Meta-Analysis

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Comparison of ofatumumab and other disease-modifying therapies for relapsing multiple sclerosis: a network meta-analysis

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Aim: To compare the efficacy of ofatumumab to other disease-modifying therapies (DMTs) for relapsing multiple sclerosis (RMS). **Materials & methods:** A network meta-analysis was conducted to determine the relative effect of ofatumumab on annualized relapse rate and confirmed disability progression at 3 months and 6 months. **Results:** For each outcome, ofatumumab was as effective as other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab and ocrelizumab). **Conclusion:** Ofatumumab offers beneficial outcomes for RMS by reducing relapse and disability progression risk.

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Multiple sclerosis (MS) is a chronic, irreversible disease of the central nervous system (CNS) involving inflammation and demyelination [1]. Relapsing MS (RMS) is defined by the presence of intermittent disease exacerbations of existing or new symptoms, while progressive MS is defined by progressive deterioration into disability that occurs independently of relapses [2]. For approximately 85% of patients with MS, the course of the disease starts with intermittent relapses but without progressive disease (i.e., relapsing-remitting MS [RRMS]) [3]. The risk of transition from RRMS to secondary progressive MS (SPMS) increases with each passing year [4].

For patients with MS, many disease-modifying therapies (DMTs) are available and range from moderately effective to highly effective in reducing relapses [5]. According to the 2018 clinical guideline developed jointly by the European Committee for Treatment and Research in Multiple Sclerosis and the European Academy of Neurology, recommended DMTs for RRMS in Europe include alemtuzumab, cladribine, daclizumab (since withdrawn because of safety concerns [6]), dimethyl fumarate, fingolimod, glatiramer acetate, IFN-β-1a, IFN-β-1b, natalizumab, ocrelizumab, peginterferon β-1a and teriflunomide [7].

Ofatumumab is a human monoclonal antibody that binds selectively to CD20 [8]. Although other currently available monoclonal antibody therapies for RMS are administered by intravenous infusion (e.g., alemtuzumab, natalizumab and ocrelizumab), ofatumumab is administered subcutaneously [9]. ASCLEPIOS I (NCT02792218) and ASCLEPIOS II (NCT02792231) were recent, identically designed (double-blind, double-dummy, active-controlled, parallel-group and multicenter) Phase III randomized controlled trials (RCTs) evaluating the efficacy and safety of ofatumumab in adult patients with RMS. Approximately 900 patients per trial were randomized to receive ofatumumab or teriflunomide for up to 30 months. Ofatumumab met the primary end point in both trials, demonstrating a significant and clinically meaningful decrease in annualized relapse rate (ARR) relative to teriflunomide [10]. Ofatumumab also met key secondary end points of delaying time to 3-month confirmed disability worsening and time to 6-month confirmed disability worsening.

Future Medicine

Effective treatment of patients with MS requires an understanding of the comparative efficacy and safety of different DMTs. Other than the ASCLEPIOS trials, direct comparisons (i.e., head-to-head RCTs) between ofatumumab and other DMTs used to treat patients with RMS have not been conducted. Therefore, indirect treatment comparisons (e.g., network meta-analysis [NMA]) are needed to inform the relative efficacy of ofatumumab. The objective of this study was to compare the efficacy of ofatumumab with other DMTs for the treatment of adult patients with RMS.

Materials & methods

Identification & selection of relevant trials

A systematic literature review (SLR) was conducted and employed a robust methodology for identification of evidence as recommended by the National Institute of Health and Care Excellence (NICE) [11]. Implementation and reporting of the SLR followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. The aim of the SLR was to identify all RCTs assessing the efficacy and safety of DMTs used for the treatment of patients with RMS. The searches were conducted in December 2019. Two reviewers independently screened the titles and abstracts of additional retrieved records against the eligibility criteria (Appendix A of the Supplementary Materials). In the second stage, citations considered to describe potentially eligible articles were independently evaluated in full-text form by two reviewers according to the same criteria. Disagreements were resolved by a third independent reviewer.

The eligibility criteria of the SLR were broader than necessary for the present analysis. For the purpose of informing the comparative analyses, trials identified by the SLR were excluded from the NMA if the population was more than 25% SPMS (without relapses), primary progressive multiple sclerosis (PPMS) and/or progressive-relapsing MS; if the only interventions and comparators were inappropriate or irrelevant (see Appendix A of the Supplementary Materials for a list of relevant DMTs); if the only comparator was best supportive care; if the trial objectives did not include directly comparing the efficacy of any of the aforementioned interventions to any other included DMT or placebo; if the trial did not report any of ARR, time to 3-month (or 12-week) confirmed disability progression (CDP)/worsening or time to 6-month (or 24-week) CDP/worsening; or if the trial duration was less than 48 weeks. The NMA eligibility criteria were aligned with a recently published SLR and NMA [13]. Additional details on the search and screening methodology can be found in Appendix A of the Supplementary Materials.

Data extraction & risk of bias

Data extraction was performed by two independent reviewers using a standardized data extraction form designed in Microsoft Excel® (Microsoft Corporation, WA, USA). Trial design characteristics (e.g., author, year and journal), intervention details (e.g., treatment, dose, route and frequency), patient eligibility criteria, patient characteristics (e.g., age, gender, baseline Expanded Disability Status Scale [EDSS] score, and duration of disease), target efficacy outcomes (i.e., ARR and CDP/worsening) and trial-specific outcome definitions were extracted for all RCTs, where reported. Discrepancies in collected data were resolved by consensus or a third independent reviewer. A risk of bias assessment of each included trial was conducted (Appendix A of the Supplementary Materials) following the principles recommended in the Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare [14].

Feasibility assessment

The validity of results generated by NMAs based on summary-level published data is dependent on the evidence meeting the exchangeability assumption [15]. Under this assumption, all interventions being studied could have been included as comparators in a clinical trial. Failure to meet this assumption can result in biased estimates of comparative effect. As such, a rigorous qualitative assessment of between-trial heterogeneity was conducted based on trial design, patient eligibility criteria, baseline patient characteristics, placebo response and trial-specific outcome definitions (Appendix B of the Supplementary Materials), based on published recommendations regarding the assessment of NMA feasibility [16–18].

Data synthesis & analysis

Outcome measures

The key efficacy outcomes selected for the NMAs were ARR and CDP/worsening at 3 and 6 months, as these are the most reported clinical outcomes in RMS trials. We used the term CDP instead of confirmed disability worsening because CDP is most used in clinical trials in RMS. Please see, the Results section for further details.

Additional analyses were undertaken wherein the ASCLEPIOS patient data were reanalyzed to align with the definition of CDP reported for the ocrelizumab OPERA I and II trials [19]. As such, for each CDP outcome, we present results of an NMA using the predefined CDP data from ASCLEPIOS ('predefined CDP') as well as an NMA using the CDP data from ASCLEPIOS aligned with the definition from OPERA ('OPERA-aligned CDP'). For the OPERA-aligned analysis, the definition was aligned with OPERA in the following ways: disability progression criteria (the required increase in EDSS score as related to baseline EDSS score), definition of baseline EDSS score, confirmatory time window during which the initial progression had to be sustained (e.g., 12 weeks vs 3 months) and confirmation of progression.

For the predefined criteria, CDP required an increase of at least 0.5 points in EDSS score from a baseline score of $\geq$5.5, an increase of at least 1 point from a baseline score of 1 to 5, or an increase of at least 1.5 points from a baseline score of 0. Baseline EDSS was defined as the last EDSS assessment prior to the first dose of study medication. Disability progression had to be sustained for $\geq$90 days for CDP-3 and $\geq$166 days for CDP-6. Progression was confirmed at a scheduled visit in the absence of (confirmed or unconfirmed) relapse if, over the required time interval, all assessments met the progression criterion.

For the OPERA-aligned criteria (i.e., aligned with the OPERA trials), CDP required an increase of at least 0.5 points in EDSS score from a baseline score of >5.5 or an increase of at least 1 point from a baseline score of 0 to 5.5. Baseline EDSS was defined as the mean (without rounding) of the EDSS scores at the screening and baseline visits. Disability progression had to be sustained for $\geq$84 days for CDP-3 and $\geq$161 days for CDP-6. Progression was confirmed at a regularly scheduled visit; nonconfirmatory EDSS score assessments (if any) between the initial disability progression and the confirmation of disability progression were required to be at least as high as the minimum change required for progression.

Data analysis

The NMAs were performed using a Bayesian framework as described in the NICE Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) series [20]. Random effects (RE) models were conducted for the base case analyses because RE makes less stringent assumptions about the consistency of effects [21]. All analyses were conducted using R version 3.6.1, Just Another Gibbs Sampler version 4.3.0 and WinBUGS version 1.4.3, and were based on burn-in and sampling durations of 60,000 iterations each. We generated probability of being best (p-best) and the Surface Under the Cumulative RAnking curve (SUCRA), which are measures of effect commonly presented for Bayesian NMAs [22]. The SUCRA, expressed as a percentage, is the relative probability of an intervention being among the best options or better than other interventions [22]. For interpretation, both p-best and SUCRA values range between 0 and 1, and values nearer to 1 are preferred [22]. To assess whether the models had adequate fit to the data, we compared the posterior mean of the residual deviance (ResDev) from each NMA to the corresponding number of unconstrained data points (approximately equal if the fit is adequate), as well as the deviance information criterion. To ensure that convergence was reached, the Brooks-Gelman-Rubin statistic was assessed [23]. Input data for each NMA are provided in Appendix C of the Supplementary Materials.

