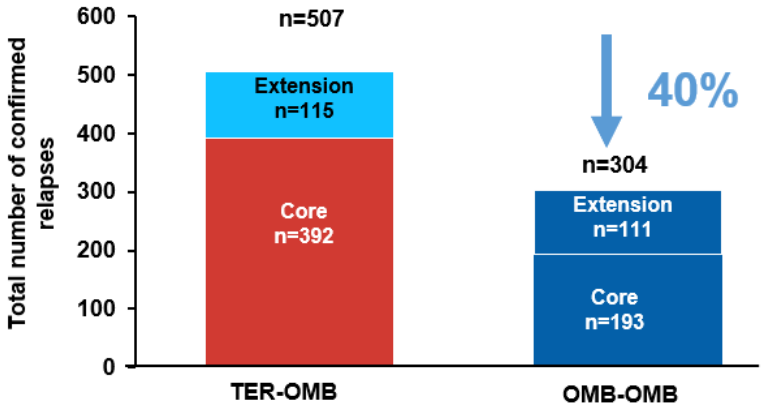
(A)



(B)



(C)

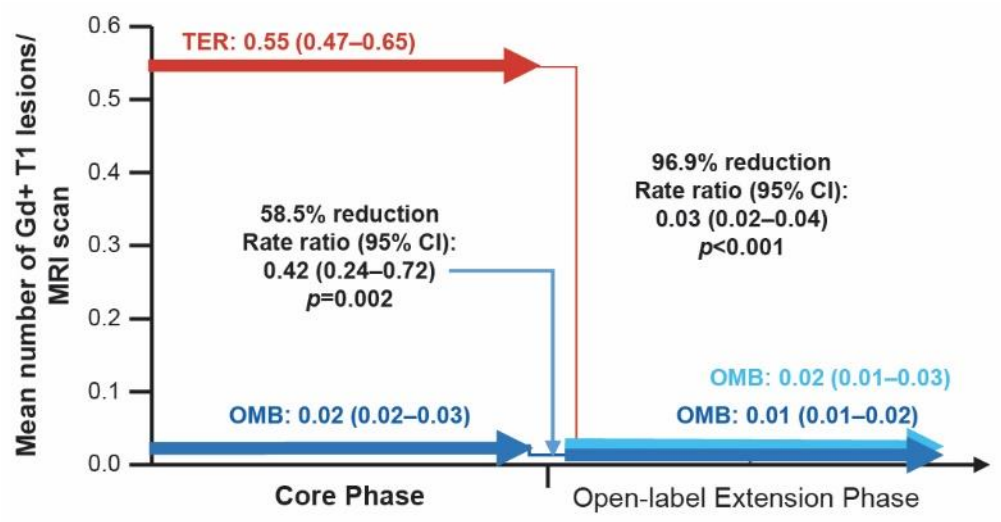


Patient numbers at corresponding years for ARR may differ due to missing covariates. Obtained from fitting a piecewise negative binomial model for the time period (core phase and extension phase) with log link, adjusted for treatment and region as factors, and number of relapses in previous year, baseline EDSS, baseline number of Gd+ T1 lesions, and the patient's age at baseline as covariates. The natural log of the time-in-study (in years) by visit is used as offset to annualise the relapse rate at each visit. Baseline variables are from the core study baseline. The between-group comparison was 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, number of relapses in previous year, baseline EDSS, baseline number of Gd+ T1 lesions, and the patient's age at baseline as covariates. The natural log of the time-in-study (in years) by visit is used as offset to annualise the relapse rate at each visit. Baseline variables are from the core study baseline. All *p* values are nominal *p* values.

