Multiple Sclerosis and Related Disorders 115 (2026) 107953

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Long-term comparative outcomes in relapse activity and disability progression among anti-CD20 therapies in relapsing multiple sclerosis: An unanchored matching-adjusted indirect comparison

Ralf Gold [a], Amir Ansaripour [b,*], Klaus Schmierer [c,d], Michael Barnett [e,f], Hans Peter Hartung [g], Bassem Yamout [h], Jerome de Seze [i], Krzysztof Selmaj [j], Diego Centonze [k], Nikolaos Grigoriadis [l], Mehdi Javanbakht [m], Hari Miskin [n], Andreas B. Schmitt [o,p], Gary Cutter [q,*]

[a] Ruhr-University Bochum, Department of Neurology, Bochum, Germany
[b] Optimax Access Ltd, Rotterdam, 3032 AC, the Netherlands
[c] Queen Mary University of London, Faculty of Medicine & Dentistry, The Blizard Institute, Centre for Neuroscience, Surgery & Trauma, London, UK
[d] Barts Health NHS Trust, The Royal London Hospital, Clinical Board Medicine (Neuroscience), London, UK
[e] University of Sydney, Brain and Mind Centre, Sydney, Australia
[f] Royal Prince Alfred Hospital, Sydney, Australia
[g] Heinrich-Heine-University, Düsseldorf, Germany
[h] American University of Beirut Medical Center, Beirut, Lebanon
[i] CHU de Strasbourg and INSERM CIC-1434, Department of Neurology, Strasbourg, France
[j] University of Warmia and Mazury, Olsztyn, Center of Neurology, Lodz, Poland
[k] IRCCS Neurologico Mediterraneo Neuromed, Unit of Neurology, Pozzilli, IS, Italy
[l] Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[m] Optimax Access Ltd, Southampton, United Kingdom
[n] TG Therapeutics, USA
[o] University Hospital of Aachen, Aachen, Germany
[p] Neuraxpharm GmbH, Duesseldorf, Germany
[q] University of Alabama, Department of Biostatistics, Birmingham, AL, United States

ARTICLE INFO

Keywords:
Relapsing multiple sclerosis
Anti-CD20 therapy
Ublituximab
Matching-adjusted indirect comparison

ABSTRACT

Background: Anti-CD20 monoclonal antibodies are widely used in relapsing multiple sclerosis (RMS), but the absence of head-to-head randomized trials limits direct long-term comparisons between agents.
Methods: An unanchored matching-adjusted indirect comparison (MAIC) was conducted to explore five-year comparative outcomes in annualized relapse rate (ARR) and 24-week confirmed disability progression (CDP24) between ublituximab, ocrelizumab and ofatumumab. Individual patient data from the ULTIMATE I/II trials were reweighted to match published baseline characteristics from the OPERA I/II and ASCLEPIOS I/II trials. Long-term comparator outcomes were obtained from published follow-up data, with reconstruction of comparator patient-level data for time-to-event analyses where required. Sensitivity analyses included restricted mean survival time (RMST) for CDP24.
Results: MAIC-adjusted ublituximab ARR declined from 0.118 to 0.032 over five years versus ocrelizumab and from 0.116 to 0.030 versus ofatumumab. Ublituximab reduced the CDP24 hazard versus ocrelizumab (hazard ratio [HR] 0.560; 95% CI: 0.380–0.826) and ofatumumab (HR 0.509; 95% CI: 0.350–0.741), with 240-week RMST gains of 8 and 13 weeks, respectively.
Conclusions: These findings suggest directionally favorable long-term outcomes with ublituximab compared with the other two comparators. These findings should be interpreted carefully within the assumptions and inherent limitations of the unanchored MAIC approach.

* Corresponding authors.
E-mail addresses: amir.ansaripour@optimaxaccess.com (A. Ansaripour), cutterg@uab.edu (G. Cutter).

https://doi.org/10.1016/j.msard.2026.107953
Received 28 May 2026; Received in revised form 31 August 2026; Accepted 29 September 2026
Available online 30 September 2026
2211-0348/© 2026 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

RMS is a chronic, immune-mediated disease of the central nervous system characterized by relapses and progressive disability (Lublin et al., 2014). While relapse reduction remains important, sustained control and prevention of disability progression are increasingly central to clinical decision-making, health technology assessment (HTA) , and treatment sequencing strategies (Hauser et al., 2017; Thompson et al., 2018). As lifelong therapy is typically required, evidence beyond the first two years is increasingly relevant in modern MS management (Hauser et al., 2020b; Thompson et al., 2018).

Anti-CD20 monoclonal antibodies are cornerstone high-efficacy therapies in RMS, including ocrelizumab, ofatumumab, and ublituximab. In the pivotal OPERA I and II trials (N = 1656), ocrelizumab demonstrated significantly lower ARR (0.16 vs 0.29) and reduced risk of 12-week (HR 0.60; 95% CI 0.45–0.81) and 24-week (HR 0.60; 95% CI 0.41–0.86) confirmed disability progression compared with interferon beta-1a over 96 weeks (Hauser et al., 2017). Long-term follow-up and open-label extension studies have shown that these benefits were maintained over five years, with low relapse activity (approximately 0.10–0.07 during years 3–5) and cumulative CDP24 observed in approximately 16–18% of patients at five years (Hauser et al., 2020b). While such findings are consistent with durable treatment effects, interpretation of long-term open-label data should consider potential influences of study entrance criteria, selective dropout and follow-up-related factors (Potnis et al., 2025). Ofatumumab, evaluated in the ASCLEPIOS I and II trials (N = 1882), showed a significantly lower ARR than teriflunomide (0.11 vs 0.22) over the 96-week controlled period (Hauser et al., 2020a). In pooled analyses, ofatumumab was associated with a reduced risk of CDP24 (HR 0.68; 95% CI 0.50–0.92), although individual trial estimates were less consistent (Hauser et al., 2020a). Longer-term follow-up extending to approximately five years has demonstrated sustained relapse suppression (approximately 0.04–0.06 during years 3–5) and a stable disability profile in treated patients (approximately 15–17%) (Hauser et al., 2025). Ublituximab was evaluated in the ULTIMATE I and II trials (N = 1094), where it demonstrated significantly lower ARR than teriflunomide over 96 weeks (approximately 0.08–0.09 vs 0.18–0.19) (Steinman et al., 2021). In pooled analyses, ublituximab also showed numerically lower rates of CDP24 compared with teriflunomide (HR 0.66; 95% CI 0.38–1.15) (Steinman et al., 2021). Although this difference did not reach statistical significance at the primary analysis time point, the hazard ratio is broadly consistent with those observed for other anti-CD20 therapies, suggesting that the lack of statistical significance may be related in part to the smaller sample size of the ublituximab trials rather than a difference in treatment effect. Five-year follow-up data from the ULTIMATE program demonstrated that the low ARR observed during the controlled phase was maintained through Year 5, with ARR values of 0.053, 0.032, and 0.020 in Years 3, 4, and 5, respectively. In extension analyses, the cumulative risk of CDP24 was lower among patients receiving continuous ublituximab compared with those who switched from teriflunomide after two years (HR 0.612; 95% CI 0.414–0.904) (Cree et al., 2026). This observation may reflect cumulative benefits of sustained B-cell depletion, but also selection bias in extension studies, where patients with ongoing activity discontinue or switch. Overall, pivotal and long-term data indicate sustained suppression of inflammatory activity with anti-CD20 therapies in RMS; however, differences in trials design, patient populations, comparators, and follow-up duration preclude direct long-term comparison across treatment.

