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External Assessment Group Report

Cost comparison evaluation process

Ublituximab for treating relapsing multiple sclerosis

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

A Zhou critiqued the cost-comparison analyses and wrote Sections 5 and 6 of this report.

E Uphoff and M Corbett critiqued the clinical evidence and wrote Sections 2, 3 and 4 of this report.

H Fulbright provided information science support.

C Rothery critiqued the cost-comparison analyses, contributed to writing Sections 5 and 6 of the report and had overall responsibility for the cost-comparison.

M Simmonds had overall responsibility for the clinical sections of the report and contributed to the writing of the report.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted].

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List of abbreviations

AE	adverse event	MRI	magnetic resonance imaging
ARR	annualised relapse rate	MS	multiple sclerosis
BNF	British National Formulary	MSQOL-54	Multiple Sclerosis Quality of Life-54
CDI	confirmed disease improvement	NEDA	no evidence of disease activity
CDP	confirmed disease progression	NHS	National Health Service
CI	confidence Interval	NICE	National Institute for Health and Care Excellence
CS	company submission	NMA	network meta-analysis
CSR	Clinical Study Report	OR	odds ratio
DMT	disease-modifying therapy	PAS	patient access scheme
EAG	Evidence Assessment Group	PfC	points for clarification
EDSS	expanded disability status scale	QALY	quality-adjusted life year
Gd	Gadolinium	RCT	randomised controlled trial
h	hour	RMS	relapsing multiple sclerosis
HR	hazard ratio	RRMS	relapsing-remitting multiple sclerosis
HRQoL	health-related quality of life	RR	risk ratio
HTA	health technology assessment	SAE	serious adverse event
ICER	incremental cost-effectiveness ratio	SC	subcutaneous
IRR	infusion-related reactions	SD	standard deviation
IV	intravenous	SF-36	Short Form-36
mAb	monoclonal antibody	SLR	systematic literature review
MAIC	matching-adjusted indirect comparison	SPMS	secondary progressive multiple sclerosis
MHRA	Medicines and Healthcare products Regulatory Agency	SUCRA	surface under the cumulative ranking curve

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

1.1 Summary of clinical evidence

The clinical evidence supplied by the company included the two ULTIMATE trials of ublituximab and a network meta-analysis of treatments for RRMS. The ULTIMATE trials showed that ublituximab appears to be an effective treatment for RRMS, being superior to teriflunomide in reducing relapse rates. However, the trials did not show a benefit of ublituximab compared to teriflunomide for worsening disability outcomes at 12 and 24 weeks. It is unclear whether this result is driven by the low proportion of patients experiencing a worsening of disability over the trial periods.

The network meta-analyses suggested that ublituximab may have similar efficacy to ocrelizumab and ofatumumab for reduction of relapse rates and slowing of disease progression. There was, however, considerable uncertainty in the results, and some evidence of network inconsistency. Results for disease progression at 12 months and treatment discontinuation were in the direction of favouring ocrelizumab and ofatumumab over ublituximab, although any differences were not statistically significant.

1.2 Summary of cost-effectiveness evidence

The costs considered in the company's cost comparison analysis comprised of drug acquisition costs; drug administration costs, monitoring costs, and adverse event costs, which were estimated per patient per year. Monitoring costs did not differ by treatment. Therefore, the only difference in costs between ublituximab and its comparators are: (i) the acquisition costs in the first and subsequent years; (ii) the administration method (SC or IV) and the duration of infusion and monitoring time; and (iii) resource use associated with adverse events. Patients do not discontinue treatment in the company's base case analysis, while the impact of treatment discontinuation was explored in a scenario analysis. The total costs of ublituximab, ofatumumab, and ocrelizumab (IV or SC) are compared over a 5-year time horizon (without discounting).

1.3 EAG critique of cost-comparison approach to this technology assessment

1.3.1 Clinical evidence

The EAG notes several areas of concern with the clinical evidence presented that raise doubts as to whether ublituximab can be considered equivalent in efficacy to ocrelizumab and ofatumumab.

The EAG reanalysed some components of the ULTIMATE trials, to investigate whether the effectiveness of ublituximab varied across subgroups of patients. Of particular concern is that [redacted]

There was no direct evidence to compare ublituximab with ocrelizumab and ofatumumab, and comparisons were performed indirectly via network meta-analysis (NMA). The comparison between ublituximab and ocrelizumab was very indirect, going via IFNβ-1a, placebo and teriflunomide. This was of concern as there was evidence of network inconsistency, so the comparison may not be robust. Sensitivity analyses varying the network structure found that, for annualised relapse rate (ARR), the comparison between ublituximab and ocrelizumab was not robust. Some sensitivity analyses favoured ublituximab and others favoured ocrelizumab. All confidence intervals were wide, and no results were statistically significant, suggesting substantial overall uncertainty.

For ARR the NMAs found ublituximab to be almost identical in effect to ofatumumab, and possibly slightly superior to ocrelizumab, but confidence intervals are wide and the possibility that ublituximab is slightly inferior to the other treatments cannot be ruled out. For both disease progression at 12 months (CDP-12) and treatment discontinuation the results were in the direction of favouring ofatumumab and ocrelizumab, so it is possible that ublituximab is inferior to the other treatments on these outcomes. However, confidence intervals were wide and no result was statistically significant.

Differences across trials in healthcare settings and in how events were defined precluded comparisons of adverse event rates using NMA. Although the EAG considered that currently there is little robust evidence to suggest that ublituximab has a different safety profile to ofatumumab and ocrelizumab, the exception to this could be infusion or injection related reactions. Given the differences in how the anti-CD20s are administered, patient preferences regarding the setting, frequency and duration of administration, together with the risk of infusion or injection related reactions, may play an important role when deciding which treatment may be best to use.

1.3.2 Cost-comparison

The EAG considers the company's cost-comparison analysis to be appropriate under the assumption of near equivalence in efficacy, in terms of treatment effectiveness, disease progression and disease-related mortality, and similar safety profile (including discontinuation rates) for ublituximab and its comparators of ofatumumab and ocrelizumab. However, the EAG notes that the existing clinical evidence from the NMA for the outcomes of ARR, CDP-12 and CDP-24 suggests that there is a non-zero probability that ublituximab is less (or more) effective than ofatumumab and ocrelizumab (IV).

Therefore, we can only conclude that there is not sufficient evidence to distinguish between the treatments.

The company's inclusion of differential adverse event costs in the first year of treatment appears unnecessary given the underlying assumption that the safety profile is comparable between the treatments and the company's assumption that there is no difference in the discontinuation rate between treatments (to switch to next subsequent treatment). The EAG concludes that the inclusion of separate AE costs, whilst not considering their HRQoL impact, is unnecessary in the company's cost comparison analysis. Furthermore, the EAG's clinical advisor did not consider there to be any reason for differential rates of the more-costly adverse event of depression between the treatments (0.7% for ublituximab, 4.8% for ofatumumab and 7.8% for ocrelizumab (IV)).

The CS did not consider the impact of the quick 'under-the-skin' injection for ocrelizumab on its acquisition and administration costs. The EAG requested at points for clarification to update the revised version of the model to reflect the changes to the acquisition and administration costs of ocrelizumab 'under-the-skin' injection. The company included the ocrelizumab 'under-the-skin' injection as a new comparator, ocrelizumab (SC), in the cost comparison analysis. Uncertainty remains about the percentage of patients to use different forms of ocrelizumab (IV or SC).

1.4 Overall summary

The EAG generally agrees with the rationale for a cost comparison approach, given that ublituximab is assumed to have a similar mechanism of action to the other anti-CD20 monoclonal antibodies (ocrelizumab and ofatumumab), which have been approved by NICE for relapsing-remitting multiple sclerosis.

The EAG, informed by clinical advice, considers it plausible that ublituximab could provide similar health benefits (and have a similar safety profile) as ocrelizumab and ofatumumab. The EAG considers that the evidence presented broadly supports this position, and ublituximab could reasonably be used as an alternative therapy to ocrelizumab and ofatumumab.

However, the EAG has some concerns as to whether the evidence presented by the company is sufficiently robust to be confident that ublituximab is equivalent in efficacy to ocrelizumab and ofatumumab, for the purposes of a cost-comparison analysis. This is particularly because of the indirect nature of the comparison between ublituximab and the other treatments, with network meta-analysis results having considerably uncertainty as to the exact effectiveness of any of the treatments.

2 BACKGROUND

In this report the EAG has reviewed the company submission (CS) from Neuraxpharm UK to NICE on the cost comparison of ublituximab (Briumvi) within its marketing authorisation for treating relapsing multiple sclerosis (RMS) in adult patients who have active disease defined by clinical or imaging features.

2.1 Rationale for using a cost comparison approach in the appraisal

The EAG agrees with the rationale for a cost comparison approach, given that ublituximab is assumed to have a similar mechanism of action to the other anti-CD20 monoclonal antibodies (mAb) (ocrelizumab and ofatumumab), which have been approved by NICE for relapsing-remitting multiple sclerosis (RRMS) in 2018[1] and 2021[2], respectively.

Evidence cited by the company ahead of the decision problem meeting to support a cost comparison approach included the two ULTIMATE trials of ublituximab, a published network meta-analysis (NMA) of treatments for RMS[3], and a report on oral and monoclonal antibody treatments for RMS by the Institute for Clinical and Economic Review (ICER).[4]

The EAG, informed by clinical advice, considers it plausible that ublituximab could provide similar health benefits (and have a similar safety profile) as ocrelizumab and ofatumumab but this is subject to uncertainty. Our appraisal of the evidence is discussed in section 4, and a critique of the cost comparison in section 5.2.

2.2 Description of relapsing multiple sclerosis and the treatment pathway

The company provided an acceptable description of multiple sclerosis (MS). In response to clarification question A11, the company estimated that 14,958 patients in the UK are living with RRMS with active disease and may be eligible to receive treatment with ublituximab in the first year of market entry.