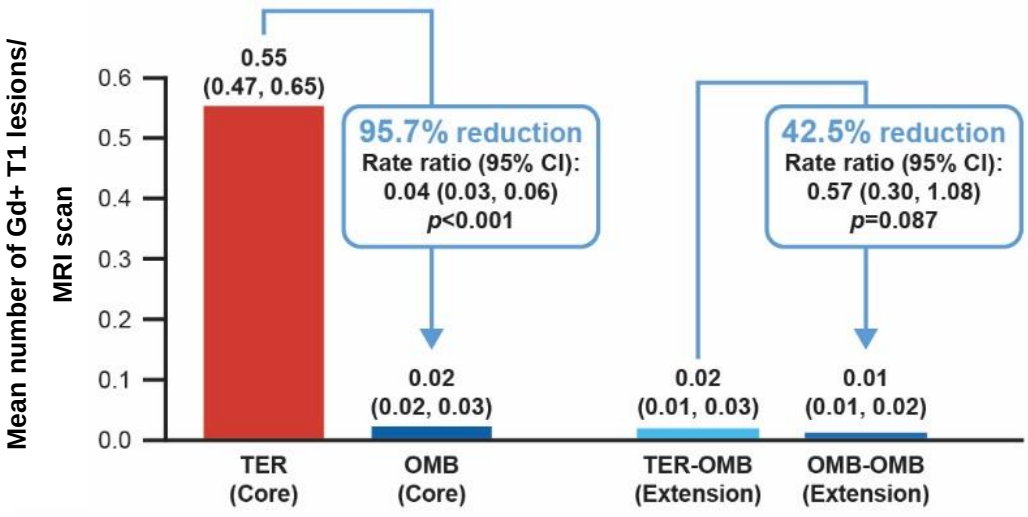
ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, month; OMB, ofatumumab; n, number of patients; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Figure S10. Mean number of Gd+ T1 lesions in the core and extension periods: (A) within-group comparison between the core and extension periods (OMB-OMB and TER-OMB group); (B) between-group comparison between the core and extension periods (OMB-OMB and TER-OMB groups); (C) cumulative number of Gd+ T1 lesions during the core and extension periods (efficacy analysis set)

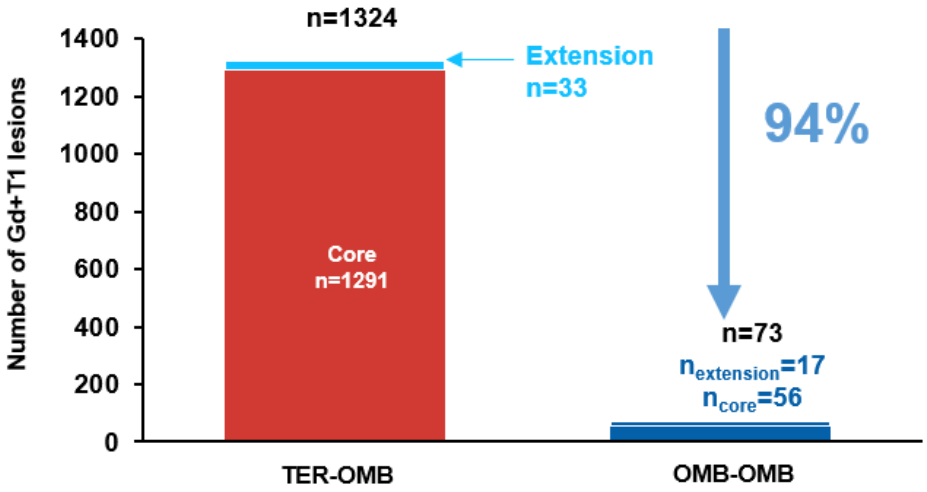
(A)



(B)



(C)