In the absence of head-to-head trials, network meta-analyses (NMAs) have compared anti-CD20 therapies using short-term data (Carlson et al., 2024; Moloney et al., 2024; Samjoo et al., 2023). These analyses consistently rank these agents among the most effective treatments for reducing relapse activity and MRI lesions but are limited by reliance on aggregate data, heterogeneous comparators, and an inability to adjust for cross-trial differences in prognostic factors or long-term follow-up (Samjoo et al., 2023).

Although ublituximab demonstrated very low ARR and favorable disability outcomes, these arose from trials with different comparators and/or populations than those for ocrelizumab and ofatumumab, so observed differences may reflect cross-trial heterogeneity. Population-adjusted indirect comparison methods such as MAIC address this by reweighting individual patient data to match comparator populations (Phillippo et al., 2016; Remiro-Azócar et al., 2021),assuming all relevant prognostic and effect-modifying variables are adequately captured; otherwise, residual confounding may remain. Anchored indirect comparisons were not feasible due to lack of a common comparator, and inconsistent long-term data; therefore, an unanchored MAIC approach can be applied to perform an indirect treatment comparison (NICE, 2013).

The objective of this study was to explore five-year comparative outcomes in relapse activity and CDP24 between ublituximab and ocrelizumab and ofatumumab using an unanchored MAIC, providing long-term comparative insights under clearly stated methodological assumptions. Five years was selected as a common long-term horizon for which follow-up data were available across all three treatment programs.

2. Methods

An unanchored MAIC analysis was conducted in accordance with methodological principles outlined in NICE Decision Support Unit Technical Support (DSU) Document 18 (Phillippo et al., 2016), which provides guidance on population-adjusted indirect comparisons in the absence of head-to-head randomized evidence. As emphasized in NICE DSU guidance, unanchored MAICs rely on strong assumptions regarding adjustment for prognostic and effect modifying factors. Accordingly, this post-hoc analysis is exploratory, rather than confirmatory.

Individual participant data (IPD) were obtained from the ULTIMATE I and ULTIMATE II phase III clinical trials, which enrolled participants between September 2017 and October 2018, followed by an open-label extension providing up to five years of follow-up. For the present analysis, pooled IPD (545 ublituximab-treated participants) from the randomized trials and their extension were analyzed from baseline through the Year 5 follow-up. The core trials had a double-blind treatment period of approximately 96 weeks, followed by an open-label extension (OLE). For the present analysis, combined IPD were used, with up to five years from randomization. IPD included baseline demographic and disease characteristics measured at study entry, including prior relapse history before randomization, as well as longitudinal follow-up data collected during the double-blind trial period and open-label extension, including relapse events and disability outcomes. Aggregate-level data for ocrelizumab and ofatumumab were extracted from published reports of the OPERA I/ II trials (Hauser et al., 2017) and the ASCLEPIOS I/II trials (Hauser et al., 2020a), respectively, as well as from available long-term extension and follow-up publications reporting outcomes up to approximately five years (Hauser et al., 2025, 2020b). Published baseline characteristics and reported long-term outcomes were used as MAIC targets. For disability outcomes, for the comparator trials, published Kaplan–Meier curves were digitized and used to reconstruct pseudo–individual patient data for time-to-event analyses (Guyot et al., 2012). The reconstruction procedure estimates both event times and censoring patterns based on the digitized survival probabilities and reported numbers at risk.

All participants with complete data for the matching covariates were included in the analysis. Participants were not excluded according to their degree of similarity to the comparator population. Instead, comparison-specific MAIC weights were assigned to align the weighted baseline characteristics of the ublituximab population with the published aggregate characteristics of the comparator trials.

ARR was consistently defined across the three pivotal trial programs as the number of confirmed relapses per patient-year of follow-up. ARR

was evaluated longitudinally over the five-year follow-up period. As confidence intervals for long-term ARR estimates were not consistently reported for the comparator trials, ARRs were estimated separately for each follow-up year using intercept-only weighted Poisson regression models with log(person-years) as an offset. Published ARRs from the comparator studies were used as reference values for indirect comparison. CDP24 sustained for at least 24 weeks was used as the long-term disability endpoint, defined according to the Expanded Disability Status Scale (EDSS) criteria with the trial-specific definitions and assessment schedules for confirmation of progression were retained in the analysis. CDP24 events were not further classified as progression independent of relapse activity or relapse-associated worsening. Definitions of 24-week confirmed disability progression were broadly comparable across ULTIMATE, OPERA and ASCLEPIOS, and minor differences in the EDSS thresholds and confirmation procedures were not expected to materially affect the comparison.

Covariates for population adjustment were selected based on clinical relevance, prior RMS literature, and the availability across trials. Candidate covariates included demographic variables (e.g., age, sex) and baseline disease characteristics (baseline EDSS score, the proportion of patients with ≥1 gadolinium-enhancing (Gd+) lesion at baseline, T2 lesion volume (cm^3), and prior relapse history (number of relapses before randomization, and time since diagnosis at baseline). These variables were considered potential prognostic factors or effect modifiers for relapse and disability outcomes. Covariates were included in each comparison only if the corresponding aggregate data were reported in the comparator trials. Several clinically important variables, however, such as prior disease-modifying therapy exposure and sequencing, and detailed MRI disease burden were not consistently reported and therefore could not be adjusted for. In line with NICE DSU guidance, this was considered as a potential source of residual confounding.