For ARR, a Poisson model was used with vague priors for treatment effects and between-trial variances. Inputs for the model were ARR (mean), trial duration, and patient number. For each study, trial duration was extracted in weeks; where only the number of months or years was reported by a study, it was assumed that 1 year = 52 weeks and 12 months = 1 year. Time to 3-month CDP (CDP-3) and time to 6-month CDP (CDP-6) were modeled as a continuous survival model on a log hazard scale with vague priors for treatment effects, and an informative prior distribution for between-trial variances (pharmaceutical vs pharmaceutical interventions; cause-specific mortality/major morbidity event: $\tau\wedge2 \sim$ log normal [-3.95, 1.792]). Mean hazard ratio (HR) for the time-to-event outcome and its 95% CI were preferentially extracted for CDP. Log-HR and its standard error (SE) were derived for the analysis by taking the natural log (Ln) of the mean HR and dividing the width of Ln of the CI limits by 1.96×2, respectively. When the time-to-event outcome was not reported, but the proportion of patients with the event was, the log-HR and its SE were derived using formulae reported in Watkins and Bennett [24].

Additional analyses

Sensitivity analyses were conducted to examine the impact of: including individual trials that were excluded from the base case NMAs, using fixed effect (FE) models instead of RE models, and excluding trials published prior to 2004.

We also conducted qualitative and quantitative (i.e., NMA) comparisons of relevant discontinuation- or adverse event (AE)-related outcomes, the methods and results of which are provided in Appendix F (qualitative comparisons) and Appendix G (NMAs) of the Supplementary Materials. It should be noted that cross-trial comparisons of discontinuation- or AE-related outcomes suffer from many confounding factors. In particular, induction therapies tend to have a low rate of discontinuation because of the inpatient administration schedule, recorded events only account for AEs occurring during the study period and so do not provide a meaningful understanding of long-term safety profiles, and it can be difficult to interpret quantifications of AE-related outcomes when the safety profiles between drugs are very dissimilar and outcomes definitions are infrequently reported.

Results

Literature search

The SLR identified 699 records that met the eligibility criteria after full-text review and removal of duplicates, representing 82 RCTs; 10,533 records were considered irrelevant during the screening and 2,541 were excluded in the full-text appraisal (Appendix A of the Supplementary Materials). Of these 82 RCTs, 34 met the eligibility criteria for inclusion in the indirect treatment comparisons (NMAs), as they had a duration of at least 48 weeks, involved adult patients with RMS, evaluated clinically relevant interventions, reported the outcomes of interest (ARR and/or CDP) and were designed to study clinical outcomes.

Of the 34 RCTs, four were excluded from the base case analyses but explored in sensitivity analyses for the following reasons. The ASSESS trial was excluded as the data were from a poster, not a publication [25]. The ADVANCE trial (peginterferon β-1a vs placebo) [26] was excluded because the NICE committee determined this trial to be an outlier and disregarded its impact in the technology appraisal guidance for ocrelizumab [27]. As noted by the NICE committee in the appraisal, inclusion of the ADVANCE trial in an NMA of time to CDP-6 caused clinically implausible results: peginterferon 'appeared to be more effective than other β interferons and high-efficacy treatments such as natalizumab. The committee heard this was contrary to clinical experience, so it disregarded the comparison with pegylated interferon for this appraisal' [27]. Similarly, the INCOMIN trial (IFN-β-1b SC vs IFN-β-1a IM) [28] was excluded because its result was not reflective of clinical practice; McCool *et al.* [13] and a previous review of interferon trials [29] identified INCOMIN as an outlier, noting that the trial reported significantly different efficacy results between interferon therapies, a result not seen in other head-to-head interferon trials. Finally, the Boiko *et al.* trial was excluded because it was a noninferiority trial comparing different formulations of the same DMT [30].

The risk of bias assessment based on Centre for Reviews and Dissemination guidance is presented in Appendix A of the Supplementary Materials. Across the 34 trials included in the NMA, the overall risk of bias was generally low. There was some risk of bias related to the adequate concealment of treatment allocation and the blinding of care providers, participants and outcome assessors. Otherwise, the risk of bias was low in terms of randomization, prognostic factors, withdrawals and discontinuations, outcomes measured and an appropriate intention-to-treat analysis.

Feasibility assessment

Overall, relapse and ARR definitions were considered sufficiently similar for comparison (Tables 1 & 2). For the outcome of time to CDP, some between-trial differences were noted for the magnitude of increase in EDSS score required to be considered progression (Tables 3 & 4). Apart from ocrelizumab, the outcome definitions for the pivotal ofatumumab trials (ASCLEPIOS) were in alignment with those used for pivotal trials of the other monoclonal antibody therapies – alemtuzumab (CAMMS223 and CARE-MS) and natalizumab (AFFIRM). As described previously in the Materials & Methods section, to account for differences in the time to CDP definition between ASCLEPIOS and the pivotal ocrelizumab trials (OPERA), we conducted an additional analysis with the ASCLEPIOS definition for time to CDP aligned with the OPERA definition.

Definitions of disability progression/worsening varied between trials, but it was commonly defined as a specific increase in EDSS score sustained for a specified length of time (i.e., 3 or 6 months). The use of the terms 'progression' or 'worsening' when referring to disability also varied between published trials. Lublin *et al.* [2] suggest that disability

Table 1. Summary of trial definitions of relapse.

Definition	Trials using definition
New/recurrent/worsening neurological symptoms/abnormalities that lasted for at least 24 hours	ADVANCE; AFFIRM; ASCLEPIOS I; ASCLEPIOS II; ASSESS; BEYOND; CLARITY; CombiRx; CONFIRM; DEFINE; EVIDENCE; FREEDOMS; FREEDOMS II; IFNB MS; INCOMIN; OPERA I; OPERA II; PRISMS; Stepien *et al.* (2013); TEMSO; TENERE; TOWER; TRANSFORMS
New/recurrent/worsening neurological symptoms/abnormalities that lasted for at least 48 hours	Bornstein *et al.* (1987); BRAVO; CAMMS223; CARE-MS I; CARE-MS II; Copolymer 1 MS trial; GALA; MSCRG; REGARD

Definition not reported for Boiko *et al.* [30], Calabrese *et al.* [48] and Bornstein *et al.* [50]
Trials were sorted by the required duration of relapse symptoms, in alignment with McCool *et al.* [13].
Relapse definitions additionally varied between trials in numerous minor ways.

Table 2. Summary of trial definitions of annualized relapse rate.

Definition	Trials using definition
Estimated using a negative binomial model with the cumulative number of confirmed relapses by patient as the response variable and the natural log of time in study in years as an offset variable	ASCLEPIOS I; ASCLEPIOS II
Total number of relapses divided by the total number of patient-years in the study	ADVANCE; AFFIRM; CombiRx; CONFIRM; DEFINE; MSCRG; OPERA I; OPERA II
Total number of confirmed relapses divided by the total days in the study multiplied by 365.25	ASSESS; CLARITY; FREEDOMS II
Exacerbations per patient per year	Boiko *et al.* (2018)
Estimated using a negative binomial model with the total number of confirmed relapses on-study	BRAVO
Estimated using a Poisson regression model with the number of relapses as the dependent variable and the log total amount of follow-up for each participant as an offset variable	CAMMS223
Estimated using a negative binomial model with the total number of relapses by patient as the dependent variable and the log total amount of follow-up for each participant as an offset variable	CARE-MS I; CARE-MS II
Relapses per patient per time on study	EVIDENCE
Number of confirmed relapses per year	FREEDOMS
Cumulative number of confirmed relapses divided by the number of person-years of exposure to treatment	GALA
Total number of relapses across all patients divided by the total time on study across all patients	REGARD
Total number of confirmed relapses that occurred during the treatment period divided by the sum of the treatment durations	TEMSO; TENERE; TOWER
The number of confirmed relapses during a 12-month period	TRANSFORMS

Definition not reported for BEYOND; Calabrese *et al.* [48]; Copolymer 1 MS trial; IFN-β MS; INCOMIN and Stepien *et al.* [49].
ARR: Annualized relapse rate.

'progression' should be limited to the progressive phase of MS (SPMS or PPMS), while disability 'worsening' should be used in the context of RMS. The ASCLEPIOS I and II trials, which included patients with RMS, used the terminology 'worsening.' In contrast, the recent OPERA I and II trials, which also included patients with RMS, used the term 'progression' [19]. In this paper, we used the term 'progression' (i.e., CDP) because it is the most commonly used term across clinical trials in RMS.