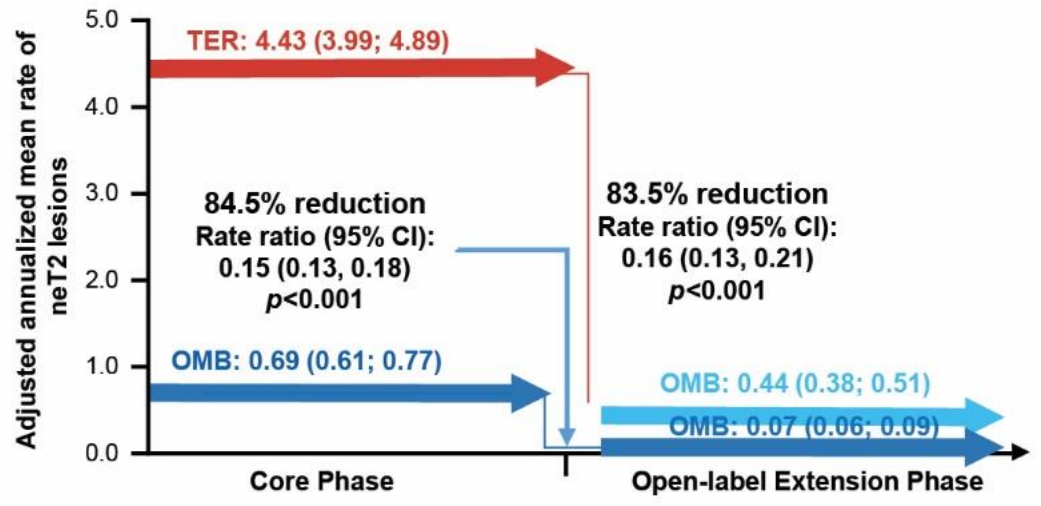


Data are from the efficacy analysis set. Patient numbers at corresponding years for Gd+ T1 lesions may differ due to missing covariates and post-baseline MRI visits. Estimated from fitting a piecewise negative binomial model for core and extension periods with log link, adjusted for treatment and region as factors, and baseline number of Gd+ T1 lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable Gd+ T1 lesion counts by visit is used as offset to obtain the lesion rate per scan at each visit. Baseline variables are from the core study baseline. The between-group comparison was estimated 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 baseline number of Gd+ T1 lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable Gd+ T1 lesion counts by visit is used as offset to obtain the lesion rate per scan at each visit. Variables are from the core study baseline. All p values are nominal p values.

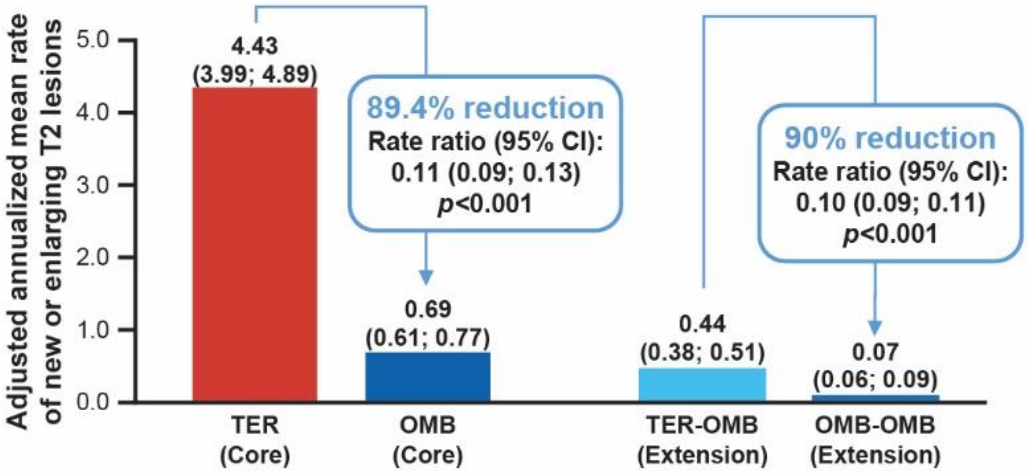
CI, confidence interval; Gd+, gadolinium-enhancing; n, number of patients; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; MRI, magnetic resonance imaging; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Figure S11. Mean number of neT2 lesions in the core and extension periods: (A) within-group comparison between the core and extension periods (OMB-OMB and TER-OMB group); (B) between-group comparison between the core and extension periods (OMB-OMB and TER-OMB groups); (C) cumulative number of neT2 lesions during the core and extension periods (efficacy analysis set)