MAIC weights were estimated at randomization (trial baseline) by reweighting ublituximab IPD to match published baseline aggregate characteristics of each comparator. As long-term follow-up populations represent subsets of the original trial cohorts, matching was based on randomized populations. Post-baseline discontinuation, treatment switching, loss to follow-up and selection into extension phases were not incorporated because the required participant-level data were unavailable for the comparator studies. Weights were derived using a method-of-moments approach, as described in NICE DSU Technical Support Document 18 (Phillippo et al., 2016). Covariate balance before and after weighting was assessed using standardized mean differences (SMD) <0.1. Weights were applied to all outcomes across follow-up and Effective sample size (ESS) was calculated to quantify information retained following the reweighting.

Weighted ARRs were estimated using Poisson regression models with log(person-years) included as an offset. Time-to-event analyses for CDP24 were conducted using weighted Cox proportional hazards models (Cox, 1972). Proportional hazards assumptions were assessed visually and analytically using Schoenfeld residual tests (Grambsch and Therneau, 1994) implemented with the cox.zph function in R (Therneau, 2026). As a sensitivity analysis, the MAIC weights used to align the ULTIMATE population with ASCLEPIOS were applied to the randomized ULTIMATE teriflunomide arm, and the resulting weighted ARR was compared with the published ASCLEPIOS teriflunomide ARR over the controlled treatment period. Given potential non-proportional hazards over extended follow-up, RMST (Royston and Parmar, 2013) was used as a sensitivity analysis for CDP24 because it provides an estimate of treatment effect that does not rely on the proportional hazards assumption. RMST was calculated by integrating weighted Kaplan–Meier survival curves up to a prespecified truncation time of 240 weeks. Uncertainty around RMST differences was quantified using a nonparametric bootstrap with 2000 resamples and percentile-based 95% confidence intervals. Additional sensitivity analyses assessed the robustness of results to alternative MAIC weighting specifications and to assumptions underlying reconstruction of comparator patient-level data from published Kaplan–Meier curves. In accordance with NICE DSU guidance (Phillippo et al., 2016), key assumptions were prespecified, including: (1) adequate adjustment for prognostic factors and treatment effect modifiers, (2) consistency of outcome definitions, and (3) stable covariate effects over time.

3. Results

Baseline characteristics of the unweighted ublituximab individual patient population differed from those of ocrelizumab and ofatumumab trials, including age, baseline EDSS score, gadolinium-enhancing (Gd+) lesion prevalence, T2 lesion volume (cm^3), prior ARR, and time since diagnosis at baseline. After MAIC weighting, baseline characteristics closely matched both comparator populations (Table 1). SMDs were substantially reduced across covariates to below commonly accepted thresholds, indicating successful alignment on observed baseline variables (Appendix Fig. A1).

In a common-arm sensitivity analysis, the ARR ratio for weighted ULTIMATE versus ASCLEPIOS teriflunomide was 0.86 (95% CI 0.68–1.05), with no statistically significant difference between the estimates.

The pooled ublituximab source population comprised 545 participants. Of these, 544 participants with complete data for all required baseline matching covariates were included in both comparator analyses. One participant was excluded because both baseline Gd-enhancing lesion status and T2 lesion volume were missing. No additional participants were excluded because of missing ARR or CDP24 outcome data. Unanchored MAIC weighting reduced ESS relative to the original ublituximab IPD, reflecting the increased variability in weights required to align baseline characteristics across target trials. The ESS was 453.5 (83.4%) for ocrelizumab and 471.9 (86.7%) for ofatumumab. Despite this reduction, both comparisons retained a high proportion of the original study population, indicating good overlap between the weighted ublituximab population and the comparator trial populations. Weights were well behaved for both comparisons, with no evidence of extreme weights. The higher ESS observed in the comparison with ofatumumab indicates greater overlap between the ublituximab and ASCLEPIOS trial populations relative to the OPERA population. The modest ESS reduction reflects baseline differences and is consistent with unanchored MAIC, with slightly greater uncertainty in the ocrelizumab comparison.

ARRs for ublituximab were lower over the five years versus ocrelizumab and ofatumumab with consistent trends across follow-up, though differences varied over time (Table 2). As long-term ARR variance estimates were not consistently reported, formal statistical comparisons

Table 1
Baseline Characteristics Before and After MAIC Weighting.

Covariate	Comparator	Target Mean	Ublituximab Unweighted Mean (SD)	Ublituximab Weighted Mean
Age (years)	Ocrelizumab	37.10	35.40 (8.64)	37.10
	Ofatumumab	38.20		38.20
Female proportion	Ocrelizumab	0.65	0.63 (0.48)	0.65
	Ofatumumab	0.68		0.68
Baseline EDSS	Ocrelizumab	2.80	2.88 (1.26)	2.80
	Ofatumumab	2.90		2.90
Gd+ lesion prevalence	Ocrelizumab	0.41	0.47 (0.50)	0.41
	Ofatumumab	0.39		0.39
T2 lesion volume (cm^3)	Ocrelizumab	10.80	15.31 (14.83)	10.80
	Ofatumumab	13.15		13.15
Prior ARR	Ocrelizumab	1.32	1.29 (0.65)	1.32
	Ofatumumab	1.28		1.28
Time since diagnosis at baseline (years)	Ocrelizumab	3.92	5.00 (5.46)	3.92
	Ofatumumab	5.62		5.62

Table 2
Unanchored MAIC-Adjusted ARR Over Five Years.

Follow-up Year	Ublituximab vs Ocrelizumab ARR (95% CI)	Ublituximab vs Ofatumumab ARR (95% CI)
Year 1	0.118 (0.086–0.163) vs 0.140	0.116 (0.087–0.154) vs 0.128
Year 2	0.063 (0.041–0.097) vs 0.130	0.069 (0.046–0.105) vs 0.090
Year 3	0.056 (0.035–0.090) vs 0.100	0.054 (0.034–0.087) vs 0.053
Year 4	0.042 (0.023–0.077) vs 0.080	0.041 (0.023–0.072) vs 0.063
Year 5	0.032 (0.017–0.062) vs 0.070	0.030 (0.016–0.056) vs 0.034

Values represent unanchored MAIC-adjusted ARR estimates for ublituximab with 95% confidence intervals and corresponding published long-term ARR estimates for ocrelizumab and ofatumumab.

were not feasible, and ARR findings are interpreted as exploratory comparative analyses (Fig. 1). Pearson dispersion estimates ranged from 0.90 to 1.59 across both comparisons, indicating mild-to-moderate overdispersion in some years.