Other characteristics of the trials included in the NMA are summarized in Appendix B of the Supplementary Materials. The included trials were published between 1987 and 2019. Overall, the trials included in the NMA were of similar design. Most trials were Phase III, double-blind and multicentric with parallel allocation. Notably, all included alemtuzumab trials (CAMMS223, CARE-MS I and CARE-MS II) were open-label. Eligibility criteria were broadly similar across RCTs with respect to age range, type of MS, baseline EDSS score, relapse history and recent relapses. Some differences were noted in patient eligibility criteria for the required disease duration, prior gadolinium-enhancing (Gd^+) lesions and previous DMT experience. Heterogeneity in several baseline characteristics was observed across the included RCTs: time since first symptoms, number of Gd^+ lesions, volume of T2 lesions and proportion of patients with previous DMT experience.

Placebo response was also compared across placebo-controlled trials as a proxy for overall heterogeneity (Appendix B of the Supplementary Materials). Of the 34 RCTs included in the analysis, 17 had a placebo arm. For ARR and the proportion of patients with CDP-3 and CDP-6, placebo-arm outcomes were generally consistent across trials of similar duration, although qualitatively, placebo-arm ARR was relatively higher in older trials (1987–2003).

Table 3. Trial definitions of time to confirmed disability progression-3 and their alignment with the ASCLEPIOS trials.

Trial name	Definition	Baseline EDSS score range	Required increase in EDSS score to qualify as progression based on baseline EDSS score			
			Baseline EDSS score = 0	Baseline EDSS score = 1–5	Baseline EDSS score = 5.5	Baseline EDSS score >5.5
ASCLEPIOS I and II	An increase in EDSS score of at least 1.5 points if baseline score was 0, of at least 1 point if baseline score was 1–5 or of at least 0.5 points if baseline score was at least 5.5, sustained for at least 3 months	0.0–5.5	1.5	1.0	0.5	NA
ADVANCE	≥1.0-point increase on the EDSS from a baseline EDSS ≥1.0 sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks	0.0–5.0	1.5‡	1.0‡	NA	NA
AFFIRM	An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse)	0.0–5.0	1.5‡	1.0‡	NA	NA
BEYOND	A 1-point change in the score that was sustained for 3 months	0.0–5.0	1.0	1.0‡	NA	NA
Bornstein *et al.* (1987)	An increase of at least one unit in the Kurtzke score that was maintained for at least 3 months	0.0–6.0	1.0	1.0‡	1.0	1.0
BRAVO	A 1.0-point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5-point increase if baseline score was 5.5, sustained for 3 months	0.0–5.5	1.0	1.0‡	0.5	NA
CAMMS223	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse	0.0–3.0	1.5‡	1.0 (Baseline EDSS = 1.0–3.0)	NA	NA
CLARITY	Time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0†	0.0–5.5	1.5‡	1.0†,‡	1.0†	NA
CONFIRM	An increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later	0.0–5.0	1.5‡	1.0‡	NA	NA
Copolymer 1 MS trial	An increase of at least one full step on the EDSS that persisted for at least 3 months	0.0–5.0	1.0	1.0‡	NA	NA
DEFINE	At least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks	0.0–5.0	1.5‡	1.0‡	NA	NA
EVIDENCE	Progression by 1 point on the EDSS scale confirmed at a visit 3 months later without an intervening EDSS value that would not meet the criteria for progression	0.0–5.5	1.0	1.0‡	1.0	NA
FREEDOMS	An increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression	0.0–5.5	1.0	1.0‡	0.5‡	NA
FREEDOMS II	A 1-point EDSS increase from baseline or 0.5-point increase if baseline EDSS is ≥5.5, confirmed 3 months later	0.0–5.5	1.0	1.0‡	0.5‡	NA

†Definition on ClinicalTrials.gov (NCT00213135) differs from the pivotal publication, as it additionally specifies an EDSS score increase of 0.5 was required for a baseline EDSS score of 5 or greater.
‡Matches ASCLEPIOS.
Where the thresholds for EDSS score increase requirements differ from those in ASCLEPIOS, the baseline EDSS score category of the comparator trial has been clarified in brackets.
CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; NA: Not applicable.

Table 3. Trial definitions of time to confirmed disability progression-3 and their alignment with the ASCLEPIOS trials (cont.).

Trial name	Definition	Baseline EDSS score range	Required increase in EDSS score to qualify as progression based on baseline EDSS score			
			Baseline EDSS score = 0	Baseline EDSS score = 1–5	Baseline EDSS score = 5.5	Baseline EDSS score >5.5
IFNB MS	Two consecutive EDSS scores, separated by 90 days, that were identical, with both showing a 1.0-point increase over the baseline score	0.0–5.5	1.0	1.0‡	1.0	NA
OPERA I and II	An increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks	0.0–5.5	1.0	1.0‡	1.0	NA
PRISMS	An increase in EDSS of at least 1 point sustained over at least 3 months	0.0–5.0	1.0	1.0‡	NA	NA
TEMSO	An increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks	0.0–5.5	1.0	1.0‡	1.0	NA
TOWER	An increase from baseline of at least 1 EDSS point (or ≥0.5 points when baseline EDSS score was >5.5 points) that persisted for at least 12 weeks	0.0–5.5	1.0	1.0‡	1.0	NA
TRANSFORMS	A 1.0-point increase in EDSS score (0.5-point increase for baseline EDSS score ≥5.5), confirmed 3 months later in the absence of relapse	0.0–5.5	1.0	1.0‡	0.5‡	NA

†Definition on ClinicalTrials.gov (NCT00213135) differs from the pivotal publication, as it additionally specifies an EDSS score increase of 0.5 was required for a baseline EDSS score of 5 or greater.
‡Matches ASCLEPIOS.
Where the thresholds for EDSS score increase requirements differ from those in ASCLEPIOS, the baseline EDSS score category of the comparator trial has been clarified in brackets.
CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; NA: Not applicable.

NMA results

The base case evidence network diagrams of the possible comparisons for evaluated outcomes are described below. Results of each evaluated outcome were visualized as forest plots of ofatumumab versus comparator and DMT versus placebo, with the latter provided in Appendix D of the Supplementary Materials. Results were also summarized using SUCRA and p-best values.

ARR network

The network diagram for ARR is presented in Figure 1. This network consisted of 17 treatments (including placebo) informed by 30 trials. For ARR (Figure 2), ofatumumab administered subcutaneously (SC) 20 mg once every four weeks (Q4W) was statistically superior to dimethyl fumarate administered orally (PO) 240 mg twice a day (BID), fingolimod PO 0.5 mg once a day (QD), glatiramer acetate SC 20 mg QD, glatiramer acetate SC 40 mg three times per week (TIW), IFN-β-1a administered intramuscularly (IM) 30 µg once per week (QW), IFN-β-1a SC 22 µg TIW, IFN-β-1a SC 44 µg TIW, IFN-β-1b SC 250 µg every two days (Q2D), placebo, teriflunomide PO 7 mg QD and teriflunomide PO 14 mg QD. Ofatumumab SC 20 mg Q4W was numerically but not statistically superior to cladribine PO 3.5 mg/kg, cladribine PO 5.25 mg/kg, natalizumab administered intravenously (IV) 300 mg Q4W and ocrelizumab IV 600 mg Q24W. Finally, ofatumumab SC 20 mg Q4W was numerically inferior to alemtuzumab IV 12 mg, but this result was not statistically significant. Overall, the NMA results demonstrated that ofatumumab was similar in efficacy to other highly efficacious monoclonal antibody therapies (i.e., alemtuzumab, natalizumab and ocrelizumab) and ranked among the most efficacious DMTs in terms of reducing ARR in patients with RMS. The probability that ofatumumab was the best treatment with respect to ARR was 28% (Appendix D of the Supplementary Materials). The SUCRA value for ofatumumab was 91% (Appendix D).

CDP networks

Overall, the NMA results demonstrated that ofatumumab was similar in efficacy to other highly efficacious monoclonal antibody therapies (i.e., alemtuzumab, natalizumab and ocrelizumab) and ranked among the most efficacious DMTs in terms of time to CDP-3 and time to CDP-6 (Figures 4 & 6). The results were similar whether the data from ASCLEPIOS used the predefined or OPERA-aligned criteria for CDP.

Table 4. Trial definitions of time to confirmed disability progression-6 and their alignment with the ASCLEPIOS trials.