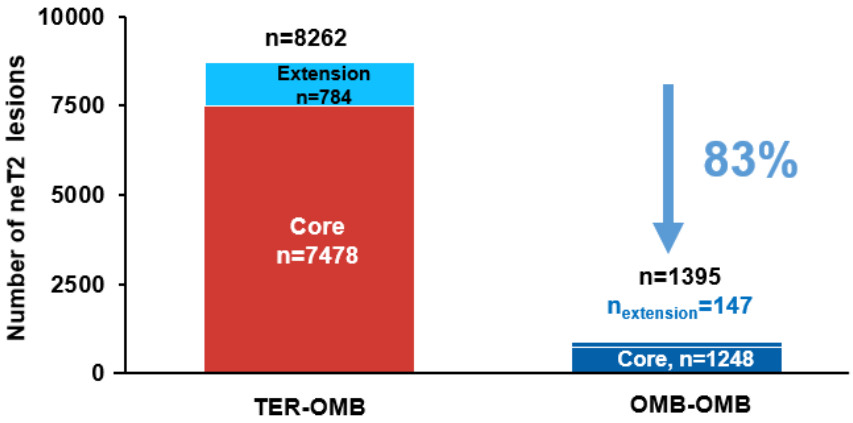
(A)



(B)



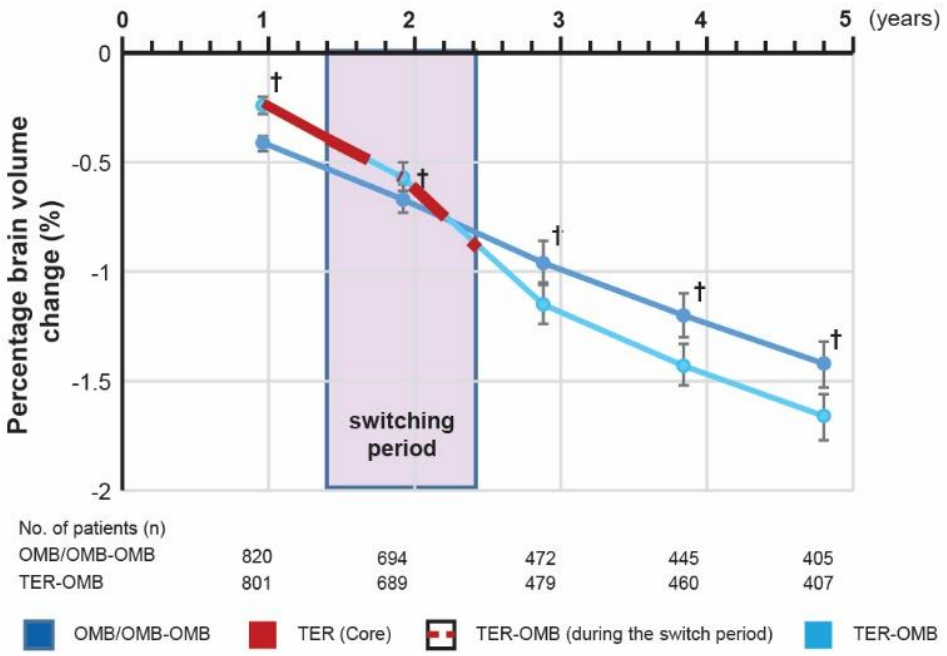
(C)



Data are from the efficacy analysis set. Patient numbers at corresponding years for neT2 lesions may differ due to missing covariates and post-baseline MRI visits. Estimated from fitting a piecewise negative binomial model for core and extension periods with log link, adjusted for treatment and region as factors, and baseline number of neT2 lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable neT2 lesion counts by visit is used as offset to obtain the lesion rate per scan at each visit. Baseline variables are from the core study baseline. The between-group comparison was 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 volume of T2 lesions and patient's age at baseline as covariates. The natural log of the time-in-study (in years) by visit is used as offset to annualise the lesion rate at each visit. 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; MRI, magnetic resonance imaging; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Figure S12. Percentage brain volume change (PBVC) up to 5 years (efficacy analysis set)