In unanchored MAIC analyses, ublituximab was associated with lower risk of CDP24 over long-term follow-up when compared with both ocrelizumab and ofatumumab (Table 3). For the comparison with ocrelizumab, the MAIC-adjusted hazard ratio (HR) for CDP24 was 0.560

Table 3
Unanchored MAIC-Adjusted CDP24 Outcomes.

Outcome	Ublituximab vs Ocrelizumab	Ublituximab vs Ofatumumab
Hazard ratio (95% CI)	0.560 (0.380–0.826)	0.509 (0.350–0.741)
Cumulative CDP24 at 240 weeks – Ublituximab	9.3%	9.4%
Cumulative CDP24 at 240 weeks – Comparator	16.1%	17.9%
Relative hazard reduction	44.0%	49.1%

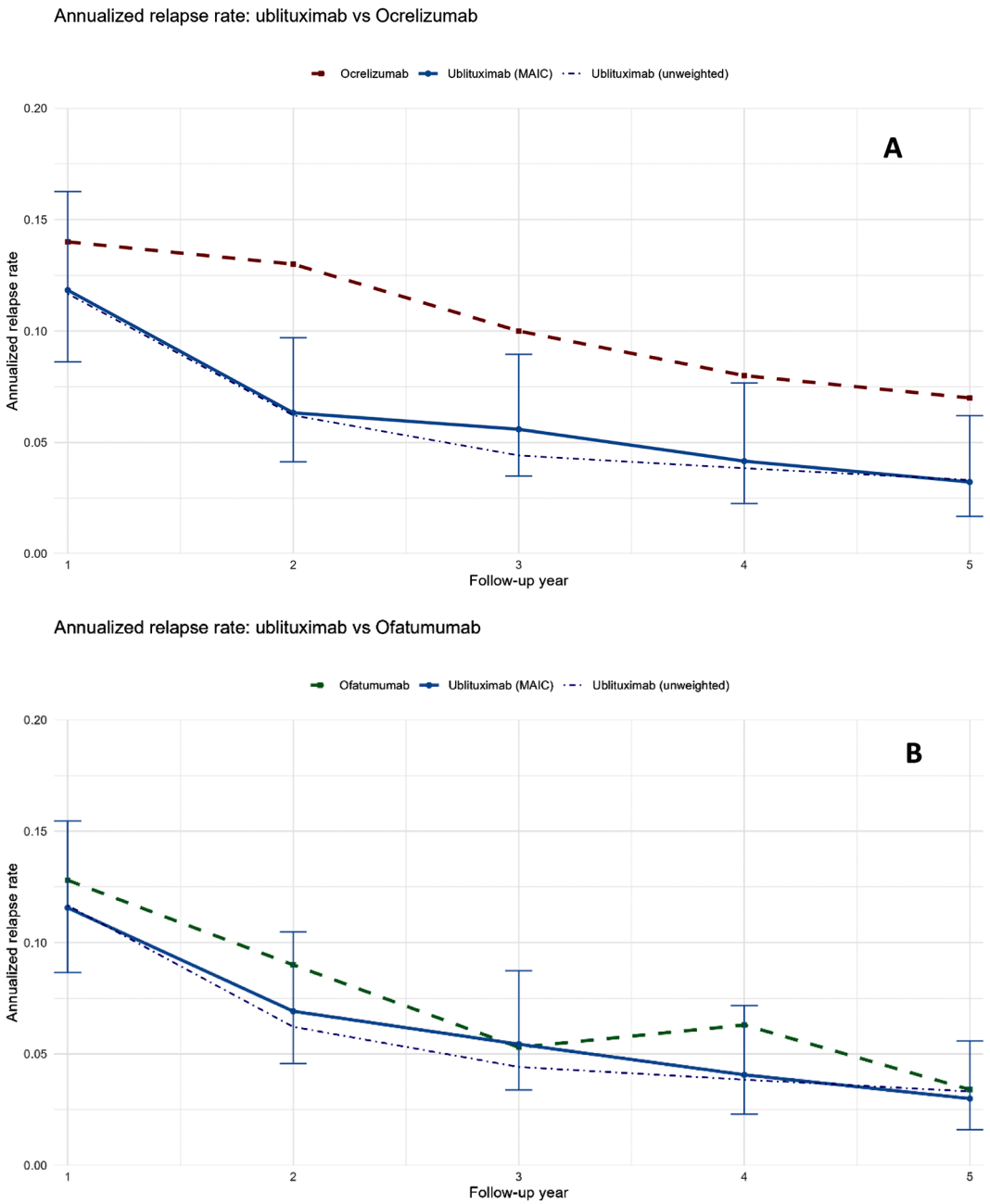


Fig. 1. Unanchored MAIC-Adjusted ARR by follow-up year for ublituximab compared with (A) ocrelizumab and (B) ofatumumab.

(95% CI: 0.380–0.826), indicating a lower estimated risk of disability progression for ublituximab over the follow-up period. For the comparison with ofatumumab, the corresponding HR was 0.509 (95% CI: 0.350–0.741).

Kaplan–Meier analyses demonstrated separation of the cumulative CDP24 curves in both comparisons. The MAIC-adjusted hazard ratios indicated a lower risk of CDP24 with ublituximab compared with both ocrelizumab and ofatumumab, corresponding to relative reductions in the risk of confirmed disability progression of 44.0% and 49.1%, respectively. At the pre-specified 240-week time point, cumulative CDP24 incidence was 9.3% for ublituximab compared with 16.1% for ocrelizumab and 9.4% for ublituximab compared with 17.9% for ofatumumab (Table 3; Fig. 2).