Trial name	Definition	Baseline EDSS score range	Required increase in EDSS score to qualify as progression based on baseline EDSS score			
			Baseline EDSS score = 0	Baseline EDSS score = 1–5	Baseline EDSS score = 5.5	Baseline EDSS score >5.5
ASCLEPIOS I and II	An increase in EDSS score of at least 1.5 points if baseline score was 0, of at least 1 point if baseline score was 1–5 or of at least 0.5 points if baseline score was at least 5.5, sustained for at least 6 months	0.0–5.5	1.5	1.0	0.5	NA
ADVANCE†	At least a 1-point increase from baseline EDSS ≥1, or 1.5-point increase for patients with baseline EDSS of 0, sustained for 24 weeks	0.0–5.0	1.5§	1.0§	NA	NA
AFFIRM	An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 24 weeks (progression could not be confirmed during a relapse)	0.0–5.0	1.5§	1.0§	NA	NA
BRAVO	A 1.0-point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5-point increase if baseline score was 5.5, sustained for 6 months	0.0–5.5	1.0	1.0§	0.5§	NA
CAMMS223	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse	0.0–3.0	1.5§	1.0 (Baseline EDSS = 1.0–3.0)	NA	NA
CARE-MS I	An increase from baseline of at least 1 EDSS point (or ≥1.5 points if baseline EDSS score was 0) confirmed over 6 months	0.0–3.0	1.5§	1.0 (Baseline EDSS = 1.0–3.0)	NA	NA
CARE-MS II	An increase from baseline of at least 1 EDSS point (or ≥1.5 points if the baseline EDSS score was 0) confirmed over 6 months	0.0–5.0	1.5§	1.0§	NA	NA
CLARITY	Definition for CDP-6 was not reported. Definition was assumed to match that reported for CDP-3 with regard to required increase in EDSS: Time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0‡	0.0–5.5	1.5§	1.0‡,§	1.0‡	NA
CombiRx	A 1.0 increase in the EDSS from baseline, when baseline ≤5.0; or an increase of 0.5 from baseline, when baseline ≥5.5, sustained for 6 months (two successive quarterly visits)	0.0–5.5	1.0	1.0§	0.5§	NA
CONFIRM†	A ≥1.0-point increase on the EDSS from a baseline EDSS score ≥1.0 that was confirmed at least 24 weeks later, or a ≥1.5-point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 24 weeks later	0.0–5.0	1.5§	1.0§	NA	NA
DEFINE†	A ≥1.0-point increase on the EDSS from a baseline EDSS score ≥1.0 that was confirmed at least 24 weeks later, or a ≥1.5-point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 24 weeks later	0.0–5.0	1.5§	1.0§	NA	NA
EVIDENCE	Progression by 1 point on the EDSS scale confirmed at a visit 6 months later without an intervening EDSS value that would not meet the criteria for progression	0.0–5.5	1.0	1.0§	1.0	NA

†Definition not found in the pivotal publication, so refers to a Summary of Product Characteristics or European Medicines Agency assessment report associated with the trial.
‡Definition on ClinicalTrials.gov (NCT00213135) differs from the pivotal publication, as it additionally specifies an EDSS score increase of 0.5 was required for a baseline EDSS score of 5 or greater.
§Matches ASCLEPIOS.
Where the thresholds for EDSS score increase requirements differ from those in ASCLEPIOS, the baseline EDSS score category of the comparator trial has been clarified in brackets.
CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; NA: Not applicable.

Table 4. Trial definitions of time to confirmed disability progression-6 and their alignment with the ASCLEPIOS trials (cont.).

Trial name	Definition	Baseline EDSS score range	Required increase in EDSS score to qualify as progression based on baseline EDSS score			
			Baseline EDSS score = 0	Baseline EDSS score = 1–5	Baseline EDSS score = 5.5	Baseline EDSS score >5.5
FREEDOMS	An increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 6 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression	0.0–5.5	1.0	1.0§	0.5§	NA
FREEDOMS II	A 1-point EDSS increase from baseline or 0.5-point increase if baseline EDSS is ≥5.5, confirmed 6 months later	0.0–5.5	1.0	1.0§	0.5§	NA
INCOMIN	An increase in EDSS of at least 1 point sustained for at least 6 months and confirmed at the end of follow-up	1.0–3.5	NA	1.0 (Baseline EDSS = 1.0–3.5)	NA	NA
MSCRG	Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months	1.0–3.5	NA	1.0 (Baseline EDSS = 1.0–3.5)	NA	NA
OPERA I and II	An increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 24 weeks	0.0–5.5	1.0	1.0§	1.0	NA
REGARD	Disability progression at the 6-month follow-up visit was confirmed as follows: if the EDSS score at baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5–4.5 at baseline, then a change of 1.0 point or more was required; and if the EDSS at baseline was 5 points or more, then the change required was 0.5 points or more	0.0–5.5	1.5	1.0 (Baseline EDSS = 0.5–4.5)	0.5§	NA
TEMSO†	At least 1-point increase on EDSS score from baseline, if the baseline EDSS score was ≤5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was >5.5; this increase in EDSS score was to be persistent for at least 24 weeks	0.0–5.5	1.0	1.0§	1.0	NA
TOWER†	At least 1-point increase on EDSS score from baseline, if the baseline EDSS score was ≤5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was >5.5; this increase in EDSS score was to be persistent for at least 24 weeks	0.0–5.5	1.0	1.0§	1.0	NA

†Definition not found in the pivotal publication, so refers to a Summary of Product Characteristics or European Medicines Agency assessment report associated with the trial.
‡Definition on ClinicalTrials.gov (NCT00213135) differs from the pivotal publication, as it additionally specifies an EDSS score increase of 0.5 was required for a baseline EDSS score of 5 or greater.
§Matches ASCLEPIOS.
Where the thresholds for EDSS score increase requirements differ from those in ASCLEPIOS, the baseline EDSS score category of the comparator trial has been clarified in brackets.
CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; NA: Not applicable.

Time to CDP-3 network

The network diagram for time to CDP-3 is presented in Figure 3. This network consisted of 16 treatments (including placebo) informed by 20 trials and a previously published Haute Autorité de Santé (HAS) meta-analysis of the three included alemtuzumab trials (CAMMS223, CARE-MS I and CARE-MS II) [31]. The HAS meta-analysis reported a pooled time to CDP-3 estimate derived from these three trials. This approach, which was in alignment with McCool *et al.* [13], was necessary because the CARE-MS trials (I and II) did not publicly report the results for the outcome of time to CDP-3. Reports by health technology assessment bodies (i.e., HAS and NICE) and recently published RMS NMAs [13,32] were searched for time to CDP-3 data from the CARE-MS trials, but these data were either absent or redacted in each case.

For time to CDP-3 using the predefined criteria (Figure 4A), ofatumumab SC 20 mg Q4W was statistically superior to fingolimod PO 0.5 mg QD, glatiramer acetate SC 20 mg QD, IFN-β-1a IM 30 µg QW, IFN-β-1b SC 250 µg Q2D, placebo, teriflunomide PO 7 mg QD and teriflunomide PO 14 mg QD. Ofatumumab SC