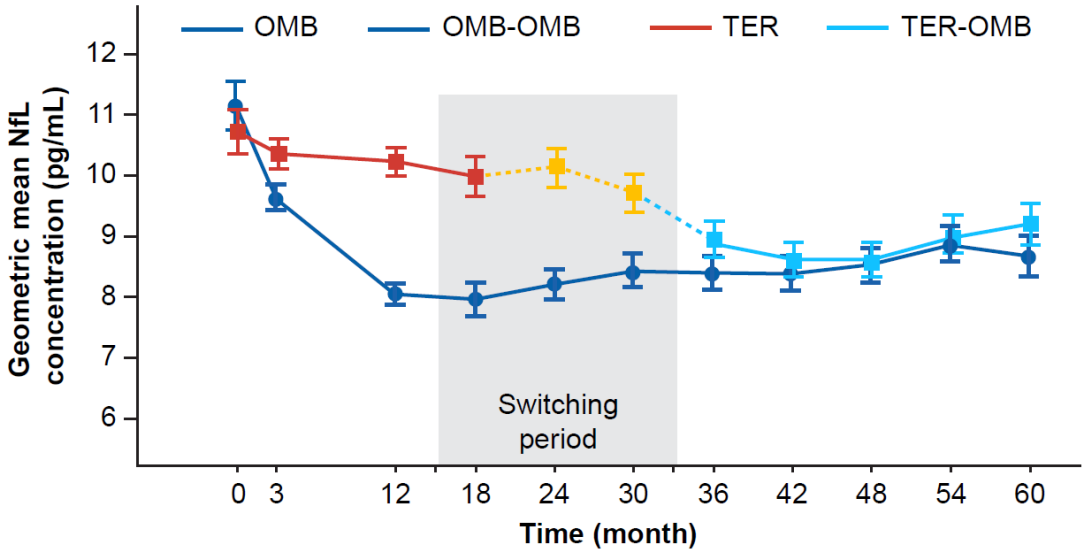
†Statistically significant between-group comparison at each year for PBVC.

PBVC estimates are obtained from a mixed model for repeated measure. PBVC comparisons were made versus baseline at each time point (e.g., for Year 1, the comparison was the difference in percent change from baseline to Year 1 between the two treatment groups).

OMB, ofatumumab; OMB-OMB, continuous ofatumumab; PBVC, percentage brain volume change; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

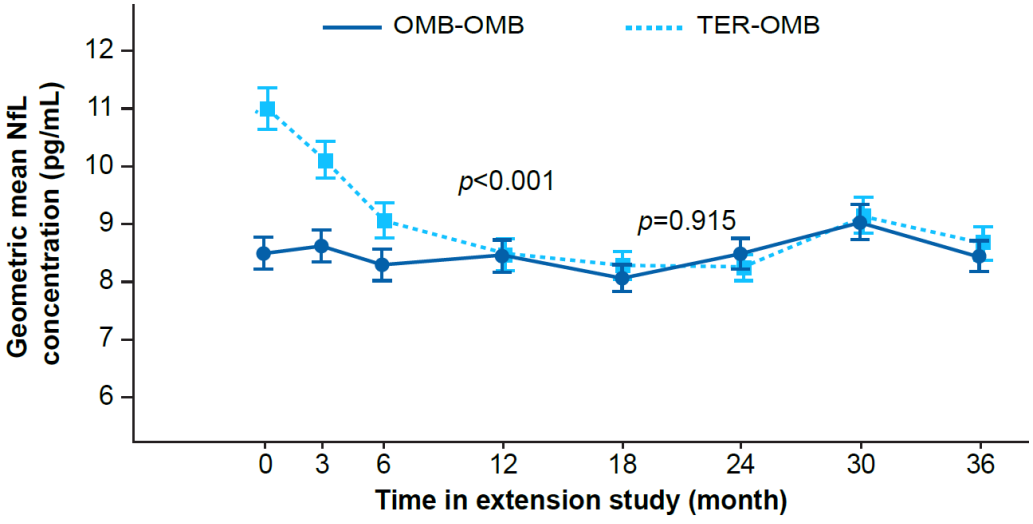
Figure S13. (A) Serum neurofilament light chain (sNfL) concentrations in the overall period (cumulative data for up to 5 years of treatment); (B) sNfL levels over time (ALITHIOS extension period) (efficacy analysis set)