RMST analyses were broadly consistent with the primary CDP24 results. Over 240-week follow-up horizon, the estimated RMST for ublituximab was 227.8 vs 219.6 weeks for ocrelizumab, corresponding to an average difference of 8.1 weeks in time free from confirmed disability progression (95% bootstrap CI: 2.3 to 14.1 weeks) . In the comparison with ofatumumab, the estimated RMST over 240 weeks was 227.5 vs 214.4 weeks, corresponding to an average difference of 13.1 weeks in time free from confirmed disability progression (95% bootstrap CI: 6.7 to 19.3 weeks) (Table 4). Across comparisons, ublituximab showed longer average time free from confirmed disability progression. Both comparisons showed statistically significant RMST gains for ublituximab.

4. Discussion

In this unanchored MAIC, ublituximab demonstrated directionally favorable long-term outcomes in relapse activity and disability progression compared with ocrelizumab and ofatumumab. After adjustment for baseline differences, ublituximab was associated with consistently lower ARRs over five years and a lower estimated risk of CDP24 in both comparisons. These relevant findings were supported by RMST analyses, indicating a longer duration free from disability progression over 240 weeks.

Relapse outcomes were consistent with those observed in the ULTIMATE trials and with sustained relapse suppression reported across the anti-CD20 class (Steinman et al., 2022). In this analysis, ARR for ublituximab remained lower than for both comparators across all follow-up years.

For disability outcomes, adjusted analyses indicated lower CDP24 with ublituximab versus both comparators. Kaplan–Meier curves showed separation over time (Fig. 2), with fewer progression events at 240 weeks in the weighted ublituximab population. RMST analyses were consistent with hazard-based results, supporting longer progression-free duration without relying on proportional hazards assumptions (Table 4).

Although anchored indirect comparison methods are generally preferred when a valid common comparator exists, such an approach was not feasible in this context. While both ublituximab and ofatumumab were evaluated against teriflunomide, ocrelizumab was evaluated against interferon beta-1a, precluding a shared comparator across all trials. Furthermore, long-term outcome data for comparator arms were not consistently available, and differences in trial design, eligibility criteria, and follow-up duration further limited the validity of an anchored approach. Consistent with NICE Decision Support Unit guidance, an unanchored MAIC was therefore applied to explore long-term comparative outcomes while explicitly acknowledging the strength of the underlying assumptions.

Reassuringly, application of the ASCLEPIOS-targeting weights to the randomized ULTIMATE teriflunomide arm produced an ARR statistically compatible with that reported for teriflunomide in ASCLEPIOS (ARR ratio 0.86, 95% CI 0.68–1.05), although this provides only partial validation of population adjustment during the randomized period and cannot establish exchangeability during long-term follow-up.

Several factors may contribute to the observed comparative outcomes. While all three therapies target CD20-positive B cells, they differ in molecular structure, mechanisms of cytotoxicity, dosing schedules, and routes of administration. Ublituximab is glycoengineered to enhance antibody-dependent cellular cytotoxicity, which may influence the depth or durability of B-cell depletion. However, given the indirect nature of the comparisons and the absence of head-to-head randomized evidence, mechanistic explanations remain speculative and cannot be confirmed within the present analysis.

The findings of this study may be interpreted with caution, given methodological considerations inherent to unanchored MAICs. While differences between B-cell–depleting therapies were observed, these may reflect residual confounding and limitations of cross-trial comparisons. The validity of the analyses relies on the assumption that all relevant prognostic factors and treatment effect modifiers have been measured, and adequately adjusted for, however unmeasured confounders may fully account for the observed differences. Although MAIC weighting substantially improved balance on observed baseline characteristics, such balance does not ensure comparability with respect to unmeasured or unavailable prognostic factors. While MAIC weighting improved balance in observed baseline characteristics, several clinically relevant variables, such as prior disease-modifying therapy exposure and sequencing, and more granular MRI measures, were not consistently available and could not be included. Baseline differences in age and MRI disease burden, prior to weighting suggest that other unreported disease features may also have varied across trials. In addition, trial-level differences, including study locations and healthcare systems variations, represent additional sources of uncertainty not captured by MAIC. Consequently, residual confounding cannot be excluded. Additional uncertainty arises from reliance on reconstructed comparator patient-level data for disability outcomes, the absence of consistently reported variance estimates for long-term ARR, and reduced precision over extended follow-up due to attrition and censoring. These limitations, along with potential selection biases, preclude causal inference and support cautious interpretation of long-term differences. Nevertheless, long-term follow-up of ublituximab-treated patients suggests that sustained disease control can be achieved in a substantial proportion of individuals with RMS.

Despite these limitations, this analysis provides long-term comparative insights beyond the time horizons typically evaluated in network meta-analyses and aggregate-level indirect comparisons. The broadly similar short-term outcomes across anti-CD20 therapies are consistent with the previous NMA, which found no statistically significant differences between ublituximab and other monoclonal antibodies during randomized trial follow-up (Moloney et al., 2024). By leveraging IPD and population adjustment, it addresses an important evidence gap regarding the relative durability of anti-CD20 therapies over five years, a timeframe increasingly relevant for treatment selection and sequencing in RMS.

From an HTA perspective, this analysis illustrates how unanchored MAICs can inform long-term comparisons when head-to-head evidence and mature common-comparator data are unavailable. In RMS, where treatment durability and disability outcomes drive reimbursement and sequencing decisions, exploratory long-term results may complement short-term trials and NMAs. Alternative measures, such as RMST, may provide more interpretable estimates when proportional hazards assumptions are uncertain. Although unanchored MAICs cannot support confirmatory conclusions, their transparent use under stated assumptions may help characterize uncertainty and inform HTA decision-making. Overall, this analysis provides exploratory long-term comparative insights and highlights the need for confirmatory head-to-head trials and real-world evidence.