Disease-modifying therapies (DMTs) relevant to the population in scope include moderate efficacy therapies and higher efficacy therapies. Ublituximab, along with the two relevant comparators ofatumumab and ocrelizumab, are classed as higher efficacy therapies. The EAG's clinical advisor agrees with the company that early intervention with a higher efficacy DMT appears to be associated with better long-term outcomes; moderate efficacy treatments are the preferred option for a minority of patients, for example because of comorbidities, patient preference for oral medication, or for older patients with very mild symptoms who would prefer a gentler treatment option.

2.3 Differences and similarities between ublituximab and relevant comparators

2.3.1 Indication

Ublituximab is indicated for treating RRMS in adults with active disease defined by clinical or imaging features. This differs from the final scope issued by NICE (see section 3) but is in line with the indications for ofatumumab and ocrelizumab. Ocrelizumab is only recommended for adults with RRMS and active disease if alemtuzumab is contraindicated or unsuitable. However, the EAG's clinical advisor explained that alemtuzumab is now rarely used because of toxicity concerns.

Clinical advice to the EAG indicates that ublituximab may be considered as an alternative to ofatumumab or ocrelizumab in all suitable positions in the clinical pathway. However, clinicians would usually not opt for a second anti-CD20 mAb if one in an earlier line of treatment showed a lack, or loss, of efficacy.

2.3.2 Mechanism of action

The company described the mechanism of action of ublituximab in Table 2 (p. 13) and on p. 31 of the CS. Ublituximab induces death of CD20 expressing B-cells, which play a role in the autoimmune reaction targeting the central nervous system. The company mention four distinct mechanisms which lead to the death of CD20 expressing B-cells. By counteracting the autoimmune reaction damaging the central nervous system, the frequency of relapses and the occurrence and severity of neurological disability are reduced.

The EAG's clinical advisor explained that the anti-CD20 mAb treatments ocrelizumab and ofatumumab have similar working mechanisms, and that all three treatments cause profound B-cell suppression. There are differences in the extent to which each treatment relies on different biological pathways to achieve cell death of CD20 expressing B-cells. However, in practice this is unlikely to lead to differences in the efficacy of the three treatments, since CD20 cell death is the important outcome (rather than mechanism of cell death).

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

3.1 Population

NICE's final scope encompasses adults with relapsing multiple sclerosis with active disease; this covers both RRMS and relapsing forms of secondary progressive MS (SPMS) and reflects ublituximab's full marketing authorisation. The company's submission addressed a narrower population, focussing on adults with RRMS with active disease (defined by clinical or imaging features). Although this is narrower than the population in NICE's scope, it is nevertheless the same as the populations defined in NICE's recommendations for both the comparators in this appraisal, i.e. ofatumumab (TA 699) and ocrelizumab (TA 533). The company's submission also notes that the ublituximab evidence base for the active SPMS population is limited, since less than 2% of participants in the ULTIMATE I and II trials had SPMS at baseline.

3.2 Intervention

This is in line with NICE's scope. Ublituximab is administered during an outpatient appointment through intravenous (IV) infusion in week 0, week 2, and subsequently every 24 weeks.

3.3 Comparators

The EAG's clinical adviser considered that the comparators (ofatumumab and ocrelizumab) considered in the decision problem in both the company's submission and in NICE's scope were appropriate and reflected current NHS practice. Both ofatumumab and ocrelizumab are anti-CD20 therapies (like ublituximab) and both have a significant market share, being higher efficacy therapies.

Ofatumumab differs notably from ublituximab in its mode, setting and frequency of administration, being given as a subcutaneous injection by the patient at home, using a pre-filled injection pen, at weeks 0, 1, 2, 4, and monthly thereafter. Until recently, and as described in the CS, ocrelizumab was administered using the same mode and (very similar) frequency of delivery as ublituximab i.e., as an IV infusion at weeks 0, 2, and every six months thereafter. However, in July 2024, following the publication of results of the OCARINA II randomised trial, the Medicines and Healthcare products Regulatory Agency (MHRA) approved ocrelizumab for subcutaneous administration. Ocrelizumab can therefore now be administered subcutaneously in NHS outpatient settings. The EAG's clinical adviser stated that this will shorten ocrelizumab's administration time, which will be good for patients and for NHS capacity.

As the subcutaneous ocrelizumab issue was not covered in the company's submission, the EAG asked the company (in clarification question A9) to comment on how it might affect: i) what the most

relevant comparator is, ii) the importance of ublituximab to patients, given that it will be the only anti-CD20 therapy for MS to be given intravenously and iii) the submission claims that ublituximab reduces IV time and monitoring burden. The company response stated that patient preference for subcutaneous or IV options varies and that ocrelizumab remains the most relevant comparator (despite the availability of a subcutaneous ofatumumab), due to its similar dosing schedule to ublituximab and because the option to deliver it intravenously will remain. The company acknowledged though that less resource use would be required with subcutaneous ocrelizumab when compared with its IV delivery.

Given the anticipated similarities in efficacy and safety profiles across the three anti-CD20 therapies considered in the submission, patient preferences regarding mode, setting, frequency and duration of administration may play an important role when deciding which treatment to use. Section 5.2.4 describes the cost implications of these differences in administration.

3.4 Outcomes

The outcomes covered in the company's submission were in line with those specified in the NICE scope, except for severity of relapse; this outcome was not evaluated in the ublituximab trials. The EAG's clinical adviser indicated that severity of relapse is not usually reported in MS trials, with relapse typically being viewed in terms of being present or absent, rather than by severity.

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1 Critique of the methods of the review

The original company submission included searches to identify clinical evidence for adult patients with relapsing forms of multiple sclerosis (RMS). A description of the searches and most of the search strategies were included in Appendix D (pp. 2-15). In response to the EAG's points for clarification, the company provided additional information, search strategies, and corrections to errors. Overall, the searches were conducted appropriately using a small range of relevant databases, conference proceedings, and a single trials registry. See appendix 1for the full report of the search strategies.

The systematic review included randomised studies published in English of adult patients with RMS receiving ublituximab, alemtuzumab, natalizumab, ocrelizumab, ofatumumab, interferon beta-1a [Rebif®], or teriflunomide. Fifteen RCTs were included, of which two were trials of ublituximab (ULTIMATE I and ULTIMATE II). Appendix D of the CS lists excluded trials; there is no record of individual papers or records that were excluded.

An extension study to the ULTIMATE trials is currently ongoing (TG1101-RMS303). In this single-arm study, participants who have completed the treatment phase of either trial are treated with ublituximab up to 312 weeks.[5]

4.2 Critique of the direct evidence

4.2.1 Trial designs and critical appraisal

Protocols of the ULTIMATE trials were previously published alongside study results.[6] The EAG received the Clinical Study Reports (CSRs) ahead of the clarification response.

In the ULTIMATE RCTs, patients received ublituximab or teriflunomide for 96 weeks, followed by a 20-week follow-up period. The trials were double-blind, with patients in the ublituximab arm receiving a placebo tablet and patients in the teriflunomide arm receiving placebo injections (CS section B.3.3). The EAG judges the trial designs to be appropriate.

A host of previous treatments were listed as exclusion criteria, including alemtuzumab, natalizumab, teriflunomide, stem cell transplantation, and anti-CD20 or other B-cell directed treatments. The EAG's clinical adviser notes that this is not reflective of clinical practice in the NHS. Excluding patients who would be eligible to receive ublituximab in practice may be a risk to the generalisability of trial results. A single-arm trial is ongoing to assess the efficacy of ublituximab after switching from ocrelizumab, rituximab, or ofatumumab.[7]

The EAG's clinical adviser considered baseline characteristics of study samples (CS Table 8, p. 48) to be generally representative of UK clinical practice, and similar to trials of ocrelizumab and ofatumumab.[8, 9] Most participants were recruited from centres [redacted]

Information provided by the company as part of the clarification response (Q A2) shows that participants in the combined teriflunomide study arms were slightly older than participants in the combined ublituximab arms ([redacted]).

The company presents risk of bias assessments of ULTIMATE I and II using Cochrane's Risk of Bias 2 tool (CS Appendix D). The EAG agrees with the company's judgements of low risk of bias in all risk of bias domains. However, it is unclear which outcome was used to assess the outcome-specific domains of the Risk of Bias 2 tool. The company has identified the double-blinded, dummy-controlled nature of the trials as a strength. The EAG agrees, with the caveat that the common occurrence of infusion-related reactions in the ublituximab study arms may have made it possible for treating clinicians to identify the medication received (see section 4.4.1).

4.2.2 Efficacy of ublituximab versus teriflunomide – main analyses

The CS reports on the primary analysis of data from the modified intention-to-treat (mITT) analyses of 545 patients in ULTIMATE I and 544 patients in ULTIMATE II. Outcomes include annualised relapse rate (ARR), number of Gadolinium (Gd) enhancing lesions per T1 and T2-weighted MRI scans, disability measured with the Expanded Disability Status Scale (EDSS), confirmed disease progression at 12 weeks (CDP-12) and 24 weeks (CDP-24), and health-related quality of life (HRQoL) measured with the Multiple Sclerosis Quality of Life 54 scale (MSQOL-54), which includes Short Form-36 (SF-36).

The importance of the results of the ULTIMATE trials for this appraisal is limited because teriflunomide, being a moderate efficacy therapy, is not a relevant comparator. Key results at 96-week follow-up are presented in table 11 of the CS (pp. 66-67). Results were broadly consistent ULTIMATE I and ULTIMATE II.

The absolute number of confirmed relapses was very low (Table 1). ARR was adjusted for region and baseline EDSS score. The ARR was lower in the ublituximab study arms than the teriflunomide arms in ULTIMATE I (rate ratio 0.41, 95% CI 0.27; 0.62) and ULTIMATE II (rate ratio 0.51, 95% CI 0.33; 0.78).