(A)



Patient population										
OMB	855	817	332	711	622	559	527	535	525	488
TER	826	802	330	710	628	558	538	535	523	468

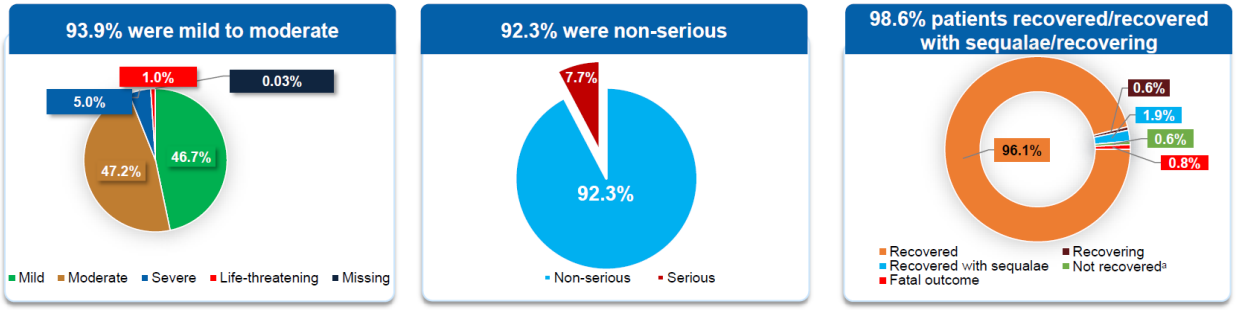
(B)



Patient population								
OMB-OMB	637	634	596	543	526	557	544	506
TER-OMB	640	628	594	565	531	548	543	487

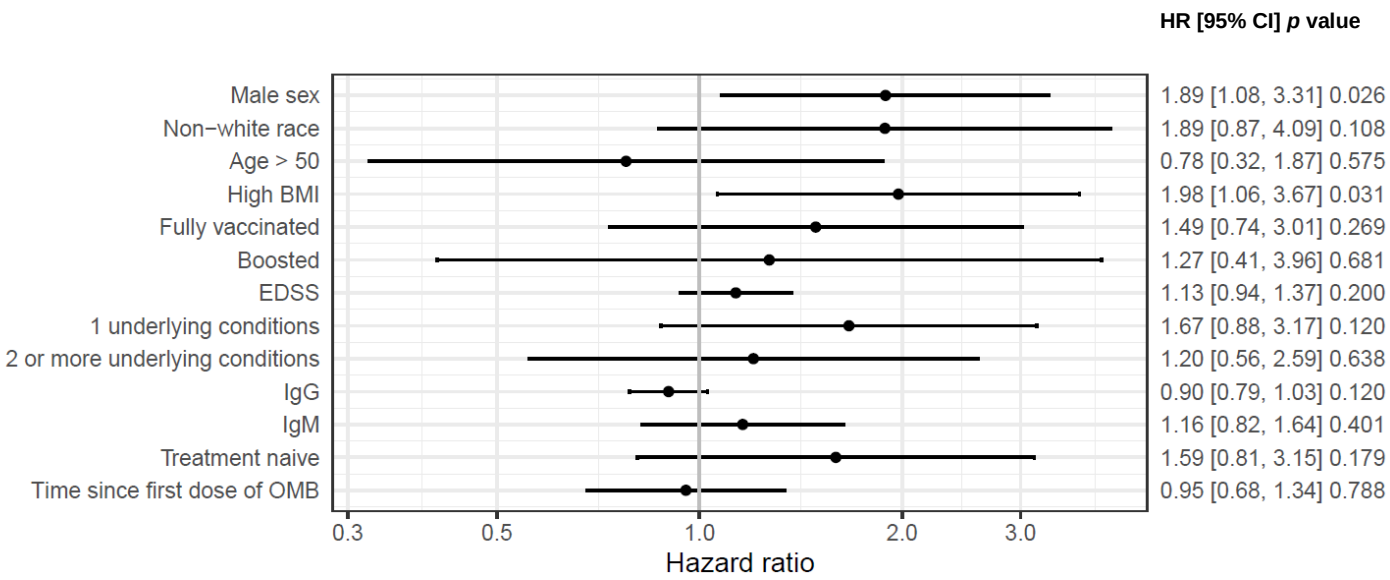
Adjusted geometric means with 95% CIs at each time point are from repeated measures model. Geometric mean NfL concentrations at baseline are derived as exponentiated arithmetic mean of natural logarithmic of raw values of NfL concentrations. CI, confidence interval; NfL, neurofilament light chain; OMB, ofatumumab, TER, teriflunomide.