5. Conclusions

In the absence of head-to-head randomized trials, this unanchored MAIC explored long-term comparative outcomes between ublituximab

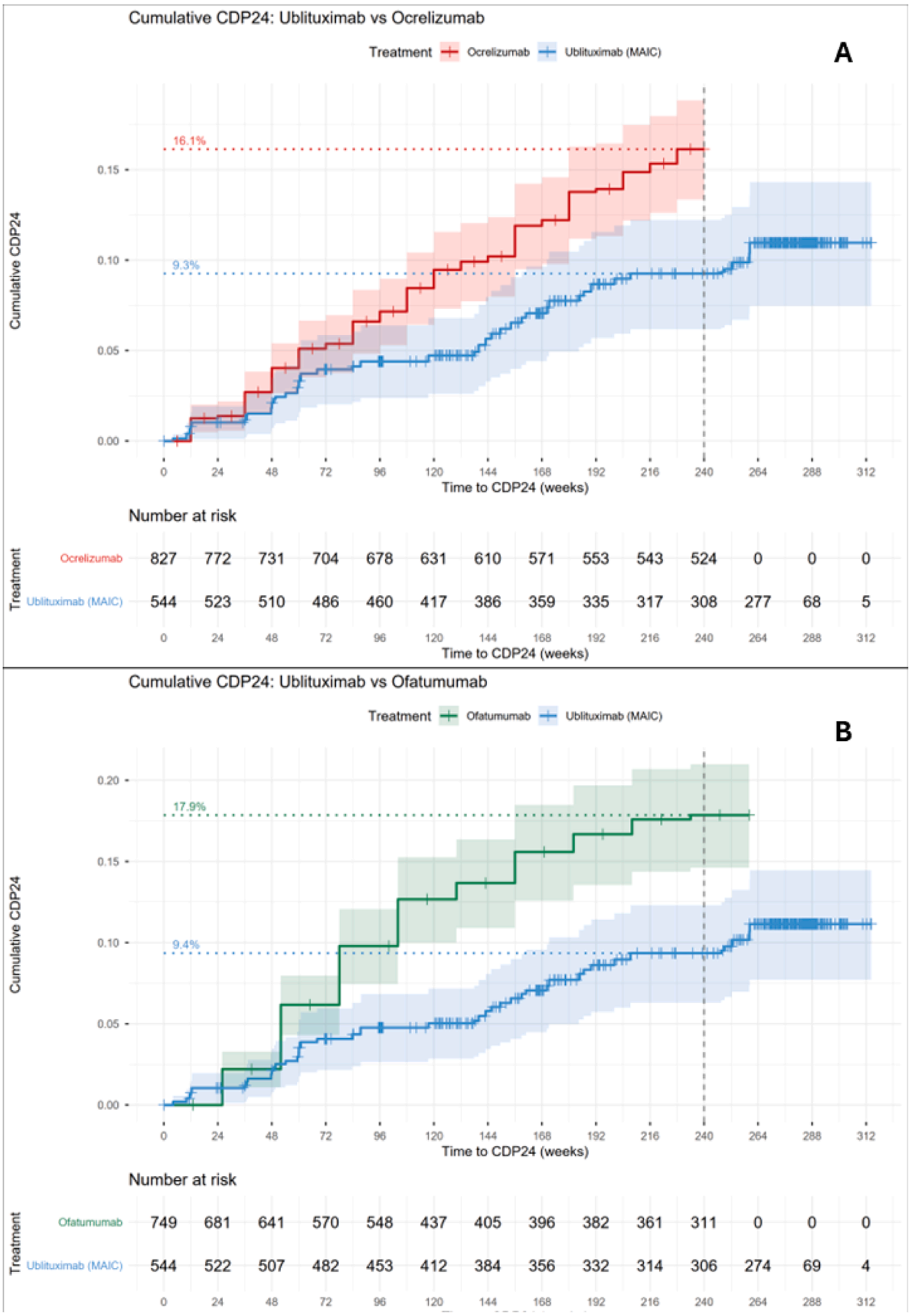


Fig. 2. Unanchored MAIC-Adjusted Cumulative incidence of CDP24 over time for ublituximab compared with (A) ocrelizumab and (B) ofatumumab.

Table 4
RMST for CDP24 ($\tau = 240$ weeks).

Comparison	RMST – Ublituximab (weeks)	RMST – Comparator (weeks)	RMST Difference (weeks)	95% CI
Ublituximab vs Ocrelizumab	227.759	219.623	8.136	2.3 to 14.1
Ublituximab vs Ofatumumab	227.476	214.393	13.084	6.7 to 19.3

and other anti-CD20 therapies in RMS. Under the required assumptions, results suggested directionally favorable long-term outcomes for ublituximab in relapse activity and disability progression compared to ocrelizumab and ofatumumab. These findings provide insights and should be interpreted within the assumptions of the unanchored MAIC framework including the potential for residual confounding arising from differential dropout, unmeasured differences in patient populations, and differences in site-level care practices across studies. They should be considered complementary to previous short-term randomized treatment evidence, pending confirmation from direct comparative studies or robust real-world evidence.

Funding

This study was funded by Neuraxpharm, the European commercialization partner for ublituximab (BRIUMVI) under its agreement with TG Therapeutics, the developer of ublituximab. Optimax Access Ltd., formerly part of iGES GmbH at the time of study, received funding from Neuraxpharm to conduct the analyses. Individual investigators who are not employees of these companies were not paid to participate.

This study has been sponsored by Neuraxpharm Arzneimittel GmbH.

CRediT authorship contribution statement

Ralf Gold: Writing – review & editing, Writing – original draft. **Amir Ansaripour:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **Klaus Schmierer:** Writing – review & editing, Writing – original draft. **Michael Barnett:** Writing – review & editing, Writing – original draft. **Hans Peter Hartung:** Writing – review & editing, Writing – original draft. **Bassem Yamout:** Writing – review & editing, Writing – original draft. **Jerome de Seze:** Writing – review & editing, Writing – original draft. **Krzysztof Selmaj:** Writing – review & editing, Writing – original draft. **Diego Centonze:** Writing – review & editing, Writing – original draft. **Nikolaos Grigoriadis:** Writing – review & editing, Writing – original draft. **Mehdi Javanbakht:** Methodology. **Hari Miskin:** Writing – review & editing, Writing – original draft. **Andreas B. Schmitt:** Writing – review & editing. **Gary Cutter:** Writing – review & editing, Validation, Methodology.