Table 1 Summary of ARR results (mITT population)

	ULTIMATE I		ULTIMATE II	
	Ublituximab (N=271)	Teriflunomide (N=274)	Ublituximab (N=272)	Teriflunomide (N=272)
Mean duration of treatment (years)	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses during treatment	[redacted]	[redacted]	[redacted]	[redacted]
Mean number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Median number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum number of relapses per participant[a]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted ARR	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ARR	0.08	0.19	0.09	0.18

Source: CSRs ULTIMATE trials.

a. During treatment period.

Data on worsening of disability were pooled and showed no conclusive difference between study arms at 12 weeks (HR 0.84, 95% CI 0.50; 1.41) and 24 weeks (HR 0.66, 95% CI 0.36; 1.21) (Table 2). The EAG's clinical adviser explained that this finding is disappointing and may be explained by a relatively low percentage of participants showing worsening of disability (5.5% at 12 weeks and 4.0% at 24 weeks). In addition, the clinical adviser indicated that teriflunomide is more effective at reducing disability than it is at preventing relapse.

Table 2 Results for worsening of disability ULTIMATE trials

	POOLED DATA ULTIMATE TRIALS	
	Ublituximab (N=543)	Teriflunomide (N=546)
Worsening of disability at 12 weeks		
No. of patients (%)	28 (5.2)	32 (5.9)
HR	0.84 (0.50; 1.41)	
Worsening of disability at 24 weeks		
No. of patients (%)	18 (3.3)	26 (4.8)
HR	0.66 (0.36; 1.21)	

Abbreviations: HR; Hazard Ratio

Table 3 summarises results for secondary and tertiary outcomes. Measures of disease activity and time to confirmed relapse indicated a benefit of ublituximab compared to teriflunomide.

Table 3 Results for other secondary and tertiary outcomes ULTIMATE I and II

	ULTIMATE I		ULTIMATE II	
	Ublituximab (N=271)	Teriflunomide (N=274)	Ublituximab (N=272)	Teriflunomide (N=272)
DISEASE ACTIVITY				
Gd-enhancing lesions per T1-weighted MRI scan				
Mean	0.02	0.49	0.01	0.25
RR (95% CI)	0.03 (0.02; 0.06), p<0.001		0.04 (0.02; 0.06), p<0.001	
New or enlarging hyperintense lesions per T2-weighted MRI scan				
Mean	0.21	2.79	0.28	2.83
RR (95% CI)	0.08 (0.06; 0.10), p<0.001		0.10 (0.07; 0.14), p<0.001	
Percentage change in brain volume baseline to week 96				
Least-squares mean (95% CI)	-0.20 (-0.23; -0.17)	-0.13 (-0.16; -0.10)	-0.19 (-0.23; -0.16)	-0.18 (-0.21; -0.15)
Difference (95% CI)	-0.07 (-0.11; -0.04)		-0.02 (-0.05; 0.02)	
DISABILITY-RELATED OUTCOMES				
Time to first confirmed relapse				
No. of participants with at least one confirmed relapse during treatment (%)	36 (13.3)	68 (24.8)	34 (12.5)	72 (26.5)
HR	0.50 (0.33; 0.75), p<0.001		0.43 (0.28; 0.65), p<0.001	
NEDA[a]				
No. of participants (%)	121 (44.6)	41 (15.0)	117 (43.0)	31 (11.4)
OR (95% CI)	5.44 (3.54; 8.38)		7.95 (4.92; 12.84)	

a. Including no confirmed relapses, no MRI activity, and no worsening of disability.
Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; NEDA, no evidence of disease activity; OR, odds ratio.

The company summarise results for HRQoL data in Table 9 and Table 10 of the CS (pp. 63-65). There was a benefit for ublituximab compared to teriflunomide for some but not all domains of the Multiple Sclerosis Quality of Life 54 (MSQOL-54), including change in health, energy, mental health, physical health, and role limitations due to physical problems. HRQoL measured with the SF-36 showed a statistically significant improvement for ublituximab when compared to the teriflunomide study arm for physical functioning, the role-physical component, and vitality.

4.2.3 Subgroup analyses

No subgroup analyses are presented in the CS, though a published abstract reports on results from pooled analyses of the ULTIMATE trials in a subgroup of participants with highly active disease.[10] The unadjusted ARR in patients with highly active disease was higher for ublituximab (0.145, N=88)

than teriflunomide (0.496, N=80). Confirmed disability progression at 12 weeks was 8% for ublituximab versus 5% for teriflunomide.

4.2.2.1 Subgroup analyses performed by the EAG

The CSRs report additional subgroup analyses for ARR. The EAG notes that the trials were not powered for these analyses and the absolute number of annual relapses is very low, limiting the statistical power to detect differences.

[redacted]

The EAG performed additional subgroup analyses by combining data reported in the CSRs for both trials. These analyses are based on reported ARR values and their confidence intervals as the original trial data was not available to the EAG. Standard deviations were calculated from confidence intervals assuming normally distributed data. ARRs and their variances were pooled across the two trials for each subgroup and each trial arm using a simple weighted average with sample size as the weights. Standard t-tests were then used to test for differences between arms within subgroups, and for difference between subgroups.

The EAG notes that these summary analyses are simplistic and may not reflect exactly what would be found using a proper analysis of the original trial data, particularly due the assumption of normality. Results are presented here to summarise potential concerns with the trial data. Table 4 presents the results of the EAG subgroup analyses. It shows the estimated ARR and its 95% confidence interval for each subgroup, and the p-value for the t-test comparing the subgroups.

[redacted]

[redacted]

Table 4 Subgroup analyses for ARR in the pooled ULTIMATE trials performed by the EAG

Factor	Subgroup	ARR	95% CI		P - value
Gender	Female	[redacted]	[redacted]	[redacted]	
	Male	[redacted]	[redacted]	[redacted]	[redacted]
Age	<38	[redacted]	[redacted]	[redacted]	
	≥38	[redacted]	[redacted]	[redacted]	[redacted]
Region	USA or Western Europe	[redacted]	[redacted]	[redacted]	
	Eastern Europe	[redacted]	[redacted]	[redacted]	[redacted]
EDSS	≤3.5	[redacted]	[redacted]	[redacted]	
	>3.5	[redacted]	[redacted]	[redacted]	[redacted]
Relapses	0 or 1	[redacted]	[redacted]	[redacted]	
	2	[redacted]	[redacted]	[redacted]	
	3 or more	[redacted]	[redacted]	[redacted]	[redacted]
Prior drug use	Yes	[redacted]	[redacted]	[redacted]	
	No	[redacted]	[redacted]	[redacted]	[redacted]
Gd-enhancing lesions	0	[redacted]	[redacted]	[redacted]	
	1 or more	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; EDSS, expanded disability status scale; Gd, Gadolinium

4.3 Critique of the indirect treatment comparisons

No trial has directly compared ublituximab to the comparator treatments, ocrelizumab and ofatumumab. The company therefore performed a series of network meta-analyses to compare the three treatments.

4.3.1 Summary of the trials included in the indirect treatment comparisons

Risk of bias assessment results were reported in Table 26 of the CS appendices document. This reported that all six trials of ublituximab, ocrelizumab and ofatumumab were judged to be at low risk of bias. However, the reporting of these results was limited, since no clarifying text was provided to justify how judgements were derived.

Table 21 in the appendices document of the CS compared trial baseline characteristics of the trials included in the NMAs, although there was no accompanying text discussing the data. In clarification question A4, the EAG therefore asked the company to describe possible effect modifiers and discuss whether they were similar enough across trials to justify whether the transitivity assumption had been met (for the NMAs). In clarification question A7, the EAG also asked about the robustness of the NMAs and to justify adopting an NMA approach (rather than a matching-adjusted indirect comparisons (MAIC) approach). Data tables comparing trials for possible effect modifiers were

included in the company responses to both clarification questions. A modified version of Table 16 (time since symptom onset has been added) from the company's clarification response is presented here as Table 5.

Table 5 Comparison of baseline characteristics across trials (adapted from Table 16 of company's clarification response)

Characteristic	ASCLEPIOS I	ASCLEPIOS II	OPERA I	OPERA II	ULTIMATE I	ULTIMATE II
	Ofatumumab (n = 465)	**Ofatumumab (n = 481)**	**Ocrelizumab (n = 410)**	**Ocrelizumab (n = 417)**	**Ublituximab (n = 271)**	**Ublituximab (n = 272)**
Age*	38.9±8.8	38.0±9.3	37.1±9.3	37.2±9.1	36.2±8.2	34.5±8.8
% Female	68	66	66	65	61	65
Race – white (%)	88	87	NR	NR	97	99
Time since diagnosis, years*	5.77±6.05	5.59±6.38	3.82±4.80	4.15±4.95	4.9±5.2	5.0±5.6
Time since symptom onset, years*	8.4±6.8	8.2±7.4	6.7±6.4	6.7±6.1	7.5±6.5	7.3±6.5
RRMS %	94.2	94.0	NR	NR	97.4	98.5
No. relapses in past year (mean, SD)	1.2±0.6	1.3±0.7	1.31±0.65	1.32±0.69	1.3±0.6	1.3±0.6
EDSS score*	2.97±1.36	2.90±1.34	2.86±1.24	2.78±1.30	3.0±1.2	2.8±1.3

*Mean, SD

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability disease scale; SD, standard deviation

The company stated that the baseline characteristics indicate very little variability in effect modifiers across trials and that the transitivity assumption holds. The EAG identified a systematic review and NMA which compared anti-CD20 monoclonal antibodies for relapsing-remitting multiple sclerosis.[11] The possible effect modifiers listed in that paper were: age, time since symptom onset, time since diagnosis, EDSS score, and the number of relapses in the past year. These characteristics were covered in the company's submission and responses to clarification. Although the EAG agrees that the trials were similar enough to warrant using NMAs to compare trial outcomes, the EAG also notes (and agrees with) the company's assertion that NMAs were not appropriate for adverse event outcomes due to heterogeneity across trials in event definitions and follow up durations (see also Section 4.4).