Figure S14. COVID-19 outcomes (safety analysis set)



[a]At the time of the data cutoff.

Figure S15. Risk factors of serious COVID-19 infection[a] (safety analysis set)



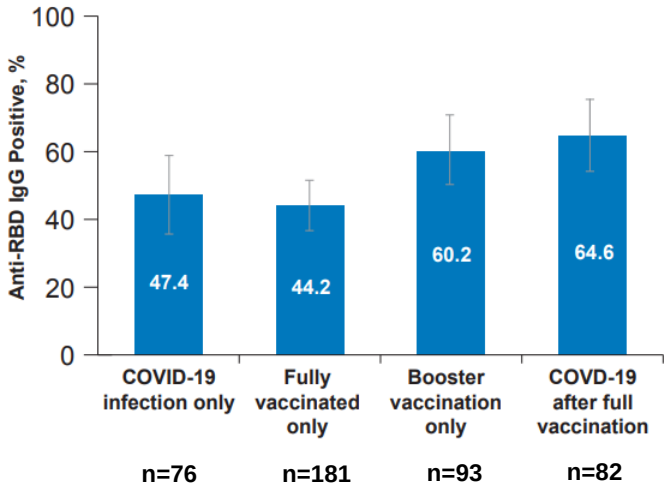
[a]The analysis was based on 1668 ALITHIOS subjects who were 'on ofatumumab' (including 100 days after the last dose) as of the beginning of 2020. Obtained from a Cox model with adjustment for sex, race, age (>50 vs. ≤50), BMI (≥30 vs. < 30), EDSS, number of underlying conditions, prior DMT, and time since first dose of OMB (years), and with vaccination status, IgG, and IgM as time-varying covariates.

A patient is considered fully vaccinated ≥14 days after completing the primary COVID-19 vaccine series.

A patient is considered boosted after receiving at least one booster dose after completing the primary series.

BMI, body mass index; CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IgG, immunoglobulin G, IgM, immunoglobulin M; OMB, ofatumumab.

Figure S16. COVID-19 seropositivity rates across subgroups of vaccination/infection status[a] (safety analysis set)



	Anti-RBD IgG concentration, (BAU/mL)	
	Geometric mean±SD	Median (Range) (min-max)
COVID-19 Infection only	8.19 (±7.57)	5.82 (1.0–6159.9)
Fully vaccinated only	6.43 (±7.86)	4.49 (1.0–1503.3)
Booster vaccination only	17.54 (±10.57)	23.69 (1.0–5657.6)
COVD-19 after full vaccination	17.82 (±10.89)	16.33 (1.0–6059.8)

[a]For each vaccination/infection status, the first available sample (mostly between 1 and 6 months) after the patient meeting that status was used to assess serological response.

BAU, binding antibody units; IgG, immunoglobin G; RBD, receptor-binding domain; SD, standard deviation.

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