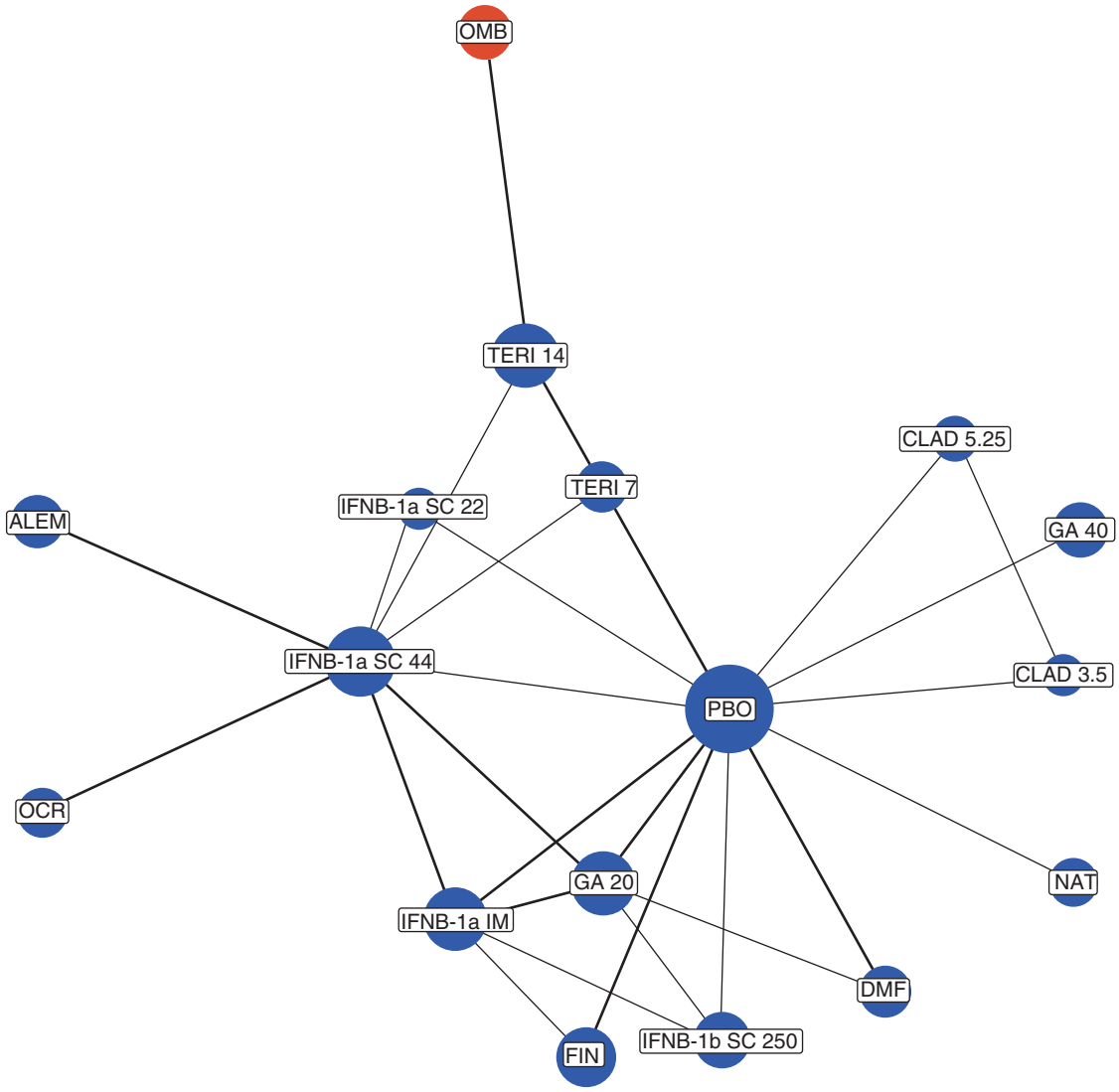

Figure 1. Network diagram for ARR.
ALEM: Alemtuzumab; ARR: Annualized relapse rate; CLAD: Cladribine; DMF: Dimethyl fumarate; FIN: Fingolimod; GA: Glatiramer acetate; IFNB: Interferon beta; IM: Intramuscular; NAT: Natalizumab; OCR: Ocrelizumab; OMB: Ofatumumab; PBO: Placebo; SC: Subcutaneous; TERI: Teriflunomide.

20 mg Q4W was numerically but not statistically superior to cladribine PO 3.5 mg/kg, cladribine PO 5.25 mg/kg, dimethyl fumarate PO 240 mg BID, IFN-β-1a SC 22 µg TIW, IFN-β-1a SC 44 µg TIW and natalizumab IV 300 mg Q4W. Finally, ofatumumab SC 20 mg Q4W was numerically inferior to alemtuzumab IV 12 mg and ocrelizumab IV 600 mg Q24W, but the results were not statistically significant. For time to CDP-3 using the OPERA-aligned criteria (Figure 4B), the direction and statistical significance of the results were the same as with the predefined criteria, except that ofatumumab SC 20 mg Q4W was not statistically superior to fingolimod PO 0.5 mg QD using the OPERA-aligned criteria. The probabilities that ofatumumab was the best treatment with respect to time to CDP-3 using the predefined and OPERA-aligned criteria were 23% and 29%, respectively (Appendix D of the Supplementary Materials). The SUCRA value for ofatumumab was 87% for time to CDP-3 using the predefined criteria and 89% using the OPERA-aligned criteria (Appendix D).

Time to CDP-6 network

The network diagram for time to CDP-6 is presented in Figure 5. This network consisted of 14 treatments (including placebo) informed by 20 trials. For time to CDP-6 using the predefined criteria (Figure 6A), ofatumumab SC

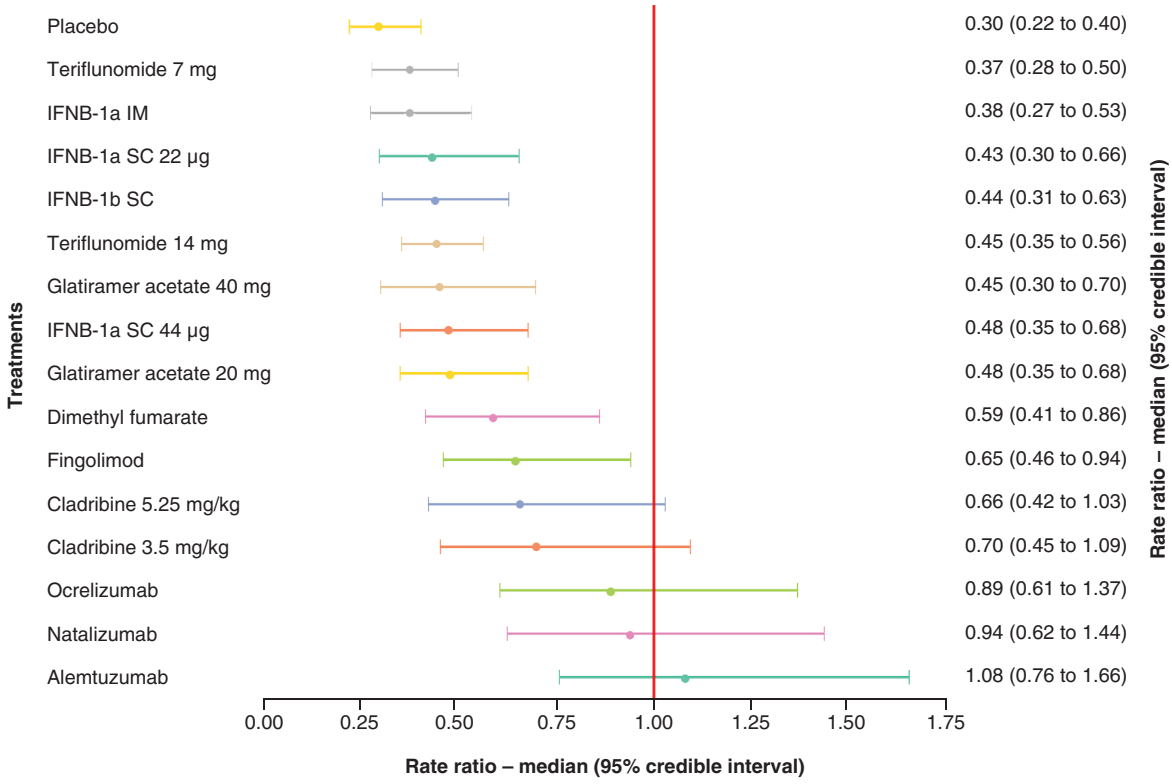

Figure 2. ARR NMA results (ofatumumab vs comparator).
ARR: Annualized relapse rate; IFNB: Interferon beta; IM: Intramuscular; NMA: Network meta-analysis; SC: Subcutaneous.

20 mg Q4W was statistically superior to placebo, teriflunomide PO 7 mg QD and teriflunomide PO 14 mg QD. Ofatumumab SC 20 mg Q4W was numerically but not statistically superior to cladribine PO 3.5 mg/kg, cladribine PO 5.25 mg/kg, dimethyl fumarate PO 240 mg BID, fingolimod PO 0.5 mg QD, glatiramer acetate SC 20 mg QD, IFN-β-1a IM 30 µg QW and IFN-β-1a SC 44 µg TIW. Finally, ofatumumab SC 20 mg Q4W was numerically inferior to alemtuzumab IV 12 mg, natalizumab IV 300 mg Q4W and ocrelizumab IV 600 mg Q24W, but the results were not statistically significant. For time to CDP-6 using the OPERA-aligned criteria (Figure 6B), the direction and statistical significance of the results were consistent with the predefined criteria, except that ofatumumab SC 20 mg Q4W was also numerically (not statistically) superior to natalizumab IV 300 mg Q4W and ocrelizumab IV 600 mg Q24W. The probabilities that ofatumumab was the best treatment with respect to time to CDP-6 using the predefined and OPERA-aligned criteria were 10% and 29%, respectively (Appendix D of the Supplementary Materials). The SUCRA value for ofatumumab was 72% for time to CDP-3 using the predefined criteria and 84% using the OPERA-aligned criteria (Appendix D).

Additional analyses

The results of each sensitivity analysis (inclusion of individual excluded trials, use of FE model, or exclusion of trials published prior to 2004) were consistent with base case NMA results for each outcome. Detailed results are provided in Appendix E of the Supplementary Materials.

Discussion

In the ASCLEPIOS trials, ofatumumab was associated with lower ARR and CDP compared with teriflunomide. However, direct comparisons with other DMTs have not been conducted. The objective of this study was therefore to indirectly compare the efficacy and safety of ofatumumab with other DMTs in the treatment of RMS. We conducted a feasibility assessment and NMAs for the key efficacy outcomes of ARR and CDP.