4.3.2 Summary and critique of the network meta-analysis methods

The company included a range of relevant treatments for MS in the NMAs, and not just the key treatments specified in the NICE scope. NMAs were performed for four outcomes as specified in the scope, namely:

- Annualised relapse rate (ARR),
- CDP-12 and CDP-24,
- Treatment discontinuation

NMAs were not performed for number of Gd-enhancing T1-lesions, confirmed disease improvement (CDI), adverse events or quality-of-life outcomes.

The EAG have examined the methods used for the NMAs and the Stata code used to perform them, and judge that all analyses were performed correctly, with appropriate consideration given to potential problems with the analyses, such as inconsistency between direct and indirect evidence.

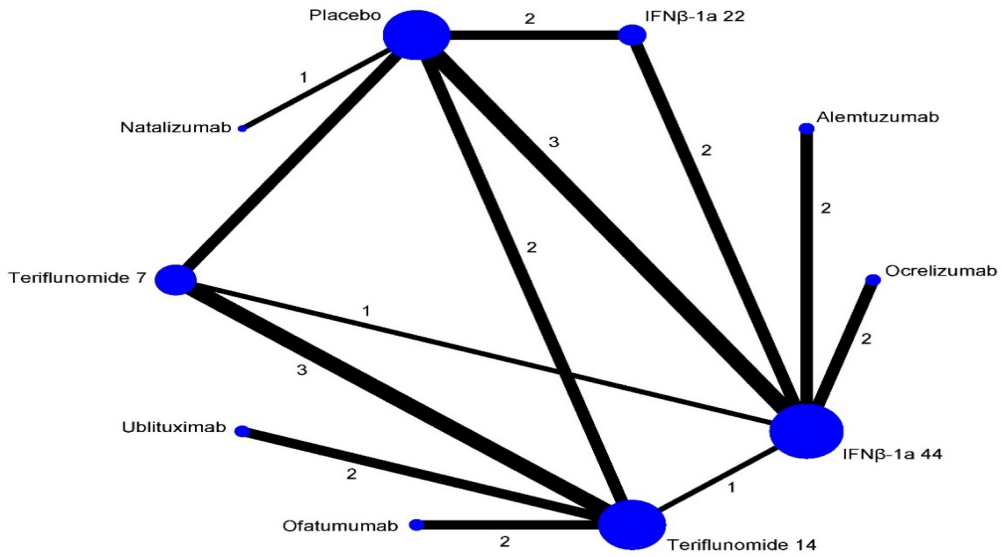
Figure 1 shows the network diagram for the analysis of ARR (taken from CS Figure 12). The EAG notes that ublituximab and ofatumumab are both "leaf nodes" connected to the network only via teriflunomide. Consequently, the comparison between ublituximab and ofatumumab essentially reduces to a simple Bucher indirect comparison of their respective trials (ULTIMATE and ASCLEPIOS). This means that the comparison between ublituximab and ofatumumab should be robust to any variations or inconsistences in the wider network, but does rely on the assumption that the trials are sufficiently similar in their conduct and recruited populations to be directly comparable.

Conversely, the comparison between ublituximab and ocrelizumab is very indirect, going via IFNβ-1a, placebo and teriflunomide. This makes the comparison much less robust and subject to bias due to inconsistency in the network or any differences in conduct or population across all the included trials.

The network also includes several treatments (alemtuzumab, natalizumab and IFNβ-1a 22), which contribute little or no information to the comparison between ublituximab, ocrelizumab and ofatumumab. The EAG requested NMAs that excluded these treatments, which were supplied by the company. The company also performed sensitivity analyses accounting for potential inconsistency in the network, accounting for different follow-up times in the trials, and removing trials where ARR or other outcomes had to be imputed.

Network diagrams for other outcomes were reported in the CS. These generally included fewer trials, and did not have any loops in the network, so it was not possible to test for inconsistency for outcomes other than ARR.

Figure 1 Network diagram for the ARR NMA (CS Figure 12)

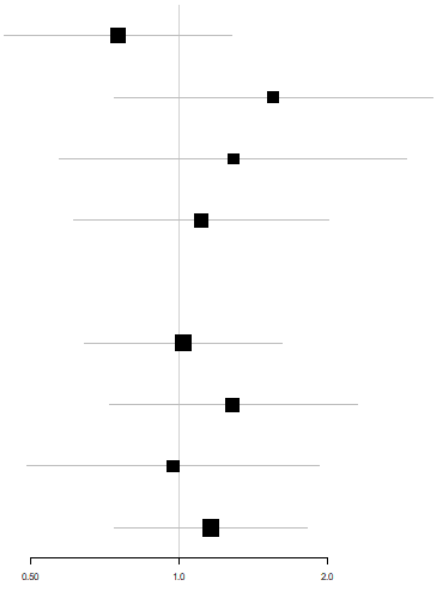


4.3.3 Summary of the network meta-analysis results

Figure 2 presents the results of the main NMAs for the four outcomes considered. This restricts presentation to the comparison between ublituximab and ocrelizumab, and between ublituximab and ofatumumab, excluding all other treatments not of relevance in this assessment. Squares to the left of a relative risk or hazard ratio of one indicate results favouring ublituximab; to the right favours the comparator.

Figure 2 Summarised results of the company NMAs

Comparator	Outcome	RR/HR	95% CI	
Ocrelizumab	ARR	0.75	0.44	1.28
	CDP-12	1.55	0.74	3.27
	CDP-24	1.29	0.57	2.9
	Discontinuation	1.11	0.61	2.01
Ofatumumab	ARR	1.02	0.64	1.62
	CDP-12	1.28	0.72	2.3
	CDP-24	0.97	0.49	1.92
	Discontinuation	1.16	0.74	1.82



Abbreviations: ARR, annualised relapse rate; CDP, confirmed disease progression; CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; RR, relative risk.

For ARR the NMAs found ublituximab to be almost identical in mean effect to ofatumumab, and possibly slightly superior to ocrelizumab. This suggests that ublituximab is plausibly similar in effect to both the other treatments. However, in both cases confidence intervals are wide and the possibility that ublituximab is inferior to the other treatments cannot be ruled out. Likewise, it is also possible that ublituximab is superior to both ofatumumab and ocrelizumab.

For both CDP-12 and treatment discontinuation the results were in the direction of favouring ofatumumab and ocrelizumab, so it is possible that ublituximab is inferior to the other treatments on these outcomes. However, confidence intervals were wide and no result was statistically significant. The estimated effect sizes were also small, so any advantage ofatumumab and ocrelizumab might have over ublituximab is likely to be modest. For CDP-24, ublituximab appeared very similar in mean effect to ofatumumab, but may be slightly inferior to ocrelizumab. Again, however, all confidence intervals were wide, and no result was statistically significant.

The company calculated Surface Under the Cumulative Ranking (SUCRA) scores in each NMA. These are summarised in Table 6. For none of the four outcomes did ublituximab have the highest SUCRA score, suggesting it would not be the preferred treatment of the three for any outcome. However, for ARR the SUCRAs for ublituximab and ofatumumab were only marginally different.

Table 6 SUCRA scores from the NMAs

	Ublituximab	Ocrelizumab	Ofatumumab
ARR	83.9	62.5	85.4
CDP-12	58.0	93.9	84.2
CDP-24	63.6	84.4	61.8
Treatment discontinuation	52.2	65.1	73.7

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disease progression

The company tested for inconsistency between direct and indirect evidence for the ARR NMA (the only analysis where this was possible). The analysis found some evidence of inconsistency in the network. This appeared to be mainly due to inconsistency in the network loops involving placebo, IFNβ-1a and teriflunomide 7. This inconsistency is unlikely to adversely impact the comparison between ublituximab and ofatumumab, but could affect the comparison with ocrelizumab. This means the comparison between ublituximab and ocrelizumab may not be robust.

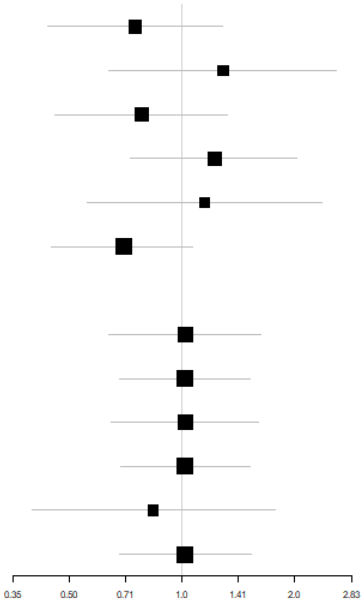
The company performed several sensitivity analyses for the NMAs. Figure 3 summarises their results for the ARR NMA. These were:

- The original analysis ("Main" in the figure)
- Accounting for network inconsistency
- Removing the OWIMS, IMPROVE or PRISM trials from the network (as ARR results were imputed for these trials rather than directly reported)
- Adjusting for variation in follow-up duration
- The EAG requested analysis removing alemtuzumab, natalizumab and IFNβ-1a 22 ("EAG reduced network")

Squares to the left of a relative risk of one indicate results favouring ublituximab; to the right favours the comparator.

Figure 3 Summary of company sensitivity analyses for the ARR NMA

Comparator	Analysis	RR	95% CI	
Ocrelizumab	Main	0.75	0.44	1.28
	Inconsistency	1.29	0.64	2.58
	No OWIMS or IMPROVE	0.78	0.46	1.32
	No OWIMS or PRISM	1.22	0.73	2.03
	Adjusted for follow-up duration	1.15	0.56	2.37
	EAG reduced network	0.7	0.45	1.07
Ofatumumab	Main	1.02	0.64	1.62
	Inconsistency	1.02	0.68	1.52
	No OWIMS or IMPROVE	1.02	0.65	1.6
	No OWIMS or PRISM	1.02	0.69	1.52
	Adjusted for follow-up duration	0.84	0.4	1.77
	EAG reduced network	1.02	0.68	1.53



Abbreviations: ARR, annualised relapse rate; CI, confidence interval; EAG, Evidence Assessment Group; NMA, network meta-analysis; RR, relative risk

Comparison between ublituximab and ofatumumab is largely robust to all sensitivity analyses. This is because the comparison is largely independent of the rest of the wider network of treatments. Adjusting for follow-up duration might lead to slightly favouring ublituximab, but confidence intervals were wide.