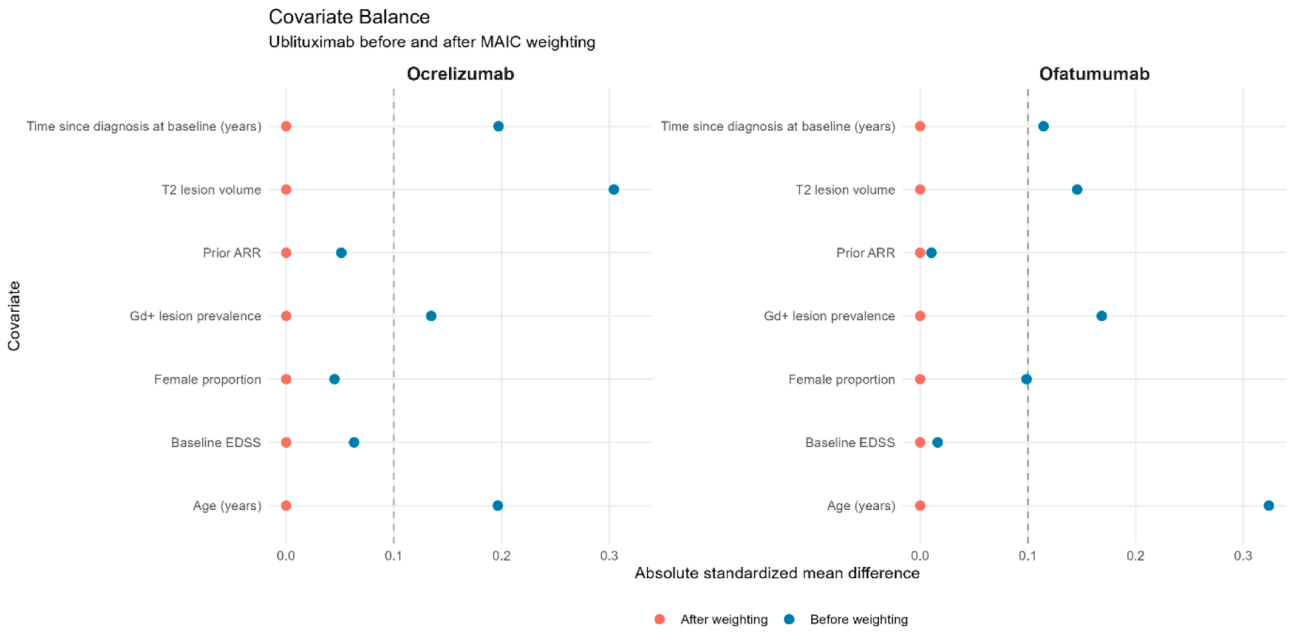
Declaration of competing interest

AA and MJ are employees of Optimax Access Ltd. Optimax Access Ltd. received funding to conduct the analyses reported in this study. ABS is employee of Neuraxpharm Arzneimittel GmbH, the sponsor of this study. MB has received speaker honoraria and/or institutional grant funding from Roche, Novartis, Biogen, and Alexion; and personal compensation for participation in the Australian ublituximab advisory board. KS is the chief investigator of ChariotMS (NCT04695080), a multicenter trial supported by the National Institute for Health Research (NIHR), MS Society of Great Britain and Northern Ireland, National MS Society (USA), Barts Charity and Merck; chief investigator of AttackMS (NCT05418010), a multicenter trial supported by Biogen & Sandoz; and co-chief investigator of AssistMS, a multicenter trial supported by the UK Department of Health and Social Care and icometrix. He is a member of advisory committees for Merck and has received research and NHS service support from Merck, Neuraxpharm, Novartis, Roche, and Sanofi; speaking honoraria from, and/or served in an advisory role for Biogen, icometrix, Merck, Neuraxpharm, Novartis, Roche, and Sanofi; and remuneration for teaching activities from AcadeMe and Medscape. NG: Honoraria and travel support, Consultancy and Lecture fees from Biogen Idec, Novartis, TEVA, BAYER, Bayer, MERCK, Genesis Pharma, Sanofi – Genzyme, Cellgene , ELPEN, ROCHE. Astra Zeneca, UCB, Medicon, Neuraxpharm; Research grants from Biogen Idec, Novartis, TEVA, MERCK, Genesis Pharma, Sanofi – Genzyme, ROCHE. DC acted as an Advisory Board member and received honoraria for speaking or consultation fees from Alexion, Almirall, Amicus, Bayer, Biogen, BMS, Celgene, Chiesi, GW Pharmaceuticals, Horizon, Janssen, Lundbeck, Merck Serono, Neuraxpharm, Novartis, Roche, Sandoz, Sanofi-Genzyme, Viatris, and Teva. He is also the Principal Investigator in clinical trials of Biogen, BMS, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Actelion. His preclinical and clinical research was supported by grants from Bayer Schering, BMS, Biogen, Celgene, Lundbeck, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. GC: Data and Safety Monitoring Boards: Applied Therapeutics, AI therapeutics, Amgen-NMO peds, AMO Pharma, Argenx, Astra-Zeneca, Bristol Meyers Squibb, CSL Behring, , DiamedicaTherapeutics, Horizon Pharmaceuticals, Immunic, Inhrbx-sanfofi, Karuna Therapeutics, Kezar Life Sciences, Medtronic, Merck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma Holdings, Prothena Biosciences, Novartis, Pipeline Therapeutics (Contineum), Regeneron, Sanofi-Aventis, Teva Pharmaceuticals, United BioSource LLC, University of Texas Southwestern, Zenas Biopharmaceuticals. Consulting or Advisory Boards: Alexion, Alira Health, Antisense Therapeutics/Percheron, Avotres, Biogen, Clene Nanomedicine, Clinical Trial Solutions LLC, Endra Life Sciences, Genzyme, Genentech, Immunic, Klein-Buendel Incorporated, Kyverna Therapeutics, Inc. , Linical, Merck/Serono, Noema, Neurogenesis, Perception Neurosciences, Protalix Biotherapeutics, Regeneron, Revelstone Consulting, Roche, Sapience Therapeutics, Tenmile. Dr. Cutter is President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

Acknowledgments

Not applicable.

Appendix



Appendix Fig. A1. Covariate Balance Before and After MAIC Weighting. Standardized mean differences for baseline covariates comparing the ublituximab population with ocrelizumab (OPERA I/II) and ofatumumab (ASCLEPIOS I/II) before and after MAIC weighting.

Data availability

Individual patient-level data from the ULTIMATE I and II trials used in this analysis were made available to the research team through the product owners, TG Therapeutics and Neuraxpharm. These data are not publicly available. However, interested parties should discuss a request with TG Therapeutics. Aggregate-level data for comparator trials were obtained from published sources.

References

Carlson, A.K., Amin, M., Cohen, J.A., 2024. Drugs targeting CD20 in multiple sclerosis: pharmacology, efficacy, safety, and tolerability. Drugs 84, 285–304. https://doi.org/10.1007/s40265-024-02011-w.

Cox, D.R., 1972. Regression models and life-tables. J. R. Stat. Soc. Ser. B 34, 187–202. https://doi.org/10.1111/j.2517-6161.1972.tb00899.x.

Cree, B.A.C., Fox, E., Hartung, H.P., Alvarez, E., Qian, P., Wray, S., Robertson, D., Selmaj, K., Wynn, D., Mok, K., Rowland, C., Bodhinathan, K., Sportelli, P., Miskin, H. P., Steinman, L., 2026. Five years of ublituximab in multiple sclerosis: ULTIMATE I and II open-label extension study. JAMA Neurol. 83, 348. https://doi.org/10.1001/jamaneurol.2026.0007.

Grambsch, P.M., Therneau, T.M., 1994. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81, 515–526. https://doi.org/10.1093/biomet/81.3.515.

Guyot, P., Ades, A.E., Ouwens, M.J.N.M., Welton, N.J., 2012. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med. Res. Methodol. 12, 9. https://doi.org/10.1186/1471-2288-12-9.

Hauser, S.L., Bar-Or, A., Cohen, J.A., Comi, G., Correale, J., Coyle, P.K., Cross, A.H., de Seze, J., Leppert, D., Montalban, X., Selmaj, K., Wiendl, H., Kerloeguen, C., Willi, R., Li, B., Kakarieka, A., Tomic, D., Goodyear, A., Pingili, R., Häring, D.A., Ramanathan, K., Merschhemke, M., Kappos, L., 2020a. Ofatumumab versus teriflunomide in multiple sclerosis. N. Engl. J. Med. 383, 546–557. https://doi.org/10.1056/nejmoa1917246.

Hauser, S.L., Bar-Or, A., Comi, G., Giovannoni, G., Hartung, H.P., Hemmer, B., Lublin, F., Montalban, X., Rammohan, K.W., Selmaj, K., Traboulsee, A., Wolinsky, J.S., Arnold, D.L., Klingelschmitt, G., Masterman, D., Fontoura, P., Belachew, S., Chin, P., Mairon, N., Garren, H., Kappos, L., 2017. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N. Engl. J. Med. 376, 221–234. https://doi.org/10.1056/nejmoa1601277.

Hauser, S.L., Cohen, J.A., de Sèze, J., Meuth, S.G., Giacomini, P.S., Nakahara, J., Oreja-Guevara, C., Robertson, D., Wray, S., Bhatt, A., Hu, X., Xi, J., Piccolo, R., Jehl, V., Sullivan, R., Boer, I., Wiendl, H., Kappos, L., 2025. Five-year safety and efficacy outcomes with ofatumumab in patients with relapsing multiple sclerosis. Neurol. Ther. 14, 1975–1992. https://doi.org/10.1007/s40120-025-00784-0.

Hauser, S.L., Kappos, L., Arnold, D.L., Bar-Or, A., Brochet, B., Naismith, R.T., Traboulsee, A., Wolinsky, J.S., Belachew, S., Koendgen, H., Levesque, V., Manfrini, M., Model, F., Hubeaux, S., Mehta, L., Montalban, X., 2020b. Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. Neurology 95, E1854–E1867. https://doi.org/10.1212/WNL.0000000000010376.

Lublin, F.D., Cutter, G., Giovannoni, G., Pace, A., Campbell, N.R., Belachew, S., 2014. Natalizumab reduces relapse clinical severity and improves relapse recovery in MS. Mult. Scler. Relat. Disord. 3, 705–711. https://doi.org/10.1016/j.msard.2014.08.005.

Moloney, E., Mashayekhi, A., Sharma, S., Kontogiannis, V., Ansaripour, A., Brownlee, W., Paling, D., Javanbakht, M., 2024. Comparative efficacy and tolerability of ublituximab vs. other monoclonal antibodies in the treatment of relapsing multiple sclerosis: a systematic review and network meta-analysis of randomized trials. Front. Neurol. 15.

NICE, 2013. Guide to the methods of technology appraisal 2013 [WWW Document]. Process methods. URL https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (accessed 9.10.21).

Phillippo, D.M.; Ades, A.E.; Dias, S.; Palmer, S.; Abrams, K.R.., Welton, N.., 2016. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submission to NICE.

Potnis, O., Biondo, G., Sukonik, R., Grzeskowiak, C., Cutter, G., Altalib, H., Kuzniecky, R., Lowenstein, D., French, J., 2025. Seizure frequency trends over time in treatment-resistant focal epilepsy. JAMA Neurol. 82, 1257. https://doi.org/10.1001/jamaneurol.2025.4085.

Remiro-Azócar, A., Heath, A., Baio, G., 2021. Methods for population adjustment with limited access to individual patient data: a review and simulation study. Res. Synth. Methods 12, 750–775. https://doi.org/10.1002/jrsm.1511.

Royston, P., Parmar, M.K.B., 2013. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Med. Res. Methodol. 13, 152. https://doi.org/10.1186/1471-2288-13-152.

Samjoo, I.A., Drudge, C., Walsh, S., Tiwari, S., Brennan, R., Boer, I., Häring, D.A., Klotz, L., Adlard, N., Banhazi, J., 2023. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. J. Comp. Eff. Res. 12. https://doi.org/10.57264/cer-2023-0016.

Steinman, L., Fox, E., Hartung, H.P., Alvarez, E., Qian, P., Wray, S., Robertson, D., Huang, D., Selmaj, K., Wynn, D., Cutter, G., Mok, K., Hsu, Y., Xu, Y., Weiss, M.S., Bosco, J.A., Power, S.A., Lee, L., Miskin, H.P., Cree, B.A.C., 2022. Ublituximab versus Teriflunomide in relapsing multiple sclerosis. N. Engl. J. Med. 387, 704–714. https://doi.org/10.1056/nejmoa2201904.

Steinman, L., Fox, E., Hartung, H.P., Alvarez, E., Qian, P., Wray, S., Robertson, D., Huang, D., Selmaj, K., Wynn, D., Weiss, M., Bosco, J., Power, S., Mok, K., Cree, B., 2021. Efficacy and safety of ublituximab versus teriflunomide in relapsing multiple

sclerosis: results of the phase 3 ULTIMATE I and II trials (4494). Neurology 96, 1–22. https://doi.org/10.1212/wnl.96.15_supplement.4494.
Therneau, T.M., 2026. A package for survival analysis in R [WWW Document]. R Packag. version 3.8-6. URL https://cran.r-project.org/package=survival.
Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintoré, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17, 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2.