Prior to conducting indirect comparisons, we assessed the suitability of synthesizing the results of multiple trials in a unified analysis based on the available clinical trial evidence [33–36]. The validity of such analyses relies on

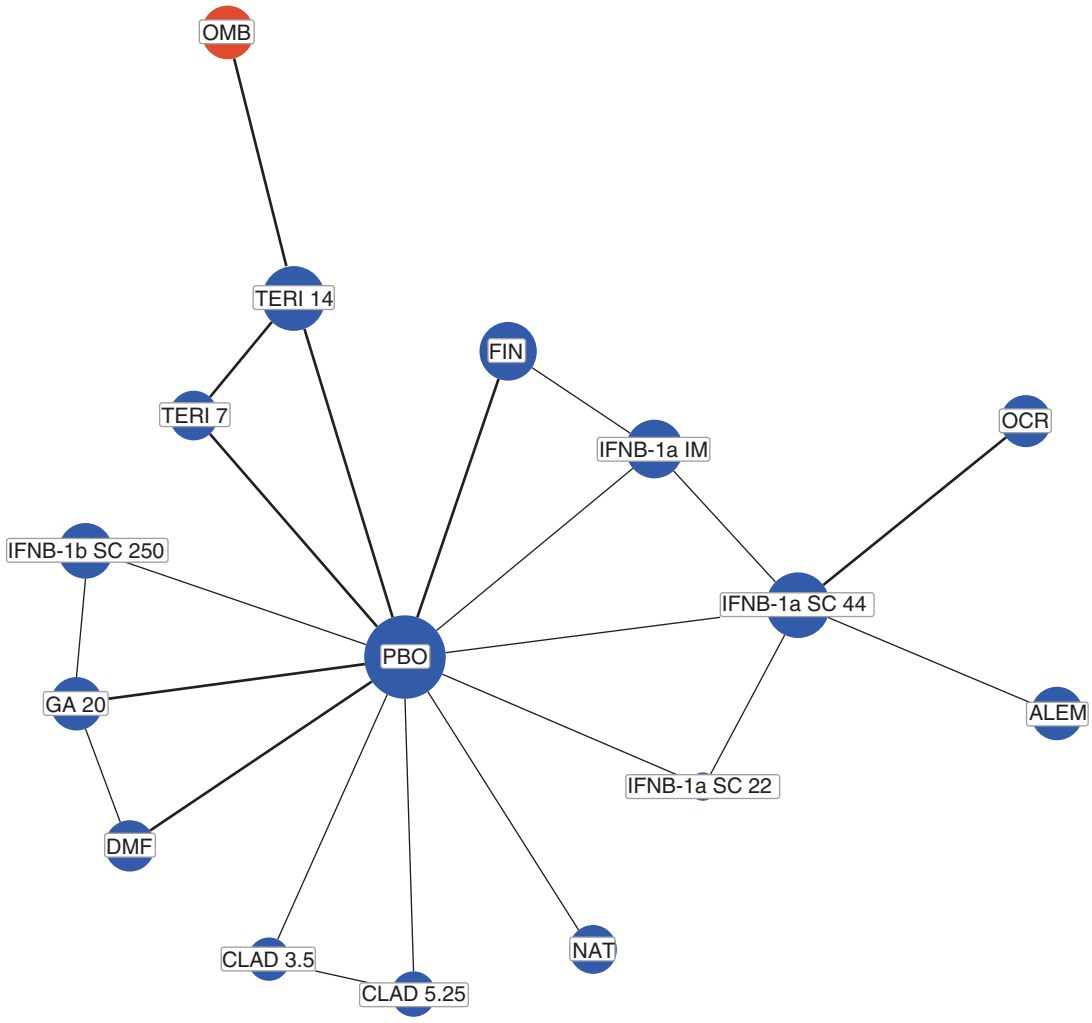

Figure 3. Network diagram for time to CDP-3.
For the time to CDP-3 NMA, a meta-analysis from the HAS [31] was used in place of the three included alemtuzumab trials (CAMMS223, CARE-MS I and CARE-MS II) [45–47]. The HAS meta-analysis reported a pooled time to CDP-3 estimate derived from these three trials. This approach, which was in alignment with McCool *et al.* [13], was necessary because the CARE-MS trials (I and II) did not publicly report the results for the outcome of time to CDP-3. Reports by health technology assessment bodies (i.e., HAS and NICE) and recently published RMS NMAs [13,32] were searched for time to CDP-3 data from the CARE-MS trials, but these data were either absent or redacted in each case.
ALEM: Alemtuzumab; CDP: Confirmed disability progression; CLAD: Cladribine; DMF: Dimethyl fumarate; FIN: Fingolimod; GA: Glatiramer acetate; HAS: Haute Autorité de Santé; IFNB: Interferon beta; IM: Intramuscular; NAT: Natalizumab; NICE: National Institute for Health and Care Excellence; OCR: Ocrelizumab; OMB: Ofatumumab; PBO: Placebo; SC: Subcutaneous; TERI: Teriflunomide.

whether there are differences among the RCTs included in the treatment comparison networks. Heterogeneity in some baseline patient characteristics and placebo arm outcomes was noted in our assessment, but these differences did not preclude NMAs. This conclusion agrees with four recently published NMAs, each of which included an evidence base similar to that of the present study and conducted sensitivity analyses that demonstrated this heterogeneity did not appreciably impact NMA results [13,32,37,38].

We considered two approaches to account for between-trial heterogeneity. First, although heterogeneity in an NMA can be accounted for with meta-regression, this approach was not considered appropriate given the limited number of trials connecting treatments in each outcome network. McCool *et al.* reported that conducting a meta-regression to explore whether follow-up time influenced the relative treatment effects did not improve the model fit over the base case model [13]. Second, ITC methodologies have been developed that can leverage individual patient data (IPD) from RCTs to adjust for potential heterogeneity, such as matching-adjusted indirect comparison

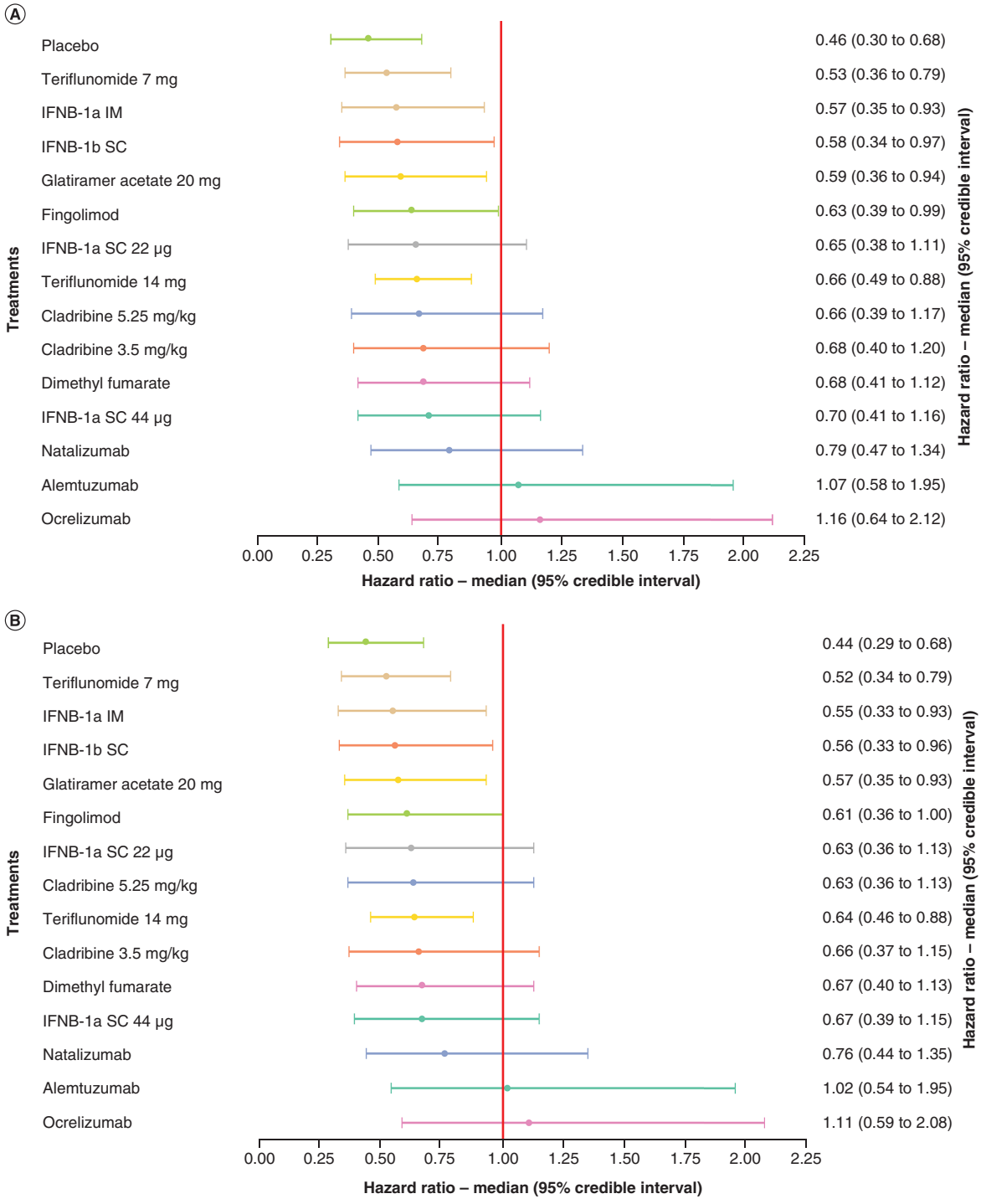

Figure 4. Time to CDP-3 NMA results (ofatumumab vs comparator). Results are shown for analyses using **(A)** the predefined criteria and **(B)** the OPERA-aligned criteria.
CDP: Confirmed disability progression; IFNB: Interferon beta; IM: Intramuscular; NMA: Network meta-analysis; SC: Subcutaneous.