In contrast, the comparison between ublituximab and ocrelizumab is not robust to the sensitivity analyses. While the original analysis and the reduced network requested by the EAG both show results in the direction of favouring ublituximab, analyses adjusted for consistency and follow-up duration are in the direction of favouring ocrelizumab. All confidence intervals are wide suggesting

substantial overall uncertainty. This demonstrates that the very indirect nature of the comparison between ublituximab and ocrelizumab (via IFNβ-1a, placebo and teriflunomide) does lead to substantial uncertainty when comparing the two treatments, and no comparison based on an NMA can be considered robust.

A smaller number of sensitivity analyses were also performed for CDP-12, CDP-24 and treatment discontinuation. Results from these were generally consistent with the main NMAs, so they are not reported in detail here.

4.4 Safety and adverse events

4.4.1 Safety of ublituximab versus teriflunomide

The comparison of safety outcomes for ublituximab and teriflunomide has limited relevance to this submission, as teriflunomide is not a relevant comparator and is known to cause fewer side effects than higher efficacy therapies such as anti-CD 20 mAbs.

Adverse reactions which occurred in the safety population of the ULTIMATE trials are described in section B.3.10 of the CS (pp. 80-84). Table 7 summarises adverse events from Table 29 of the CS (p. 82) and the CSRs. Adverse events leading to treatment discontinuation were not common, but more prevalent in the ublituximab study arms. In ULTIMATE I,

[redacted]

[redacted] Infusion-related reactions commonly occurred in the ublituximab study arms, and more frequently than for participants who received teriflunomide (with a placebo injection).

Table 7 Adverse event results for the ULTIMATE I and II trials (safety population)

Outcome	ULTIMATE I		ULTIMATE II	
	Ublituximab, n (%)	Teriflunomide, n (%)	Ublituximab, n (%)	Teriflunomide, n (%)
Any adverse event	235 (86.1%)	245 (89.1%)	251 (92.3%)	256 (93.8%)
AE ≥ grade 3	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to temporary interruption	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to treatment discontinuation	18 (6.6%)	2 (0.7%)	5 (1.8%)	2 (0.7%)
Infusion-related reactions	120 (44.0%)	19 (6.9%)	140 (51.5%)	48 (17.6%)

Abbreviations: AE, adverse event

4.4.2 Safety of ublituximab compared with ocrelizumab and ofatumumab

In clarification question A3, the EAG requested a summary of AEs and SAEs for ocrelizumab and ofatumumab from their respective trials and an indirect comparison, if feasible. The company stated that, following an advisory board meeting with methodological experts, they were strongly advised not to perform an NMA, primarily due to the likelihood of differences across trials in how AEs are defined and variation in trial follow-up durations. The company added that this approach was consistent with previous appraisals. The company provided tables of AEs for ocrelizumab and ofatumumab in their response the clarification question A3. The EAG notes that heterogeneity in how adverse events were defined could arise from the differences in trial settings, with the ublituximab trials being primarily set in Eastern European locations and the ocrelizumab and ofatumumab trials being mainly set in Western European and North American locations.

In clarification question A10, the EAG requested the company to provide a rationale and justification for the use of lower rates of depression and urinary tract infection for ublituximab in the cost-comparison analysis when compared with ocrelizumab and ofatumumab. The company said this was justified by the lower incidence of these AEs observed in the ULTIMATE I and II trials.

The EAG therefore extracted depression and urinary tract infection adverse event data for all the anti-CD20 therapy trial arms, which are summarised in Table 8. This indicates that the underlying rates of these adverse events in the ublituximab trial populations were notably lower than in the ocrelizumab and ofatumumab trial populations. In light of this, the EAG considers that it is not appropriate for the company to compare absolute adverse event rates for the anti-CD20 trial arms (which were used in the model) without also considering the variation in rates across all arms of the trials, and without considering the relative difference in rates within each trial. The EAG therefore concludes that the evidence for assuming a clear difference in anti-CD20 adverse effect profiles is inadequate, and notes the relevance here of the company's aforementioned assertion regarding adverse event heterogeneity across trials (in definitions and follow up durations), which precluded a comparison using network meta-analysis.

Table 8 Adverse event data for depression and urinary tract infections in the anti-CD20 trials

Outcome (% incidence)	Trial and arm					
	ULTIMATE I & II pooled		ASCLEPIOS I & II pooled		OPERA 1 & 2* pooled	
	Ubli	Terif	Ofa	Terif	Ocre	Inter
Urinary tract infections	4.0	5.3	10.3	8.3	11.6	12.1
Depression	1.5	2.4	4.8	5.1	6.8	6.9

Abbreviations: Inter, Interferon beta-1a; Ocre, Ocrelizumab; Ofa, Ofatumumab; Terif, Teriflunomide; Ubli, Ublituximab
*OPERA I &II depression data were calculated using data from the clinicaltrials.gov records NCT01247324 and NCT01412333.

4.5 Summary

Results from the two ULTIMATE trials provide conclusive evidence that ublituximab reduces the rate of relapse when compared to teriflunomide. However, the EAG notes that ublituximab was not conclusively superior to teriflunomide in terms of disease progression.

Ublituximab was compared to ofatumumab and ocrelizumab indirectly through network meta-analysis. The EAG notes some concerns with the very indirect nature of the comparison between ublituximab and ocrelizumab, potential inconsistencies in the network and a lack of robustness of analyses to changes in the network.

Ublituximab appeared to be similar in effectiveness to ofatumumab in terms of mean relapse rate (ARR). The comparison with ocrelizumab was very uncertain, with ocrelizumab having slightly higher, or slightly lower relapse rates depending on the analysis performed. The EAG notes that ublituximab was possibly marginally inferior to both ofatumumab and ocrelizumab for CDP-12 and treatment discontinuation, although results were not statistically significant.

Differences across trials in healthcare settings and in how events were defined precluded comparisons of adverse event rates using network meta-analysis. However, the EAG considered that currently there is little robust evidence to suggest that ublituximab has a different safety profile to ofatumumab and ocrelizumab. The exception to this could be infusion or injection related reactions, although these events rarely appear to be serious. Nevertheless, given the differences in how the anti-CD20s are administered, patient preferences regarding the setting, frequency and duration of administration, together with the risk of infusion or injection related reactions, may play an important role when deciding which treatment may be best to use.

Overall, the EAG considers that the evidence suggests that ublituximab is plausibly similar in efficacy and safety to other anti-CD20 monoclonal antibodies. However, the evidence is not particularly robust, and it is possible that ublituximab may be marginally inferior to both ofatumumab and ocrelizumab, particularly in terms of disease progression and treatment discontinuation. This raises

concerns as to whether ublituximab would be clinically preferable to the other treatments, and to whether assuming treatment equivalence in the cost-comparison analyses is robust and appropriate.

5 SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

The appropriateness of assessing the cost-effectiveness of ublituximab in the context of a cost comparison analysis relies on the validity of the assumption of equivalent efficacy, in terms of treatment effectiveness, disease progression and disease-related mortality, and similar safety profile (including discontinuation rates) for ublituximab and its comparators of ofatumumab and ocrelizumab. The EAG critique of the cost comparison evidence assumes that it is appropriate for the assessment to proceed as a cost comparison analysis, and seeks to answer under what circumstances ublituximab is likely to be cost saving or equivalent in cost to the selected comparators.

The EAG highlights throughout the subsequent subsections, features of the cost comparison that may be affected by uncertainty surrounding the validity of assuming equivalent efficacy and safety of ublituximab to ofatumumab and ocrelizumab.

5.1 Summary of company's cost comparison and assumptions

5.1.1 Summary of cost comparison

The company presents a cost comparison of ublituximab, as compared to ofatumumab and ocrelizumab (IV and SC), over a 5-year time horizon (without discounting), using a Markov model with three discrete states of 'on-treatment', 'off-treatment', and 'death' in order to simulate the proportion of living patients who receive treatment each year. The costs included in the company's cost comparison are: (i) drug acquisition costs; (ii) drug administration costs; (iii) monitoring costs; and (iv) adverse event costs. Unit costs were informed by national public sources[12-14] and previous NICE guidance[1] with inflation adjustment. Table 9 summarises the costs used in the company's cost comparison analysis.

Table 9 Summary of costs used in the company's cost comparison analysis

Item	Cost comparison analysis input	Source
Drug acquisition costs per year		
Ublituximab	List Price first year: [redacted] subsequent years: [redacted] PAS Price first year: [redacted] subsequent years: [redacted]	Ublituximab is initially administered as a 150mg IV infusion, followed by a 450mg IV infusion 2 weeks later. Subsequent doses are administered as a single 450mg IV infusion every 24 weeks. Ublituximab list price per 150mg vial is [redacted] and PAS price per 150mg vial is [redacted]
Ofatumumab	List Price first year: £20,895 subsequent years: £17,910	Ofatumumab is administered as a 20mg SC injection at weeks 0, 1 and 2, followed by subsequent monthly dosing. Ofatumumab list price per 20mg solution is £1,493.50.
Ocrelizumab (IV)	List Price first year: £19,160 subsequent years: £19,160	Ocrelizumab (IV) is initiated at a dose of 600mg, administered as two separate IV infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion. Subsequent doses of ocrelizumab (IV) thereafter are administered as a single 600mg IV infusion every 6 months. Ocrelizumab (IV) list price per 300mg vial is £4,790.00.
Ocrelizumab (SC)	List Price first year: £19,160 subsequent years: £19,160	Ocrelizumab (SC) is administrated as a 920mg SC injection every 6 months. Ocrelizumab (SC) list price per 920mg solution is £9,580.00.
Administration costs per year		
Ublituximab	First year: £1,445 Subsequent years: £544	Ublituximab involves IV infusions by accounting for the proportion of bed-day costs and nursing costs per infusion. The total time per patient for the first infusion is 6.25 hours, and 2.25 hours for the subsequent infusions, which includes preparation, infusion and monitoring time. The model uses £58.00 nurse cost per hour[14] and £426.08 bed-day cost[13] multiplied by the total time to calculate the administration cost for each infusion (the first infusion: £695.37 and the subsequent infusion: £250.33). Detailed drug administration costs associated with IV infusions are shown in company submission Table 31. Pre-medication required before IV infusions to reduce and prevent IRRs. These include 100mg IV methylprednisolone, an antihistamine (chlorphenamine maleate, 4mg) and an antipyretic (paracetamol, 500mg). The unit costs for the pre-medication were sourced from the BNF and were applied to each treatment administration.[12]
Ofatumumab	First year: £116 Subsequent years: £0	The drug administration method for ofatumumab involves a SC injection for which a cost is only attributed at treatment initiation, while subsequent administrations incur no costs. This approach is undertaken under the assumption that patients follow a two-hour training on self-administration from a MS-specialist nurse, in line with TA699.[2] Detailed drug administration cost for SC injections are shown in company submission Table 32.
Ocrelizumab (IV)	First year: £1,057 Subsequent years: £1,113	Ocrelizumab also involves IV infusion and only differs by the duration of the infusion and the monitoring time

		after the infusion at each session, compared to ublituximab. The total time per patient for the first infusion is 7.25 hours and 5.00 hours for the subsequent infusions, which includes preparation, infusion and monitoring time. And the total cost for the first infusion is £806.63 and for subsequent infusions is £ £556.30. Detailed drug administration costs associated with IV infusions are shown in company submission Table 31.
Ocrelizumab (SC)	First year: £426.50 Subsequent years: £426.50	Ocrelizumab (SC) is administered by a doctor or nurse as a subcutaneous injection. Compared to ocrelizumab (IV), it has shorter preparation time (0.5 hours) and injection time (0.17 hours). Pre-medication is also required before each injection. These include dexamethasone, 20mg, an antihistamine (chlorphenamine maleate, 4mg) and an antipyretic (paracetamol, 500mg). The unit costs for the pre-medications were sourced from the BNF and were applied to each treatment administration.[12]
Monitoring costs per year		
Ublituximab	First year: £457.32 Subsequent years: £377.88	Due to the comparable health outcomes of ublituximab, ofatumumab and ocrelizumab, it has been assumed that the resource utilisation for monitoring patients would be the same for all therapies. The costs for resource use were extracted from TA699 and were inflation-adjusted.[2]
Ofatumumab	First year: £457.32 Subsequent years: £377.88	
Ocrelizumab (IV)	First year: £457.32 Subsequent years: £377.88	
Ocrelizumab (SC)	First year: £457.32 Subsequent years: £377.88	
Adverse event costs (one-time cost)		
Ublituximab	£44.38	The costs of treating AEs were considered separately for non-serious and serious AEs (SAEs). Unit costs for treating each non-serious and SAE were obtained from TA699 and were inflation-adjusted. [2] Unit cost inputs were then weighted by the proportion of patients experiencing SAEs from the relevant clinical trials of ublituximab, ofatumumab and ocrelizumab (IV) (10.8% for patients receiving ublituximab; 9.1% for patients receiving ofatumumab; and 7.0% for patients receiving ocrelizumab (IV)). The detailed cost inputs for AE management are shown in company submission Table 34.
Ofatumumab	£91.20	
Ocrelizumab (IV)	£125.63	
Ocrelizumab (SC)	£125.63	In the company's response to EAG points for clarification, where ocrelizumab (SC) is added as an additional comparator, the company assumes that ocrelizumab (SC) has the same AE profile as ocrelizumab (IV).

Abbreviations: AE, adverse event; BNF, British National Formulary; IRR, infusion-related reactions; IV, intravenous; MS, multiple sclerosis; PAS, patient access scheme; SC, subcutaneous.

5.1.2 Assumptions

The key assumptions underlying the company's cost comparison analysis are as follows:

- Ofatumumab and ocrelizumab are the most relevant comparators for the population of adults with RRMS with active disease.
- Equivalent (or very similar) effectiveness, disease progression and disease-related mortality between ublituximab and its comparators means that it is appropriate to evaluate ublituximab in the context of a cost-comparison analysis.
- Equivalent (or very similar) safety profile between ublituximab and its comparators, although the company has included differences in the resource use and costs associated with both serious and non-serious adverse events in the cost comparison analysis.
- There are differences in the cost of IV infusion therapy for ublituximab and ocrelizumab (IV) based on hospital bed day costs, as a proxy for hospital overhead costs, and nurse cost per hour, as a proxy for labour costs. All other overhead costs attributed to IV administration are assumed the same.
- Patients receive their first administration of ofatumumab in the secondary care setting, while subsequent administrations are provided in the home setting. A two-hour training on self-administration from an MS-specialist nurse was assumed, while self-administrations are assumed to incur no costs.
- Equivalent monitoring costs between ublituximab and its comparators.
- Patients do not discontinue treatment in the company's base case analysis. The impact of treatment discontinuation is explored in a scenario analysis. In the scenario analysis, the company assumes that there is no difference in subsequent treatment costs post-discontinuation.
- A time horizon of 5 years is used to compare the costs of ublituximab and its comparators.
- Discounting of costs is not included in the company's base case analysis. The impact of discounting costs at 3.5% per annum is explored in a scenario analysis.
- No subgroup analyses presented. No differences in the dosing schedules between the overall population and the highly active or RMS subpopulation.

5.2 EAG critique of the company's cost comparison

The EAG conducted a technical validation of the executable model by cross-checking values against the company submission and auditing formulae. The EAG detected no errors in the executable model.

The EAG critique focuses on the following aspects of the cost comparison analysis:

- Uncertainty in the existing clinical evidence for equivalence of treatment effect;
- Adverse events;
- Acquisition costs
- Administration costs;

- Treatment discontinuation and subsequent treatment use;
- Time horizon and discounting.

5.2.1 Uncertainty in the existing clinical evidence

The existing clinical evidence from the NMA for the outcomes of ARR, CDP-12 and CDP-24 suggests that there is a non-zero probability that ublituximab is less (or more) effective than ofatumumab and ocrelizumab (IV) (see Section 4.3.3 . The consequences of uncertainty for patient outcomes have not been assessed, which would require a full cost-effectiveness analysis with probabilistic sensitivity analysis. The EAG notes that when the difference in effectiveness between two treatments is not statistically significant, the only valid conclusion is that there is not sufficient evidence to distinguish between the treatments, i.e., it is not sufficient to conclude that the treatments are equivalent. Therefore, there remains uncertainty about the assumption of equivalent (or very similar) effectiveness, disease progression and disease-related mortality between ublituximab and its comparators, ofatumumab and ocrelizumab (IV or SC).

Uncertainty in health outcomes will also affect uncertainty in total costs. The treatment duration of the interventions is assumed to be 5 years in the absence of other information, but if this duration differs by treatment then the length of time spent in health states and time to next treatment received will also differ. Therefore, the corresponding resource use and costs for the interventions will be different.

5.2.2 Adverse events

A key assumption in a cost comparison analysis is the equivalence (or very similar) safety profile between the interventions under comparison. Only substantial differences between interventions in costs directly relating to health outcomes that indicate that the intervention and comparator(s) may not provide similar overall health benefits should be considered in a cost comparison. The company's inclusion of differential adverse events in the first year of treatment appears unnecessary given the underlying assumption that the safety profile is comparable between the treatments and the company's assumption that there is no difference in the discontinuation rate between treatments (and switching to subsequent treatments).

The health-related quality of life (HRQoL) impact of the AEs is not included in the cost comparison. The EAG notes that if the difference in AEs is considered sufficiently important for inclusion in the company's cost comparison, then the HRQoL impact (utility decrement) for the AEs should also be considered. However, a full cost-effectiveness analysis would be required to capture the impact on HRQoL due to AEs and the consequences of discontinuing treatment.

The EAG concludes that the inclusion of separate AE costs, whilst not considering their HRQoL impact, is unnecessary in the company's cost comparison analysis. Furthermore, the EAG's clinical

advisor did not consider there to be any reason for the differential rates of the more costly AE of depression (0.7% for ublituximab, 4.8% for ofatumumab and 7.8% for ocrelizumab (IV), see Table 34 of CS), which has a unit cost of £3,822 as a serious AE and £1,046 as a non-serious AE (see also Section 4.4). The lower percentage of patients experiencing treatment-related depression (a more costly event) for ublituximab compared to the comparators is the main driver of the lower one-off AE cost included in the company's cost comparison for ublituximab (£44.34) compared to comparators (£91.20 for ofatumumab and £125.63 for ocrelizumab (IV or SC)).

5.2.3 Acquisition costs

The cost comparison model estimates acquisition costs in the first and subsequent years for ublituximab and comparators. The list price for ublituximab in the first year is [redacted] and [redacted] per subsequent year, which is higher than the list price of ofatumumab (first year: £20,895, subsequent years: £17,910) and ocrelizumab (IV or SC) (£19,160 per year). The PAS price for ublituximab is [redacted] in the first year and [redacted] per subsequent year, which is [redacted] than the comparator list price.

The EAG notes that there are confidential commercial arrangements in place for the comparator treatments. The drug acquisition costs used in the CS and in this report include only the confidential pricing agreement for ublituximab. Table 10 presents details of the treatments with confidential price which differs from the publicly available list price used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of 13th August 2024.