(MAIC) and simulated treatment comparison (STC). In RMS where numerous treatment options exist, an NMA was selected as the most appropriate and informative analytical method because it allows for the simultaneous comparison of multiple treatments in a single analysis by combining direct and indirect evidence within a network. In contrast, MAICs and STCs produce only pairwise comparisons. Given our objective was to provide a holistic

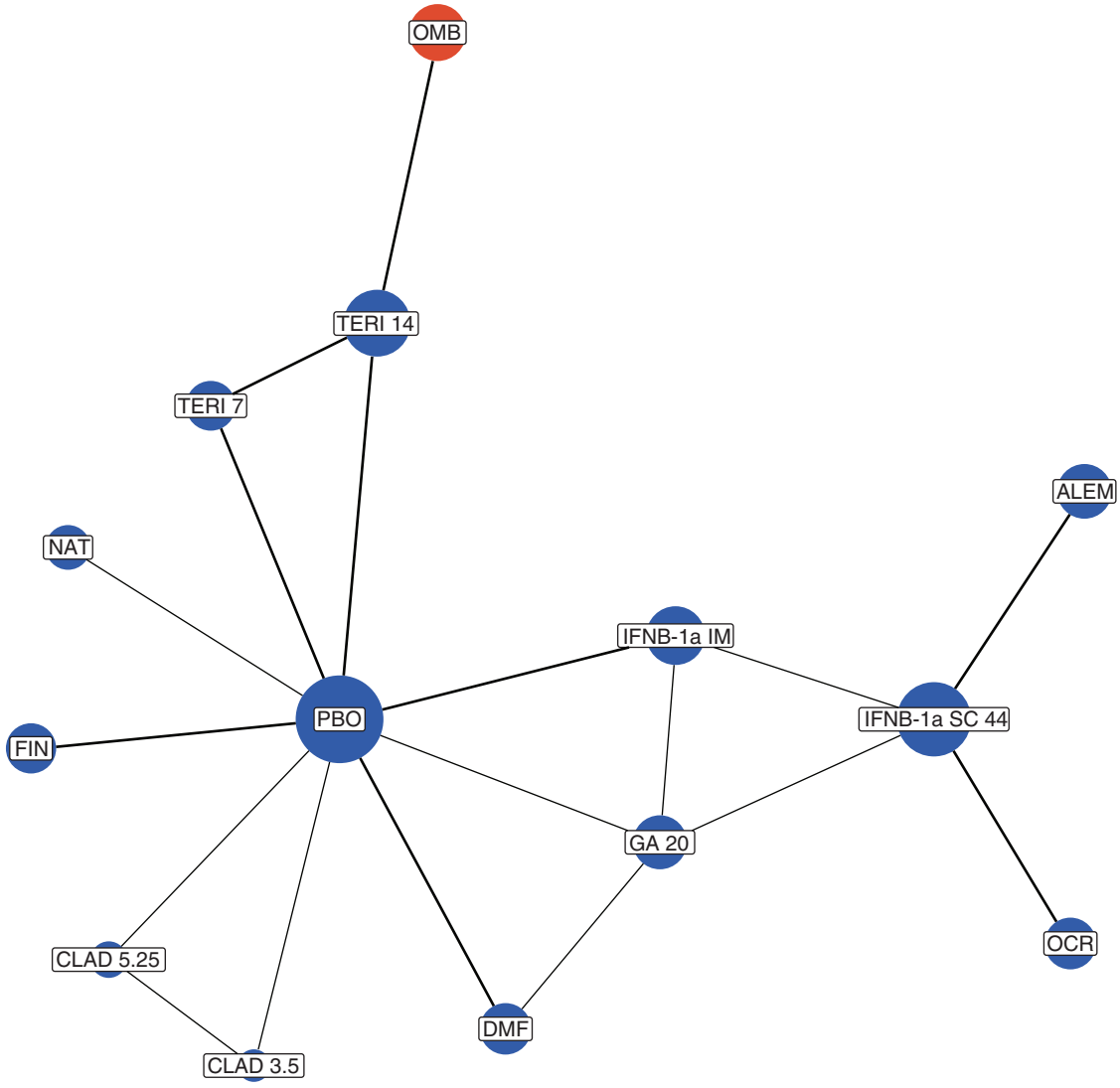

Figure 5. Network diagram for time to CDP-6.
ALEM: Alemtuzumab; CDP: Confirmed disability progression; CLAD: Cladribine; DMF: Dimethyl fumarate; FIN: Fingolimod; GA: Glatiramer acetate; IFNB: Interferon beta; IM: Intramuscular; NAT: Natalizumab; OCR: Ocrelizumab; OMB: Ofatumumab; PBO: Placebo; SC: Subcutaneous; TERI: Teriflunomide.

synthesis of the available clinical trial data across all clinically relevant DMTs for this indication, NMAs (in contrast to MAICs and STCs) were considered more appropriate because they permit comparison across the entire body of evidence at once. Because of the relatively large number of relevant therapies and therefore exponentially larger number of possible pairwise comparisons, MAICs and STCs were considered to be out-of-scope for the present analyses. However, there is a lack of data quantifying the impact of heterogenous patient characteristics in this body of evidence, and MAICs and/or STCs comparing the most clinically relevant therapies in this disease area would provide valuable insight in future analyses.

Outcome definitions for relapse, ARR, time to CDP-3 and time to CDP-6 were considered sufficiently similar for comparison throughout the network, but there were some differences. For the definition of time to CDP, trials differed in the magnitude of increase in EDSS score required to be considered progression. As previously mentioned, there is precedence for conducting NMAs in this disease area with a similar evidence base (e.g., McCool *et al.* [13]), but to our knowledge, the impact of this heterogeneity has not been explored to date. Compared with other monoclonal antibody therapies, the definition of progression was consistent between ASCLEPIOS and the trials of alemtuzumab and natalizumab, but not between ASCLEPIOS and OPERA (ocrelizumab). An analysis was

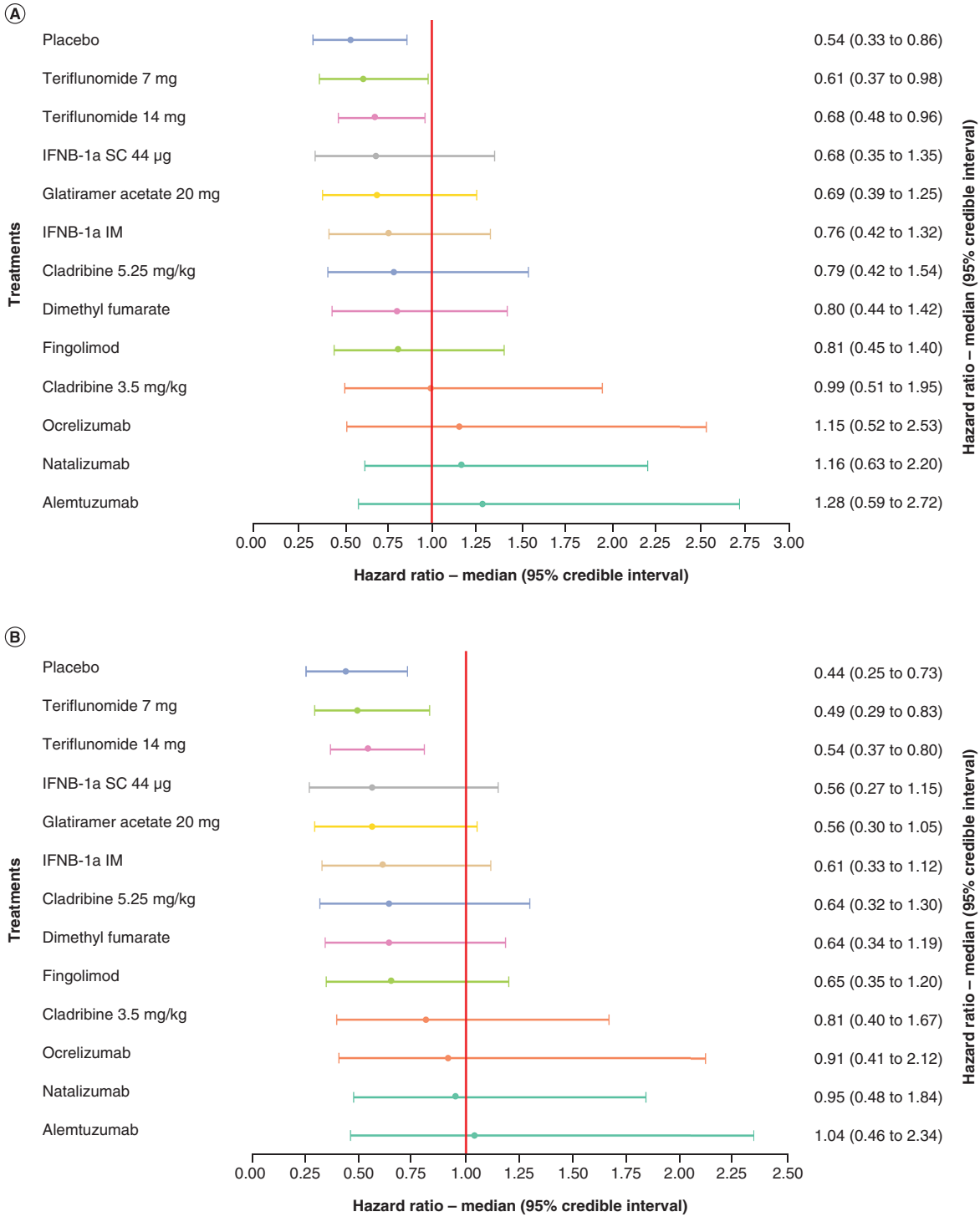

Figure 6. Time to CDP-6 NMA results (ofatumumab vs comparator). Results are shown for analyses using **(A)** the predefined criteria and **(B)** the OPERA-aligned criteria.
CDP: Confirmed disability progression; IFNB: Interferon beta; IM: Intramuscular; NMA: Network meta-analysis; SC: Subcutaneous.

therefore undertaken to explore the impact of aligning the ASCLEPIOS definition of progression to that reported by the pivotal ocrelizumab trials OPERA I and II.

Data from 34 RCTs were used to indirectly compare ofatumumab with other DMTs for the treatment of RMS using NMA methods adhering to best practices described by NICE [20]. The results of the NMAs demonstrated that ofatumumab was statistically superior to or not statistically different from other DMTs across all outcomes. For each of ARR, time to CDP-3 and time to CDP-6, ofatumumab was not statistically different in efficacy compared with other monoclonal antibody therapies (i.e., alemtuzumab, natalizumab and ocrelizumab), and ranked among the most efficacious DMTs overall. Results were robust to the alignment of the ASCLEPIOS CDP definition with OPERA, the inclusion of trials excluded from the base case analysis, the exclusion of trials published prior to 2004, and the use of a FE model instead of a RE model.

Previous NMAs have also compared the efficacy of DMTs in MS and consistently concluded that monoclonal antibodies were among the most efficacious therapies across key clinical outcomes [13,32,37–44]. The most recent of these, reported by McCool *et al.* [13], compared the relative treatment effects of ocrelizumab with other therapies approved as of 2017 for RMS. Monoclonal antibody therapies (i.e., alemtuzumab, natalizumab and ocrelizumab) demonstrated the highest efficacy in terms of ARR and time to CDP-3 and were among the most efficacious therapies in terms of time to CDP-6, a result that aligns with the analyses reported herein [13]. Lucchetta *et al.* [38] carried out an NMA of therapies in RRMS and concluded that alemtuzumab, natalizumab and ocrelizumab had the highest probability of being the best alternative for the outcome of ARR, with no significant differences identified between these three therapies. For the outcomes of time to CDP-3 and time to CDP-6, monoclonal antibody therapies were among the most efficacious DMTs [38]. Siddiqui *et al.* [32] performed an NMA to compare DMTs in patients with active RRMS and in a subgroup with high disease activity, and demonstrated that the most effective therapies in terms of ARR and time to CDP-3 were monoclonal antibodies. For time to CDP-6, monoclonal antibody therapies were among the most effective therapies [32]. An NMA conducted by Fogarty *et al.* [39] in patients with RRMS reported that the monoclonal antibody therapies alemtuzumab and natalizumab consistently ranked among the top therapies across the outcomes of ARR, time to CDP-3 and time to CDP-6. Finally, Tramacere *et al.* [43] carried out an NMA for RRMS and analyzed 24-week CDP and 12- and 24-month ARR. Alemtuzumab and natalizumab were consistently the most favorable DMTs in terms of ARR and were among the most effective therapies in preventing disability progression over 24 months [43].

For the outcome of time to CDP-6, other NMAs (e.g., [13,32,38]) ranked peginterferon and IFN-1b along with the monoclonal antibodies as the top therapies. These therapies were evaluated in the ADVANCE and INCOMIN trials, which we excluded from our base case analysis because their results were not considered reflective of clinical practice [13,27,29]. The sensitivity analyses in which these trials were included for the time to CDP-6 network align with the results of the other published NMAs.

Overall, the results and conclusions of these previous NMAs were consistent with those presented herein. The present study includes therapies made available more recently than previously published NMAs; cladribine and ocrelizumab were not considered in Tramacere *et al.* [43] or Fogarty *et al.* [39], and the present NMA is the first to include ofatumumab. It is important to note that daclizumab, which was included in the previously published NMAs, has since been withdrawn because of safety concerns, and was therefore excluded from our analyses.

The results of our analyses and other NMAs in MS were also consistent with the Association of British Neurologists (ABN) MS treatment guidelines (most recently revised in 2015), which suggested classifying monoclonal antibody therapies (i.e., alemtuzumab and natalizumab) as high efficacy as opposed to moderate efficacy based on reported average relapse reduction [5]. However, ofatumumab was not included in these guidelines or other NMAs, since ASCLEPIOS trial results were not available at the time. Our analysis provides support for expanding the high efficacy class defined by the ABN to include ofatumumab.

Several strengths should be noted for this study. First, all relevant comparators for ofatumumab were included in the analysis, and this reflects all approved DMTs in the USA and Europe for the treatment of RMS up to now. Furthermore, with the inclusion of ofatumumab, this analysis represents an update relative to previously published NMAs. Each NMA was performed in accordance with the methodology recommended by NICE. Sensitivity analyses were included to understand the impact of trials excluded from the base case analysis, and the results were robust to these analyses as well as the exclusion of trials published prior to 2004 and the use of a FE model instead of a RE model. Analyses were also conducted to evaluate the impact of different outcome definitions for time to CDP-3 and time to CDP-6 between key trials (ASCLEPIOS I and II, and OPERA I and II), which demonstrated

the results were consistent when assessing CDP based on different thresholds of EDSS score. Finally, the analyses reported herein were based on published summary-level data from RCTs.

There were several limitations to this study. Indirect treatment comparisons such as NMAs rely on the assumption that trials are sufficiently similar such that the effect estimate will not be biased by underlying differences in patient populations. In this analysis, trial design and patient eligibility criteria were relatively similar, but between-trial heterogeneity was observed in some baseline patient characteristics. There is precedence to consider these between-trial differences acceptable [13,32,37,38], but it is important to note that the impact of the heterogeneous characteristics has not been explored in this study, which represents an important area of further research. The use of IPD to conduct adjusted analyses such as MAIC or STC may be instrumental in closing this knowledge gap, in light of the sparsely connected network precluding meta-regression. On a similar note, the oldest of the included trials was published in 1987; we observed in our feasibility assessment that older trials (1987–2003) were more likely to have elevated placebo-arm (i.e., baseline risk) relapse rates, which is an unsurprising trend given the development of MS natural history, updated diagnostic criteria allowing for earlier diagnosis and improved standard of care over these past decades. However, the results of a sensitivity analysis excluding trials published prior to 2004 were similar to the base case. Also, as a result of the therapeutic advances in MS and change in treatment practices over time, the evidence networks are not centered around a single common comparator, resulting in some DMTs being connected through multiple nodes. In addition, all trial placebo arms were considered in the same network node regardless of the route of administration. This approach allowed for a holistic comparison of all approved therapies for RMS and is commonly found in published evidence synthesis literature for this disease [13,32,37–44]. The outcomes evaluated in this study were observed during short-term clinical trials and therefore may not necessarily reflect clinical outcomes experienced beyond their duration. Finally, in the time to CDP-3 NMA, the use of meta-analysis data to inform alemtuzumab comparisons was a limitation; however, the relevant trial-level data were not available for this outcome.

Conclusion

In the ASCLEPIOS I and II trials, ofatumumab demonstrated superiority over teriflunomide in a direct comparison. The results of this study demonstrate that ofatumumab, administered subcutaneously, may be as effective as other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab and ocrelizumab). Ofatumumab was superior to or not statistically different from all other DMTs in terms of reducing relapse rate and disability progression.

Summary points

- Effective treatment of patients with relapsing multiple sclerosis (RMS) requires an understanding of the comparative efficacy of different disease-modifying therapies (DMTs).
- There is a lack of direct evidence for ofatumumab, a subcutaneously administered monoclonal antibody, compared with DMTs aside from teriflunomide.
- We conducted Bayesian network meta-analyses (NMA) of key efficacy outcomes (annualized relapse rate [ARR], time to 3-month confirmed disability progression [CDP] and time to 6-month CDP) to compare ofatumumab to other DMTs for adult patients with RMS.
- For the outcomes of ARR, time to 3-month CDP and time to 6-month CDP, NMA results demonstrated ofatumumab may be similarly effective compared with other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab and ocrelizumab).
- For the outcomes of ARR, time to 3-month CDP and time to 6-month CDP, NMA results demonstrated ofatumumab was numerically superior, and in some cases statistically superior, to non-antibody DMTs.
- The results of the NMAs were robust to the conducted sensitivity analyses.
- Ofatumumab is a human monoclonal antibody that offers beneficial outcomes for RMS by reducing relapse frequency and disability progression risk.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0122

Author contributions

DA Häring, D Stoneman, N Adlard, L Klotz and C Cameron conceived of and contributed to the design of the research and provided critical revisions to the manuscript. C Cameron, IA Samjoo and E Worthington contributed to research design. E Worthington, C Drudge and M Zhao extracted data, conducted analyses and discussed analytical results. IA Samjoo drafted the manuscript. All the authors provided critical feedback of the research, analysis and manuscript.

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No writing assistance was utilized in the production of this manuscript.

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