Table 10 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Ublituximab	Simple PAS
Ofatumumab	Simple PAS
Ocrelizumab (IV & SC)	Simple PAS

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

5.2.4 Administration costs

The cost comparison analysis includes differences in the administration method and duration of infusion and monitoring time for the treatments. Ublituximab and ocrelizumab (IV) involve IV infusions that differ in the duration of the infusion and the monitoring time after the infusion at each session, which is approximated by the proportion of bed-day costs and nursing costs per infusion. Ublituximab's infusion time is assumed to be 1 hour shorter for the first infusion and 1.75 hours

shorter for subsequent infusions compared to ocrelizumab (IV). In addition, no monitoring time for subsequent infusions is required with ublituximab. Consequently, the administration costs for ublituximab are lower than ocrelizumab (IV) (see Table 31 of CS).

Ofatumumab involves a SC injection, for which an administration cost is only attributed at treatment initiation and subsequent administrations occur no costs. This method assumes that patients follow a two-hour training on self-administration from a MS-specialist nurse, in line with the approach used in TA699.[2] Consequently, the administration costs for ofatumumab are much lower than ublituximab and ocrelizumab (see Table 32 of CS).

The EAG cross-checked the administration cost assumptions with previous NICE TAs 699 and 533 and validated them with the EAG's clinical advisor.[1, 2] The approach used by the company is in line with previous TAs and is considered reasonable in the context of the cost comparison.

However, the EAG notes that the CS did not consider the impact of the new 'under-the-skin' injection for ocrelizumab on its acquisition and administration costs.[1] Ocrelizumab can now be administered via a quick 'under-the-skin' twice-yearly injection, which reduces the infusion time. Therefore, the benefits of ublituximab's shorter infusion time compared to ocrelizumab (SC) is no longer expected to hold. The EAG requested at points for clarification to update the revised version of the model to reflect the changes to the acquisition and administration costs of ocrelizumab 'under-the-skin' injection. The company included ocrelizumab 'under-the-skin' injection as a new comparator, ocrelizumab (SC), in the cost comparison analysis. Table 11 compares the resource use costs for drug administration with ocrelizumab in IV and SC forms. Compared to ocrelizumab (IV), ocrelizumab (SC) has shorter preparation time (0.5 hours) and injection time (0.17 hours). Uncertainty remains about the percentage of patients to use different forms of ocrelizumab (IV or SC). The EAG's clinical advisor considered that current patients who already use ocrelizumab (IV) are more likely to continue with IV infusions, but newly treated ocrelizumab patients are more likely to use SC injection because of the time and cost-savings. Therefore, in the long-term, it is expected that most patients treated with ocrelizumab will be administrated SC injection. The percentage of patients treated with ocrelizumab IV and SC will impact the cost comparison results.

Table 11 Drug administration cost calculations for ocrelizumab in IV and SC forms (from company response to EAG clarifications, Table 20)

Resource use per administration	Ocrelizumab IV First infusion	Ocrelizumab IV Subsequent infusions	Ocrelizumab SC injections
Preparation time (h)	1.00	1.00	0.50
Infusion/injection time (h)	5.00	2.75	0.17
Time interval between patients (h)	0.25	0.25	0.25
Total infusion/injection time per patient (h)	5.25	3.00	0.42
Monitoring after infusion/injection (h)	1.00	1.00	1.00

Total time per patient per session(h)	7.25	5.00	1.92
Patients per bed per day	1.00	1.00	4.00
Nurse costs for infusion per patient	£420.50	£290.00	£111.17
Cost per bed-day	£386.13	£266.30	£102.08
Total cost per administration	**£806.63**	**£556.30**	**£213.25**
Annual drug administration costs	**£1,056.97**	**£1,112.60**	**£426.50**

Abbreviations: h, hour; IV, intravenous; SC, subcutaneous.

5.2.5 Treatment discontinuation and subsequent treatment use

The company assumes no treatment discontinuation in its base case analysis, but a separate scenario analysis is provided where differential discontinuation rates between the three treatments are considered ([redacted] for ublituximab, [redacted] for ofatumumab, and [redacted] for ocrelizumab). The differential discontinuation rates in the scenario analysis have minimal impact on the results of the cost comparison because the costs of subsequent treatments post-discontinuation are not included in the model.

The EAG's clinical advisor considered it reasonable to assume that ublituximab, ofatumumab and ocrelizumab have very similar discontinuation rates, and that the subsequent treatments used post-discontinuation would be expected to be similar across the three interventions. Therefore, the EAG considers no treatment discontinuation to be a reasonable approximation in the context of the cost comparison, under the assumption of equivalence (or very similar) safety profile between the interventions under comparison.

5.2.6 Time horizon and discounting

The time horizon used in the company's base case is set to five years, which the company states was selected to account for higher treatment initiation costs and to allow the costs to stabilise over time. The EAG considers a 5-year time horizon to be a reasonable choice, but notes that because treatment discontinuation is not considered in the model the costs accrued annually do not change after the first year; the annual costs only change insofar as general population mortality rates are incorporated into the analysis to determine the number of patients alive each year to receive treatment (and the company's model incorporates a half-cycle correction to account for timing of death during an annual cycle). Therefore, the EAG considers it important to present the differences in annual costs between the interventions, rather than only presenting the total cost difference over a 5-year time horizon (see Table 15 in Section 6.2). The effect of increasing the annual costs over a longer time horizon provides an illustration of the budget impact per patient remaining on treatment.

The company did not include discounting in their results over a 5-year time horizon, on the basis that NICE methods guidance indicates that discounting may not be required for cost comparisons. The EAG considers it appropriate to use discounting when the differences in costs between treatments are

extended over a longer time period of five years. However, as noted above, the EAG considers it important to present the differences in annual costs between the treatments, which do not need to be discounted.

6 COMPANY AND EAG COST COMPARISON RESULTS

The following section details the results of the company's base case and scenario analyses, followed by the EAG's preferred base case. All results include the PAS price for ublituximab and list price for comparators. A separate confidential appendix presents the results of the company and EAG preferred base case when confidential PAS prices for comparators are included.

6.1 Company cost comparison results

Table 12 presents the company's base case results for ublituximab, ofatumumab and ocrelizumab (IV or SC) over a 5-year horizon. The total costs (with PAS price) for ublituximab are [redacted] than its comparators.

Table 12 Total costs for the intervention and comparator technologies over a 5-year time horizon (from CS, Table 36)

	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, list price	[redacted]	£3,649	£1,966	£44	[redacted]
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£44	[redacted]
Ofatumumab	£92,402	£116	£1,966	£91	£94,575
Ocrelizumab (IV)	£95,658	£5,526	£1,966	£126	£103,276
Ocrelizumab (SC)	£95,658	£2,150	£1,966	£126	£99,899

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

The company provided two scenario analyses: (i) costs are discounted at a rate of 3.5% per annum; and (ii) treatments are discontinued, with an annual discontinuation probability of [redacted] for ublituximab, [redacted] for ofatumumab and [redacted] for ocrelizumab based on the NMA (rates converted to annual probabilities). Table 13 below shows the results of the company's scenario analyses. The total costs (with PAS price) for ublituximab are [redacted] than its comparators for both scenarios.

Table 13 Total costs derived from scenario analyses (from CS, Table 37)

	Base case	3.5% discounting	Treatment discontinuation
Ublituximab, list price	[redacted]	[redacted]	[redacted]
Ublituximab, PAS price	[redacted]	[redacted]	[redacted]
Ofatumumab	£94,575	£88,610	£86,454
Ocrelizumab (IV)	£103,276	£96,539	£93,672
Ocrelizumab (SC)	£99,899	£93,386	£90,615

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

6.2 Results of EAG preferred base case

The EAG preferred base case reflects the assumptions included in the company's base case with the (i) exclusion of differential adverse event costs; and (ii) inclusion of discounting of costs over a 5-year time horizon (Table 14).

Table 14 Accumulated EAG base case results over a 5-year time horizon

Company base case					
	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£44	[redacted]
Ofatumumab	£92,402	£116	£1,966	£91	£94,575
Ocrelizumab (IV)	£95,658	£5,526	£1,966	£126	£103,276
Ocrelizumab (SC)	£95,658	£2,150	£1,966	£126	£99,899
Company base case + exclusion of adverse events costs					
	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, PAS price	[redacted]	£3,649	£1,966	£0	[redacted]
Ofatumumab	£92,402	£116	£1,966	£0	£94,484
Ocrelizumab (IV)	£95,658	£5,526	£1,966	£0	£103,150
Ocrelizumab (SC)	£95,658	£2,150	£1,966	£0	£99,774
Company base case + exclusion of adverse events costs + 3.5% annual discount rate (EAG base case)					
	Drug acquisition costs	Drug administration costs	Resource use costs	Adverse event costs	TOTAL COSTS
Ublituximab, PAS price	[redacted]	£3,470	£1,843	0	[redacted]
Ofatumumab	£86,560	£116	£1,843	0	£88,519
Ocrelizumab (IV)	£89,409	£5,162	£1,843	0	£96,413
Ocrelizumab (SC)	£89,409	£2,010	£1,843	0	£93,261

Abbreviations: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.

The exclusion of adverse events costs and inclusion of a 3.5% annual discount rate has only a small impact on the cost comparison results, with the total cost for ublituximab (with PAS price) [redacted] than its comparators.

The EAG also considers it important to present the results separately for the first year and subsequent years, rather than over a 5-year time period, so that the annual difference in costs between the treatments can be assessed. Table 15 shows that the differences in costs over the 5-year time horizon in the company's base case and EAG base case (without discounting) is largely from subsequent years costs.

Table 15 Company base case and EAG base case with results reported separately for the first year and subsequent years

	Ublituximab	Ofatumumab	Ocrelizumab (IV)	Ocrelizumab (SC)	Incremental Δ Ublituximab vs Ofatumumab	Incremental Δ Ublituximab vs Ocrelizumab (IV)	Incremental Δ Ublituximab vs Ocrelizumab (SC)
Company base case							
First year costs	[redacted]	£21,560	£20,807	£20,174	[redacted]	[redacted]	[redacted]
Subsequent year costs (each year)	[redacted]	£18,288	£20,655	£19,969	[redacted]	[redacted]	[redacted]
Company base case: Over 5 years (undiscounted)	[redacted]	£94,575	£103,276	£99,899	[redacted]	[redacted]	[redacted]
EAG base case							
First year costs (same as company but excluding one-time AE costs)	[redacted]	£21,468	£20,682	£20,048	[redacted]	[redacted]	[redacted]
Subsequent year costs (each year)	[redacted]	£18,288	£20,655	£19,969	[redacted]	[redacted]	[redacted]
EAG base case: Over 5 years (discounted at rate of 3.5% per year)	[redacted]	£88,519	£96,413	£93,261	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event ; EAG, evidence assessment group; IV, intravenous; SC, subcutaneous.

7 EQUALITIES AND INNOVATION

The EAG agrees with the company that introducing ublituximab to NHS practice is not likely to impact differentially on groups of patients with protected characteristics or disabled persons. As with all treatments administered in hospital, equitable access across English regions depends on the local availability of technology and personnel.

Ublituximab is an anti-CD20 monoclonal antibody, and similar in terms of mechanisms of action to comparators ocrelizumab and ofatumumab. The company does not argue that ublituximab is a novel, innovative therapy in terms of working mechanisms, safety profile, or treatment effects. In the CS, the company argued that the shorter infusion time of ublituximab compared to ocrelizumab (from the second infusion) is an improvement, though this argument is less relevant with the recent introduction of ocrelizumab subcutaneous injections (see Section 3.3).

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Conclusions on clinical evidence

The evidence for ublituximab is drawn from the ULTIMATE trials, which are large, high-quality RCTs. There is good evidence from the trials that ublituximab is superior to teriflunomide at reducing relapse rate. However, the trials did not show a benefit of ublituximab compared to teriflunomide for worsening disability outcomes at 12 and 24 weeks. Subgroup analyses of the ULTIMATE trials performed by the EAG [redacted].

The introduction of ocrelizumab by subcutaneous injection raises some doubts as to whether ublituximab, which requires IV infusion, will be preferred by patients.

Ublituximab was compared to ocrelizumab and ofatumumab using appropriate and properly conducted network meta-analyses. The results suggested that ublituximab is plausibly similar in efficacy to ocrelizumab and ofatumumab for response rate and disease progression. However, the NMAs comparing ublituximab to ocrelizumab were highly indirect, subject to network inconsistency and not robust to sensitivity analyses. This raises concerns to whether the two treatments can be considered equally effective. The NMAs also suggested that ublituximab might be marginally inferior to ocrelizumab and ofatumumab in terms of disease progression at 12 months and treatment discontinuation, although these findings were not statistically significant.

The EAG considers that currently there is little robust evidence to suggest that ublituximab has a different safety profile to ofatumumab and ocrelizumab, but the exception to this could be infusion or injection related reactions. Given the differences in how the anti-CD20s are administered, patient preferences may play an important role when deciding which treatment may be best to use.

8.2 Conclusions on cost-effectiveness

The EAG is largely satisfied with the company's approach to the cost-comparison analysis based on differential drug acquisition and administration costs. However, the EAG considers it unnecessary to include separate adverse event costs, whilst not considering their health-related quality of life impact because a key underlying assumption is that the safety profile is comparable between the treatments and there is no difference in the discontinuation rate between treatments. The lower percentage of patients experiencing treatment-related depression (a more-costly adverse event) for ublituximab compared to the comparators is the main driver of the lower one-off AE cost included in the

company's cost comparison. In the company's base case, ublituximab has [redacted] acquisition costs than the comparator list price (confidential commercial arrangements are in place for the comparator treatments). The cost comparison analysis includes differences in the administration method and duration of infusion and monitoring time for the treatments. The EAG is satisfied with the approach used by the company but noted that the CS did not consider the impact of the 'under-the-skin' injection for ocrelizumab (SC), which has shorter preparation and injection time compared to ocrelizumab (IV). Uncertainty remains about the percentage of patients to use different forms of ocrelizumab (IV or SC), which will impact the cost comparison results.

8.3 Areas of uncertainty

Table 16 lists the EAG's areas of concern, where the evidence presented may impact on the robustness and suitability of using a cost-comparison approach.

Table 16 Outstanding areas of uncertainty

Issue	Description	Report sections
Subgroup analyses of ULTIMATE trials	[redacted]	4.2.2.1
Indirect nature of comparison of ublituximab and ocrelizumab	NMAs comparing ublituximab and ocrelizumab were subject to inconsistency and were not robust to some of the sensitivity analyses. This led to uncertainty as to whether they can be considered as equivalent.	4.3.2; 4.3.3
NMAs of disease progression and treatment discontinuation	Ublituximab might be marginally inferior to ocrelizumab and ofatumumab in terms of disease progression at 12 months and treatment discontinuation.	4.3.3
Availability of ocrelizumab by subcutaneous injection	The CS does not consider the new treatment option of ocrelizumab by subcutaneous injection, which may impact on costs and patient preferences.	3.3; 5.2.4

9 REFERENCES

1. National Institute for Health and Care Excellence. *TA533: Ocrelizumab for treating relapsing–remitting multiple sclerosis*. London: NICE; 2018.

2. National Institute for Health and Care Excellence. *Ofatumumab for treating relapsing multiple sclerosis*. London: NICE; 2021.

3. Samjoo IA, Drudge C, Walsh S, Tiwari S, Brennan R, Boer I, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. *J Comp Eff Res* 2023;**12**:e230016-e.

4. Institute for Clinical and Economic Review. *Oral and monoclonal antibody treatments for relapsing forms of multiple sclerosis: Effectiveness and value*. New England: CEPAC; 2022. Available from: https://icer.org/wpcontent/uploads/2022/04/ICER_MS_Revised_Evidence_Report_122122.pdf

5. TG Therapeutics. *An open label extension study of ublituximab in subjects with relapsing multiple sclerosis*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2019. Available from: https://clinicaltrials.gov/study/NCT04130997 [accessed 29 August 2024]

6. Steinman L, Fox E, Hartung H-P, Alvarez E, Qian P, Wray S, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med* 2022;**387**:704-14.

7. TG Therapeutics. *Evaluating efficacy when transitioning from a current disease modifying therapy (DMT) to ublituximab (ENHANCE)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2023. Available from: https://clinicaltrials.gov/study/NCT05877963 [accessed 16 August 2024]

8. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;**376**:221-34.

9. Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med* 2020;**383**:546-57.

10. Alvarez E, Steinman L, Hartung H-P, Fox E, Qian P, Wray S, et al. Disease outcomes with ublituximab in participants with highly active disease: subpopulation analyses of the phase 3 ultimate I and II studies in participants with relapsing multiple sclerosis (P6-3.002). *Neurology* 2023;**100**:3092.

11. Asha MZI, Al-Asaad Y, Khalil SFH. The comparative efficacy and safety of anti-CD20 monoclonal antibodies for relapsing-remitting multiple sclerosis: A network meta-analysis. *IBRO Neurosci Rep* 2021;**11**:103-11.

12. Joint Formulary Committee. *British National Formulary (BNF)* 2024. Available from: https://www.nice.org.uk/bnf-uk-only [accessed 9 July 2024]

13. Barker KL, Room J, Knight R, Dutton SJ, Toye F, Leal J, et al. Outpatient physiotherapy versus home-based rehabilitation for patients at risk of poor outcomes after knee arthroplasty: CORKA RCT. *Health Technol Assess* 2020;**24**:1-116.

14. Jones KC, Weatherly H, Birch S, Castelli

13. Barker KL, Room J, Knight R, Dutton SJ, Toye F, Leal J, et al. Outpatient physiotherapy versus home-based rehabilitation for patients at risk of poor outcomes after knee arthroplasty: CORKA RCT. *Health Technol Assess* 2020;**24**:1-116.

14. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, JE F. *Unit costs of health and social care 2023*. University of Kent: Personal Social Services Research Unit 2024. Available from: https://kar.kent.ac.uk/105685/

10 APPENDICES

Appendix 1: Clinical Evidence Searches

The original company submission included searches to identify clinical evidence for adult patients with relapsing forms of multiple sclerosis (RMS). A description of the searches and some of the search strategies were included in CS Appendix D (pp. 2-15).

In response to the EAG's points for clarification (PfC), the company provided additional information and corrections to errors.

Table 17 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission: • no strategies were listed for the searches of conference abstracts. This was raised as a PfC. The company responded with all further strategies that were documented. • the update search for Ovid Embase was not documented with hits per line. This was raised as a PfC. The company responded with the fully documented strategy. • it was unclear why the PubMed strategy removed some MEDLINE records. This was raised as a PfC. The company explained that this was because this database had also been searched on another platform (concurrently with Embase). The company updated the names of some of the Tables to make this clearer. • the PRISMA listed 'databases and registers' but did not show the hits from clinicaltrials.gov in with the databases and registers. Instead, the PRISMA presented the number or relevant this from this source elsewhere in the diagram. This was raised as a PfC. The company responded with an updated PRISMA.
Were appropriate sources searched?	PARTLY	A small range of relevant databases, conference proceedings, and a single trials registry were searched. No dedicated HTA databases were searched (e.g. INAHTA), only one dedicated trials registry was searched, and there were no searches of websites of bodies such as NICE, etc.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with interventions and the study type. Data on adverse effects was not sought directly, even though this was part of the inclusion criteria. The EAG queried this as a PfC and the company responded that they were confident that no data on adverse effects was missed and that safety data from relevant trials had been used.
Were appropriate search terms used?	YES	Although the PubMed terms for interferon beta-1a were not as comprehensive compared with the terms used on other databases, this was acceptable since the same database had also been searched on another platform (concurrently with Embase) with more detailed search terms.
Were any search restrictions applied appropriate?	YES	Animal studies were removed appropriately
Were any search filters used, validated and referenced?	PARTLY	A randomised controlled trials filter was used but not referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE