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Ocrelizumab for treating relapsing multiple sclerosis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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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 HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Joanne Lord and Olu Onyimadu critically appraised the health economic review, critically appraised the economic evaluation, and drafted the report; Petra Harris, Jonathan Shepherd and Geoff Frampton critically appraised the clinical effectiveness review and drafted the report; Geoff Frampton project managed the ERG assessment and is the project guarantor.

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ABBREVIATIONS

ABN	Association of British Neurologists
AE	Adverse event(s)
AIC	Akaike information criterion
ALEM	alemtuzumab
ALT	Alanine aminotransferase
ARR	Annualised relapse rate
AST	Aspartate aminotransferase
BCMS	British Columbia Multiple Sclerosis
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDP	Confirmed disability progression
CDP-12	12-week confirmed disability progression
CDP-24	24-week confirmed disability progression
CDI	Confirmed disability improvement
CDI-12	12-week confirmed disability improvement
CDI-24	24-week confirmed disability improvement
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Clinically isolated syndrome
CLAD	Cladribine
CNS	Central nervous system
CrI	Credible interval
CS	Company submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
DAC	Daclizumab
DIC	Deviance information criterion
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy(s)
DSU	Decision Support Unit
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-dimensions quality of life questionnaire
ERG	Evidence review group
FDA	Food and Drug Administration
FINGO	Fingolimod
GA	Glatiramer acetate
HA	Highly active
HBV	Hepatitis B virus
HCC	Half cycle correction
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFNβ-1a	Interferon β-1a

IFNβ-1b	Interferon β-1b
IM	Intramuscular
ITT	Intention to treat
IV	Intravenous
JC virus	John Cunningham virus
K-M	Kaplan-Meier
LY	Life year(s)
LYG	Life year(s) gained
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTC	Mixed treatment comparison
NAT	Natalizumab
NEDA	No evidence of disease activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OCR	Ocrelizumab
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient access scheme
PEGβ -1a	Pegylated interferon β-1a
PH	Proportional hazards
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY/QALYs	Quality-adjusted life year/years
RCT/RCTs	Randomised controlled trial/trials
RES	Rapidly-evolving severe (multiple sclerosis)
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event(s)
RSS	UK MS Risk Sharing Scheme (RSS)
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form Survey
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SPMS	Secondary progressive multiple sclerosis
STA	Single technology appraisal
TERI	Teriflunomide

SUMMARY

Scope of the company submission

The company submission (CS) provides evidence on the clinical effectiveness and cost effectiveness of ocrelizumab, 600 mg intravenous infusion, administered once every 6 months, compared to other disease-modifying therapies (DMTs) for treating patients with relapsing forms of multiple sclerosis (MS).

The scope of the CS is generally consistent with the NICE scope for this technology appraisal, with some exceptions:

- The NICE scope specifies the population is people with relapsing forms of MS. This would include patients who have relapsing-remitting MS (RRMS) and those sho have secondary-progressive MS (SPMS) which is accompanied by relapses. The company's submission focuses on patints with RRMS since this reflects the population in the pivotal clinical trials (these included primarily patients with RRMS and a small, unquantified, number of patients with SPMS).
- The company's decision problem includes all the comparators specified in the NICE scope, but there are some differences in which patient subgroups these comparators are applied to (discussed in more detail in this report).
- Several outcomes specified in the NICE scope are not reported in the CS: severity of relapse (this was not measured in the ocrelizumab trials and so its exclusion from the company's decision problem is appropriate); EDSS scores, EQ-5D scores and fatigue scores (these have been obtained and are summarised by the ERG).

Summary of submitted clinical effectiveness evidence

Identification of evidence

The company conducted a systematic literature review (SLR) for clinical effectiveness evidence of DMTs in relapsing MS. The review was restricted to randomised controlled trials (RCTs) and included 46 trials. The ERG checked and updated the company's searches and did not find any further RCTs that should have been included.

The company did not specifically search for studies on ocrelizumab safety (which might have required non-randomised studies). However, it does not appear that the company has missed any key safety evidence in their submission.

Three of the 46 trials identified in the SLR provided direct comparisons of ocrelizumab against interferon β-1a. All 46 trials were considered by the company for inclusion in mixed treatment comparisons (MTCs) to enable effects of ocrelizumab to be estimated relative to those of the other DMTs in the NICE scope (details of the MTCs methods and results are summarised below).

Direct comparison of ocrelizumab versus interferon β-1a: Methods
Of the 46 RCTs identified, 3 included direct head-to-head comparisons of ocrelizumab against interferon β-1a in patients with RRMS aged 18-55 years:

- Phase III OPERA I and OPERA II trials: Two identical trials in which ocrelizumab was compared against interferon β-1a (Rebif) over 96 weeks, with a sample size of 410 to 418 patients randomised per arm;
- Phase II trial: A 24-week randomised comparison of ocrelizumab against interferon β-1a (Avonex) and placebo (this also included a futher hgh-dose ocrelizumab arm which is outside the scope of this appraisal and not considered by the company or ERG).

The company's direct comparison of the clinical effectiveness of ocrelizumab versus other DMTs is based entirely on the two OPERA trials, which is appropriate as these form the key evidence base. The phase II trial was used only as a source of information on advese events. Limited supporting data on clinical effectiveness and safety from an open-label extension study to the OPERA trials is also provided by the company.

The OPERA trials were double-blind double-dummy RCTs that were judged by the ERG overall to be at low risk of bias. Outcomes were assessed over a 96-week randomised treatment comparison period. The primary outcome was the annualised relapse rate (ARR), with key secondary outcomes including the proportion of patients experiencing confirmed disability progression, confirmed disability improvement, and numbers of lesions on MRI outcomes (see further details below).

Direct comparison of ocrelizumab versus interferon β-1a: Results

In both OPERA trials, ocrelizumab reduced the annualised relapse rate (ARR) over 96 weeks in the intention-to-treat (ITT) population (the primary outcome) by 46% compared to interferon β-1a (the rate ratio in the pooled analysis across both trials was 0.54; 95% CI 0.44 to 0.66). The effectiveness of ocrelizumab was also demonstrated in subgroup analyses on patients with highly active (HA) and rapidly evolving severe (RES) forms of RRMS (pre-specified and post-hoc respectively): rate ratios for the ARR in these subgroups (0.32 and 0.38 respectively) were lower than those seen in the ITT population. Post-hoc subgroup analyses according to patients' treatment history indicated that ocrelizumab effectively reduced the ARR compared to interferon β-1a both for treatment-naïve and for treatment-experienced patients (the company intends that ocrelizumab would be used either as a first-line or second-line therapy).

Secondary outcomes in the OPERA trials assessed at 96 weeks were:

- proportion of patients with disability progression (defined according to changes in Expanded Disability Status Scale [EDSS] scores), confirmed over 12 weeks (CDP-12) and confirmed over 24 weeks (CDP-24);
- proportion with disability improvement confirmed over 12 weeks (CDI-12);
- proportion with no evidence of disease activity (NEDA) – a compsite outcome based on the absence of relapses, disability progression and lesions on MRI imaging;
- magnetic resonance imaging (MRI outcomes): numbers of enhancing lesions on T1 MRI scans (indicating sites of active CNS inflammation); numbers of new or enlarged hyperintense lesions on T2 MRI scans (indicating sites of active and previous inflammation); numbers of hypointense lesions on T1 MRI scans (indicating areas of chronic irreversible CNS damage); changes in brain volume (indicating extensive structural damage; measured from 24 to 96 weeks to exclude transient initial effects of therapy);
- SF-36 Physical Component Summary (PCS) scores;
- Multiple Sclerosis Functional Composite (MSFC) scores (a patient-reported outcome measure that captures upper limb function, ambulatory fnction and cognitive impairment).

The secondary outcomes were tested in a pre-specified fixed hierarchical sequence to control the type I error rate. Following this process, the CDP-12, CDP-24, CDI-12, and MRI lesion outcomes demonstrated statistically significant effects favouring ocrelizumab over interferon β-

1a (in both OPERA trials and/or in pooled analyses), whilst in accordance with the protocol the remaining outcomes (NEDA, MSFC score, SF-36 PCS score, and change in brain volume) had to be interpreted as providing descriptive information only.

In the ITT population, ocrelizumab reduced the risk of CDP-12 by 40% compared to interferon β-1a (hazard ratio [HR] 0.60; 95% CI 0.45 to 0.81) and also reduced the risk of CDP-24 by 40% (HR 0.60; 95% CI 0.43 to 0.84). Ocrelizumab also reduced the risk of CDP-12 and CDP 24 in the HA and RES subgroups of patients but the effect was statistically significant only for CDP-12 assessed in the HA subgroup (HR 0.47; 95% CI 0.23 to 0.95). Post-hoc subgroup analyses according to patients' treatment history indicated that ocrelizumab reduced the risk of CDP-12 compared to interferon β-1a both for treatment-naïve patients (HR 0.60; 95% CI 0.42 to 0.85) and for treatment-experienced patients (HR 0.61; 95% CI 0.35 to 1.06). However, the reduction in risk of CDP-24 was statistically significant only for the treatment-naïve subgroup (HR 0.57; 95% CI 0.38 to 0.85).

For disability improvement, the proportion of patients with CDI-12 was assessed only in a subgroup of patients (pooled across both OPERA trials) who had a baseline EDSS score ≥2.0 (the company does not provide a rationale for this subgroup). The risk of CDI was significantly increased by ocrelizumab compared to interferon β-1a (risk ratio 1.33; 95% CI 1.05 to 1.68).

All three MRI lesion outcomes were statistically significantly improved by ocrelizumab compared to interferon β-1a. The rate ratios (95% CI) were 0.058 (0.032 to 0.104) for enhancing T1 lesions; 0.229 (0.174 to 0.300) for new and/or enlarged hyperintense T2 lesions; and 0.428 (0.328 to 0.557) for hypointense T1 lesions (all differences $p<0.0001$).

Further exploratory outcomes assessed in the OPERA trials which are relevant to the NICE scope but are not reported in the CS include EQ-5D scores and patient-reported fatigue scores. These are provided briefly in the current report as contextual information.

Direct comparison of ocrelizumab versus interferon β-1a: limitations

The secondary MRI outcomes, NEDA, MSFC score and SF-36 PCS score outcomes have more data missing from the interferon β-1a arm than from the ocrelizumab arm in both OPERA trials. The CDI-12 and NEDA outcomes were analysed in a subgroup (pooled across the trials) who had an EDSS score ≥2.0 at baseline but a rationale for this is not provided. However, these are

not critical outcomes for the company's economic analysis. The OPERA trials included patients aged 18 to 55 years, but clinical experts advising the ERG suggested that some patients older than this (up to age 65) would likely receive strong DMTs including ocrelizumab.

MTC analyses: methods

The company conducted MTC analyses on four outcomes which inform the company's economic analysis: ARR, CDP-12, CDP-24, and all-cause discontinuation. MTCs were performend on the ITT population and, for the ARR, CDP-12 and CDP-24 outcomes, also on the HA and RES disease activity subgroups. Sensitivity analyses investigated the inclusion/exclusion of several comparators which the company considered not to be relevant to the NICE scope (referred to as 'restricted networks') and a meta-regression was conducted to investigate whether MTC outcomes were influenced by variation in the duration of the trials. A further sensitivity analysis to test inclusion/exclusion of a specific trial was also conducted. In total, these analyses resulted in the company conducting 23 MTC analyses.

As noted above, the company's systematic review of clinical effectiveness evidence included 46 trials (the two OPERA trials and the ocrelizumab phase II trial, plus 43 RCTs on comparators). Of these, the company excluded 13 trials from MTC analyses, mainly because they had a short duration of randomised treatment comparison (<48 weeks), and/or ineligible dosing regimens. The two OPERA RCTs were included in MTC analyses but the ocrelizumab phase II trial, due to its short duration (randomised phase 24 weeks) was excluded. The ERG agrees broadly with the company's study selection process for the MTC analyses, and that it was appropriate to exclude the ocrelizumab phase II trial.

The statistical approach employed for the MTC analyses was a standard Bayesian analysis based on random-effects models, consistent with NICE guidance. Sensitivity analyses using fixed-effects models and alternative prior distributions confirmed appropriateness of the approach. Assumptions of similarity, heterogeneity and consistency were tested in the MTCs and although no concerns were raised regarding heterogeneity and consistency, the ERG is uncertain whether the similarity assumption is supported (see MTC analyses: limitations below).

MTC analyses: results:

In total, 33 RCTs informed the company's MTC analyses, ranging from 21 to 30 RCTs for the ITT analyses and 4 to 9 RCTs for the HA and RES subgroup analyses. The number of DMTs included in each analysis ranged from 15 to 17 for the ITT analyses and 5 to 10 for the HA and RES subgroup analyses.

In ITT analyses ocrelizumab was compared against 16 DMTs and against placebo (these included several different types of interferon β and some DMTs that are not in the NICE scope). In these 17 comparisons, ocrelizumab [redacted] compared to 11 DMTs and placebo; [redacted] compared to 9 DMTs and placebo; [redacted] compared to 2 DMTs (but not placebo). Ocrelizumab was most effective at reducing ARR, CDP-12 and CDP-24 when compared against [redacted].

Summary of submitted cost effectiveness evidence

The CS includes:

- A review of published cost-effectiveness studies that presented economic data in the treatment of relapsing multiple sclerosis
- An economic evaluation undertaken for the NICE STA process, comparing ocrelizumab with the following comparators in patients with RRMS: IFNβ-1a (Avonex, Rebif), IFNβ-1b, PEGβ-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, natalizumab and daclizumab.

The company conducted a systematic search to identify economic evaluations of DMTs for multiple sclerosis. This broad review was conducted to inform economic modelling and HTA across multiple countries. It identified one relevant analysis conducted by the Institute for Clinical and Economic Review, which modelled the cost-effectiveness of DMTs for MS including ocrelizumab.

The company developed an economic model building on assumptions and data sources from previous submissions, which are in line with the established model structure and natural history of RRMS. This model is a cohort health state transition model of a Markov type. It uses a one-year cycle, updating the distribution of the cohort between health states, costs and outcomes annually over a 50-year time horizon, taking the cohort from an initial age of 37 years up to 87 years. The model comprises 31 health states, including death. The health states are defined based on disease type (RRMS/SPMS), treatment status (DMT or best supportive care) and level of disability (EDSS 0 to 9).

Each year, members of the cohort may make one of the following transitions:

- Disability progression: The base case model uses transition probabilities between EDSS states estimated from natural history data. Due to the progressive nature of MS, disability tends to increase over time, although it can sometimes improve: thus the base case model allows transitions to higher or lower EDSS states. EDSS can change by more than one level in a year, but large jumps are unlikely. The same probabilities are assumed for transitions between EDSS states within SPMS as within RRMS. A different set of probabilities is used for the RES and HA subgroups, reflecting the more rapid progression of disability in these groups. Treatment modifies the probabilities of EDSS progression in accordance with CDP effects from the mixed treatment comparison (ITT, RES and HA groups). In their base case, the company uses CDP-12 as the measure of progression, but CDP-24 is used in sensitivity analysis. By assumption, treatment does not affect rates of disability regression.
- Treatment discontinuation: Patients on DMT may stop treatment for various reasons, including intolerance and inadequate response. The model assumes a constant annual probability of withdrawal for each drug in each subgroup (ITT, HA and RES), estimated by MTC of all-cause discontinuation. In addition, treatment is assumed to stop when patients progress beyond EDSS 6 or after conversion to SPMS. These stopping rules are based on NHS England policy and ABN guidelines.(2, 58) After discontinuation, patients are assumed to receive only BSC, with no lasting effects of DMT.
- Conversion to SPMS: Each year, there is a chance that patients with RRMS may convert to SPMS, estimated from natural history data. The probability of conversion is higher for patients with worse disability (higher EDSS). The conversion

probabilities by EDSS state are assumed constant over time and do not differ for the HA and RES subgroups. Treatment is assumed to modify the probability of conversion to SPMS by 50% of the effect on disability progression. By assumption, conversion to SPMS is accompanied by a one-point increase in EDSS and cessation of any DMT. SPMS is defined as a chronic state, so transition back to RRMS is not allowed.

- Mortality: Death can occur from any health state. For patients without disability (EDSS 0), mortality rates are the same as in the general population (by age and sex), but increase with EDSS. The relative risks of mortality by EDSS level are the same for RRMS (ITT, HA and RES) and SPMS. Treatment does not have a direct effect on mortality, although there is an indirect effect through delay in disability progression.

In addition to state transitions, the model includes two other important outcomes:

- Relapse rates: Each health state is associated with a mean number of relapses per year, the ARR, estimated from natural history data. ARR tends to decrease with time since diagnosis and hence with increasing EDSS. The ARR is higher for people with more active forms of RRMS, including RES and HA, and lower in SPMS. Treatment modifies the relapse rate, reducing the mean ARR at each level of EDSS. Estimates of the relative reductions in ARR for each DMT and subgroup come from the MTC.
- Adverse events: The types and incidences of AEs vary between DMT drugs. The model incorporates AEs with an occurrence of 5% or more in either arm of the pooled OPERA I and II trial data. This includes infusion-related reactions and injection site pain, a range of infections, musculoskeletal symptoms, depression, fatigue, headache and insomnia. In addition, PML was included because of its high cost and patient impact. Each of the included AEs is associated with an annual incidence for each DMT, which is assumed constant over time. Estimates of AE rates come from the pooled analysis of the OPERA data and a previous submission to NICE (Daclizumab).

The results of the economic model are presented as incremental cost per quality-adjusted life-year (QALY) as well as pair-wise ICERs of ocrelizumab versus the comparators. The company's base case results for the ITT analysis, the HA subgroup and the RES subgroup are presented in the tables below.

We note that the PAS price for ocrelizumab and the list prices for all comparators were used in the estimation of cost-effectiveness. These results are not informative for comparators with a PAS (dimethyl fumerate, fingolimod, daclizumab and teriflunomide) because they do not reflect prices paid in the NHS. We report results based on all available PAS prices in Addendum 1 to this report.

Table 1 indicates that under the company's base case for the ITT population: alemtuzumab dominates ocrelizumab; but if alemtuzumab is not an option for some patients, ocrelizumab has an ICER of £26,435 compared with blended ABCR (CS Table 59). The ICER for ocrelizumab varies between individual ABCR comparators, with a range from £22,841 compared with IFNβ-1a (Avonex) to £35,028 compared with Pegβ-1a (CS Appendix J.1.2 Table 63). The company results for the HA and RES subgroup analyses in Table 2 and Table 3 suggest that ocrelizumab is cost-effective in these subgroups. However, these tables exclude alemtuzumab, because results are not available from the subgroup MTC analysis for the outcome of CDP-12 that the company used. As in the ITT analysis, daclizumab is excluded because of the EMA safety warning. The CS also reports one-way sensitivity analysis, scenario analyses and probabilistic analysis, which are reproduced and discussed in this ERG report.

Table 1 Company ITT base case (OCR PAS; list prices for comparators)
Adapted from CS Table 57

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER (£/QALY)	
				Ocrelizumab vs. comparator [c]	incremental
Blended ABCRs	[redacted]	[redacted]	[redacted]	26,435	-
Alemtuzumab	[redacted]	[redacted]	[redacted]	OCR dominated	8,296
Teriflunomide [b]	[redacted]	[redacted]	[redacted]	9,832	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	-	Dominated
Dimethyl fumarate [b]	[redacted]	[redacted]	[redacted]	OCR dominant	Dominated
Fingolimod [a b]	[redacted]	[redacted]	[redacted]	OCR dominant	Dominated
Natalizumab [a]	[redacted]	[redacted]	[redacted]	OCR dominant	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Comparator not in scope for 'ITT' population; b PAS available but not included in this analysis; c pairwise ICERs for ocrelizumab vs. comparators calculated by ERG from company model.

Table 2 Base case HA subgroup, deterministic: Adapted from CS Table 67
(ocrelizumab PAS; list prices for comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]	-	-
Fingolimod	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Table 3 Base case RES subgroup, deterministic: Adapted from CS Table 71
(ocrelizumab PAS; list prices for comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]	-	-
Natalizumab	[redacted]	[redacted]	[redacted]	1,065,854	1,065,854

Commentary on the robustness of submitted evidence

Strengths

- The OPERA trials providing direct evidence on ocrelizumab effectiveness were well-conducted and considered to be at low risk of bias by the ERG.
- The company conducted sensitivity analyses that suggested MTC outcomes are not sensitive to the duration of trials, to the inclusion/exclusion of specific comparators that are considered not relevant to the NICE scope, to the definitions of ARR or CDP, or to the methods of adjustment of ARR for baseline covariates. A caveat is that sensitivity analyses on definitions of ARR did not cover the full range of definitions used in the trials.
- The company assessed heterogeneity and consistency in their MTC analyses and demontrated that these assumptions appear to have been satisfied.
- The model structure and choice of data sources is generally appropriate and consistent with previous NICE appraisals of DMTs for MS.
- It also includes a number of assumptions employed in previous appraisals that are appropriate, including:
    - stopping rules for DMTs: EDSS>=7 or conversion to SPMS;
    - no impact of treatment on severity or duration of relapses;
    - treatment reduces disability progression but not regression;

    - rates of withdrawal from treatment and adverse effects are constant over time; and
    - DMT does not directly affect mortality.
- The model is also well implemented. We did not identify any coding errors or important discrepancies between data sources and model parameters.

Weaknesses and Areas of uncertainty

- The MTC analyses of CDP-12 and CDP-24 assume proportional hazards. The company provided evidence to suggest that this assumption is supported for the comparison of ocrelizumab against interferon β-1a, but it is unclear whether the assumption would be supported for comparisons among other DMTs.
- To enable MTC networks to be formed for HA and RES disease severity subgroups, the company utilised ITT data from trials of 'ABCR' comparators (types of interferon β and glatiramer acetate). The underlying assumption is that, for these treatments, the treatment effect observed in the ITT population would be the same as the treatment effects in the subgroup populations. However, the company has not clearly justified that this assumption is supported. Overall, given the limitations of the subgroup analyses, including that they are post-hoc and potentially at risk of selection bias, both the company and ERG consider the MTC results for these subgroups to be unreliable.
- There are marked differences between trials included in the MTCs in the proportions of patients who were treatment-naïve and treatment-experienced, and also in the time since onset of symptoms. The the ERG is therefore uncertain whether the consistency assumption of MTC analysis is supported.
- There is uncertainty around some individual input data for the MTCs. (i) An independent MTC which the company used to provide ITT CDP-12 outcomes for some comparisons against alemtuzumab, obtained by the company from the 'HAS Reimbursement dossier' has not been critiqued by the company and the ERG is unable to locate the dossier to check it. (ii) It is unclear whether the placebo arm in the Calbrese 2012 trial was included in MTC analysis. (iii) The company does not adequately justify why the Etemadefir 2006 trial was excluded from MTC analyses of ARR.
- The company did not conduct any sensitivity analyses to investigate whether MTC outcomes were sensitive to the inclusion of trials that were judged to be at high risk of bias.

- In the OPERA trials there are unbalanced missing data for some secondary outcomes (though these outcomes do not inform the economic analysis).
- Model results were most sensitive to parameters relating to treatment effects on disability progression. Varying these parameters between lower and upper 95% confidence limits led to changes in cost-effectiveness. Inconsistencies between the company MTC results for CDP and other published estimates suggest some additional uncertainty that is not reflected in the model.
- The company used the 12 week measure of CDP effectiveness in their base case model. We believe that CDP-24 is a more robust measure, less likely to be confounded by longer-lasting temporary relapses.
- In their base case, the company assumed that DMTs reduce the rate of conversion from RRMS to SPMS by 50% of the relative effect on CDP. This assumption is not based on evidence.
- In addition, the company assumes that conversion from RRMS to SPMS is accompanied by a one-point increase in EDSS, which does not reflect clinical opinion from experts consulted by the ERG.
- The company model uses the same transition matrix (British Columbia) for RRMS and SPMS, which includes reductions in EDSS as well as increases. We have been advised that this is unrealistic for SPMS.
- The company base case model assumes no waning of treatment effects over time. This is inconsistent with assumptions in previous NICE appraisals. We favour the more conservative approach of assuming reduced effects over time.
- Rates of retreatment for alemtuzumab in the company base case model assume that 13% of patients are retreated after year 5. This is unrealistic in current UK practice.

Summary of additional work undertaken by the ERG

The ERG analysis consists of three parts:

- A rerun of the company's model after minor corrections, but essentially maintaining the company's base case assumptions. Out of scope comparators are excluded from results of this analysis.

- A base case analysis based on alternative assumptions that the ERG found more plausible following consultations with experts and after consideration of available evidence. The ERG also explores additional scenarios for individual parameters.
- A PAS analysis reported in Addendum 1 to this ERG report. As previously stated, cost-effectiveness results reported by the company do not reflect prices paid in the NHS, since the PAS price for ocrelizumab is compared to the list prices of comparators.

The rationale for our base case assumptions are stated and compared with the company's base case assumptions in section 4.5.1 of the ERG report. In Table 4 below, we present our base case results for the non-HA or RES population, based on the PAS price for ocrelizumab and list prices for comparators. Our findings show that ocrelizumab is dominated by alemtuzumab under our preferred assumptions. While ocrelizumab dominates daclizumab and DMF in Table 4, it is less cost-effective in the PAS analysis. The ICER for ocrelizumab compared with ABCR is £43,772 per QALY gained.

The results for the ERG base case analysis in the HA subgroup in Table 5 show that ocrelizumab is dominated by alemtuzumab under ERG preferred assumptions. The ICERs for ocrelizumab versus fingolimod are subject to uncertainty in the all-PAS analyses.

Table 4 ERG base case, non-HA/RES (PAS ocrelizumab; list prices for comparators)

Technologies	Total costs (£)	Total QALYs	ICER (£/QALY)	
			Ocrelizumab vs. comparator	Incremental
Blended ABCRs	[redacted]	[redacted]	£43,772	
Alemtuzumab	[redacted]	[redacted]	OCR dominated	£1,992
Teriflunomide	[redacted]	[redacted]	£10,302	Dominated
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab	[redacted]	[redacted]	OCR dominant	Dominated
Dimethyl fumarate	[redacted]	[redacted]	OCR dominant	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a PAS available but not included in this analysis

Table 5 ERG HA subgroup (OCR PAS, list prices for comparators)

Technologies	Total costs (£)	Total QALYs	OCR vs comparator (£/QALY)	Incremental ICER (£/QALY)
Alemtuzumab	[redacted]	[redacted]	OCR dominated	
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab	[redacted]	[redacted]	OCR dominant	Dominated
Fingolimod	[redacted]	[redacted]	OCR dominant	Dominated

In Table 6 (RES subgroup), it can be seen that alemtuzumab dominates ocrelizumab under all scenarios tested. Compared with natalizumab, ocrelizumab has favourable ICERs (note that ocrelizumab is estimated to be less effective but also less costly than natalizumab, so the high ICERs are favourable). Results with the PAS for daclizumab as well are shown in Tables 12 and 13 of Addendum 1 to this ERG report.

Table 6 ERG RES subgroup (OCR PAS, list prices for comparators)

Technologies	Total costs (£)	Total QALYs	OCR vs comparator (£/QALY)	Incremental ICER (£/QALY)
Alemtuzumab	[redacted]	[redacted]	OCR dominated	
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab	[redacted]	[redacted]	OCR dominant	Dominated
Natalizumab	[redacted]	[redacted]	£183,633 SW	Dominated

SW: south west quadrant – less effective and less expensive, so higher ICER indicates ocrelizumab is relatively more cost-effective.

1 INTRODUCTION

This report is a critique of the company's submission (CS) to NICE from Roche on the clinical effectiveness and cost effectiveness of ocrelizumab for relapsing forms of multiple sclerosis. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 13th December 2017. Responses from the company via NICE were received by the ERG on 9th January and 16th January 2018 and these can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of the company's description of the underlying health problem

The ERG considers that the CS provides a clear and accurate overview of the nature and clinical consequences of multiple sclerosis (MS) (CS section B.1.3). MS is an incurable neurodegenerative disorder characterised by inflammation, demyelination, and axonal loss in the brain and spinal cord. Symptoms of the disease vary widely among people and can affect any part of the body. Long-term studies have estimated that MS patients have historically had a median life expectancy around 7 years shorter than the general population, but survival rates have consistently improved through time.[1-3] Experts advising the ERG suggested that the difference in life expectancy bettween MS patients and the general population may now be around 5 years or less.

There are three types of MS: relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). The NICE scope focuses on adults with relapsing forms of MS (RRMS and SPMS).

Relapsing-remitting MS

RRMS is the most common of the three phenotypes of MS (approximately 85% of the MS population). RRMS has clearly defined inflammatory attacks (relapses), which cause lesions anywhere in the central nervous system (CNS). Over time, disability progressively worsens due to incomplete recovery from relapses. During remissions, the symptoms of MS, which can include pain, muscle weakness, sensory disturbance, lack of coordination, unsteady gait,

speech problems, incontinence, visual disturbance and cognitive impairment, may all disappear or some may continue and become permanent. According to the ERG's clinical advisors, spasticity and fatigue are usually persistent. Although there is currently no cure for RRMS, treatment with disease modifying therapies (DMTs) can reduce the frequency of relapses which improves patients' symptoms and may slow down the accumulation of disability.

Secondary progressive MS

Natural history studies have suggested that most patients with RRMS will eventually transition to SPMS, although recent prospective cohort studies on DMT-treated patients indicate that the time to conversion to SPMS and the proportion of patients who convert may be lower than previously thought.[4, 5] With the transition from RRMS into SPMS, patients may initially continue to experience a relapsing-remitting course but the frequency of relapses and remissions typically decline over time and progressive worsening of disability occurs as the underlying disease process shifts from the inflammatory course characteristic of RRMS, to a more steadily progressive phase characterised by permanent nerve damage or loss. As the frequency of relapses and remissions decline, DMTs no longer offer an effective treatment. The final NICE scope therefore only includes those patients with SPMS who continue to experience relapses. The diagnosis of SPMS is typically made retrospectively, since patients can vary considerably in the frequency and severity of their relapses and it can be difficult to tell at a given point in time whether a patient is transitioning from RRMS to SPMS. There is also inconsistency in how SPMS is defined, with no gold standard objective definition currently available.[4]

Disease prevalence

The CS states that there is an absence of accurate data concerning people with MS in the UK. Estimates from a study by Mackenzie et al.[2] are cited by the CS which suggest that there were 126,669 people living with MS in the UK at the beginning of 2010 (203.4 per 100,000 population), with 6003 new cases diagnosed during that year (9.64 per 100,000/year). The Mackenzie study was based on the General Practice Research Database (GPRD), which is a primary care database that includes approximately 65% of the England MS patient population. The study is therefore likely to be reflective of the UK population.

The study found a consistent downward trend in the incidence of MS in the GPRD during 1990-2010, with a rate of decline of 1.51% per year. However, this is countered by the increasingly expanding older population in the UK and the Mackenzie study estimated a growth rate of 2.4%

per year in the number of people with MS. Annual MS prevalence rates in database patients below the age of 50 remained unchanged over the 20-year study period (1990-2010), but increased by over 4% in patients aged ≥60 years.

Using a variety of sources combined with the Mackenzie study, the CS estimates that prevalence of people with RRMS in 2017 was 57,870. Clinical experts advising the ERG agreed that the company's estimate appears reasonable.

2.2 Critique of the company's overview of current service provision

The CS notes that there is variation in practice across the UK for the treatment of RRMS, but does not describe current service provision. The ERG understands that ocrelizumab would be administered in specialist MS clinics in a similar way to the administration of other infused DMTs. The CS does not comment on the nature of the MS clinics although we understand from clinical experts that these are likely to be hospital-based day-case units. The CS also does not comment on the interdisciplinary nature of MS care which, in addition to consultant neurologists, involves professionals such as MS nurses, physiotherapists and occupational therapists, speech and language therapists, psychologists, dietitians, social care and continence specialists, and GPs. The ERG is not aware of any key infrastructural or organisational issues that might impact on the provision of ocrelizumab therapy, other than the need (as in all areas of MS care) to ensure the availability of adequate staff with appropriate training. We understand that Specialist MS nurses could deliver ocrelizumab infusion therapy with relatively little additional training.

The CS provides a generally clear and accurate overview of the NICE recommendations and treatment guidance for RRMS provided by the Association of British Neurologists (ABN).[6] NICE provides guidelines for the management of MS in adults,[7] which covers RRMS as well as other types of MS.

Diagnosis

The CS does not explicitly describe the process for diagnosing MS or, more specifically, RRMS. Diagnosis of MS follows the McDonald criteria[8] (first published in 2001, and revised in 2005 and 2010), which are summarised in Table 7. For a diagnosis of RRMS, lesions have to have developed at different times and be in different anatomical locations.

Table 7 Revised 2010 McDonald Criteria for diagnosis of MS

Clinical presentation	Additional data needed for MS diagnosis
≥2 relapses; objective clinical evidence of ≥2 lesions; objective clinical evidence of one lesion together with reasonable historical evidence of a previous relapse	None
≥2 attacks; objective clinical evidence of one lesion	Dissemination in space shown by: ≥1 MRI detected lesions typical of MS **or** Await a further relapse that demonstrates activity in another part of the CNS
One attack; objective clinical evidence of two or more lesions	Dissemination in time shown by: MRI evidence showing both an active (current) and non-active (previous) lesion **or** MRI evidence of a new lesion since a previous scan **or** Await a further relapse
Insidious neurological progression suggestive of multiple sclerosis (typical for PPMS)	Continued progression for one year (determined by looking at previous symptoms or by ongoing observation) **plus any two of**: • ≥1 MRI detected lesions in the brain typical of MS • ≥2 MRI detected lesions in the spinal cord • Positive tests on cerebrospinal fluid drawn off by lumbar puncture

CNS, Central nervous system; MS, multiple sclerosis; PPMS. Primary progressive MS.

The NICE Guideline for managing MS in adults[7] states that:

- only a consultant neurologist should make the diagnosis
- diagnosis should be made on the basis of established up-to-date criteria such as the revised 2010 McDonald criteria[8]
- diagnosis should not be made on the basis of MRI findings alone

Induction and escalation treatment strategies

According to the literature[9-11] and clinical advice to the ERG, there are currently two main therapeutic strategies employed in clinical practice. These are mentioned, but not explained, in CS Table 5:

- Induction (or immune reset therapy)
- Escalation (or optimisation) therapy

These strategies make a distinction between DMTs that are moderately effective and have a relatively good safety profile (referred to by the ABN as category 1 DMTs), and highly effective DMTs that are associated with safety concerns (category 2 DMTs)[11] (Table 8). Induction therapy involves short-term use of a high-efficacy DMT to obtain rapid control of highly active MS (referred to as performing a 'strong immuno-intervention'[9]) which may increase the likelihood of long-term beneficial outcomes, but with risk of serious adverse events. Escalation therapy consists of starting treatment with safer category 1 DMTs and, if these are ineffective, switching to stronger DMTs.[9-11]

The CS suggests (in agreement with the literature and the ERG's clinical experts) that the choice of which DMT to prescribe in RRMS is largely based on an informed discussion and consensus between the prescribing clinician and the patient, taking into consideration the patient's level of disease activity, risk tolerance, preference and lifestyle considerations. Family planning is an important consideration as the DMTs vary in their safety profiles including the risk of teratogenicity[6] and at present only glatiramer acetate is licensed for use during pregnancy.

Table 8 ABN categories of DMTs based on efficacy[6]

Category 1	**Category 2**
Drugs of moderate efficacy (average relapse reduction 30–50%)	Drugs of high efficacy (average relapse reduction substantially more than 50%)
• β-interferons (including 'pegylated' β-interferon) • Glatiramer acetate • Teriflunomide • Dimethyl fumarate • Fingolimod	• Alemtuzumab • Natalizumab

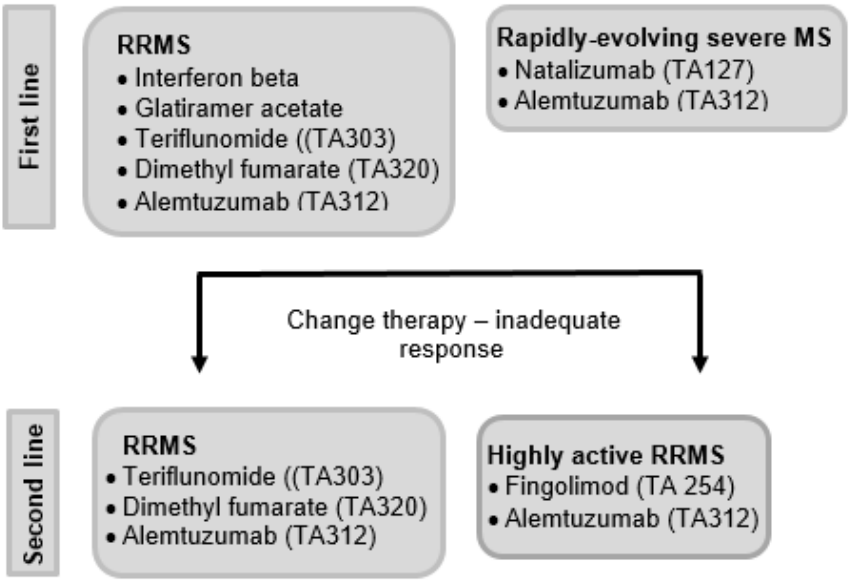
The CS suggests that the early use of DMTs is limited by safety concerns, as well as specific patient eligibility criteria as defined by EMA and NICE. ABN guidelines state that the safety profiles for DMTs such as of interferon β and glatiramer acetate have been established due to their long-term use, but that higher efficacy drugs have a more complex safety profile.[6] While drugs like interferons and glatiramer acetate have more favourable safety profiles compared to the newer more effective DMTs, the more effective DMTs carry a greater risk for life threatening infections and autoimmune disease, and carry warnings due to their risk profile.[12]

The CS provides a table listing common adverse events, safety issues and monitoring requirements for each DMT (CS Table 4), as well as a listing of the efficacy limitations of DMTs for RRMS (CS Table 5). Experts advising the ERG commented that the information on safety provided in CS Table 4 is selective. As such, this has not been reproduced here (adverse events are reported in section 3.3.9). Note that a detailed comparison of the safety profiles of the DMTs can be found in Pardo and Jones (2017)[10] (not reproduced here).

Treatment sequencing

Patients can be classified as having highly active (HA) or rapidly evolving severe (RES) forms of RRMS, depending on the frequency of relapses and lesions seen on magnetic resonance imaging (MRI) that they experienced in the previous year (for definitions of these subgroups see Table 14 in section 3.1.6.1). According to the NICE scope, patients with HA RRMS should receive fingolimod[13] or alemtuzumab,[14] whilst those with RES RRMS should receive natalizumab[15] or alemtuzumab[14]. Both HA and RES subgroups could also receive daclizumab, subject to alemtuzumab being contraindicated or otherwise unsuitable, but daclizumab use is currently restricted by an EMA alert regarding its safety (specifically liver toxicity).[16] Clinical experts advising the ERG suggested that daclizumab is unlikely to be used in the NHS until the safety concerns can be resolved.

The company emphasise that due to variations in current management of MS, there is no typical first-line therapy. Although there is currently no NICE pathway for the sequencing of DMTs, we note that NICE have discussed how first-line and second-line DMTs may be used in patients with RRMS and in the HA and RES subgroups, according to a slide in the Appraisal Committee Papers for the review of interferon β and glatiramer acetate (TA32).[17] This slide is reproduced in Figure 1 (with a minor modification, explained below).



Source: NICE committee papers of the review of TA32
MS, Multiple sclerosis; RRMS, Relapsing-remitting multiple sclerosis.

Figure 1 Current management of RRMS

Experts advising the ERG agreed that Figure 1 reflects how first-line DMTs would be used in current practice. Cladribine (although not in the NICE scope) could also be included as a first-line treatment for the RES subgroup of patients. The original slide in the TA32 Committee Papers suggested that patients would switch to second-line therapy based on adverse events. However, the ERG's clinical experts commented that changing between first-line therapies due to adverse events would not be regarded as moving to a second-line treatment; only moving therapy due to inadequate response would be considered as a switch to a second-line treatment. Figure 1 has therefore been modified from the original NICE slide to reflect this.

There were slight differences in opinion among the experts advising the ERG regarding the second-line DMTs in Figure 1. One clinical expert agreed with second-line therapy as depicted in the Figure. Another expert suggested that they would not include teriflunomide as a second-line DMT and that second-line DMTs for HA RRMS would include cladribine and probably also dimethyl fumarate.

According to the ERG's clinical experts, ocrelizumab could provide an alternative treatment option for either first-line or second-line treatment.

Stopping rules

The CS points out that there are no standard stopping rules for DMT therapy, but (based on ABN guidance), clinicians should consider stopping a DMT: (1) if there are significant side-effects; (2) non-relapsing SPMS develops; (3) in pregnancy; or (4) when loss of mobility occurs (an EDSS score of 6.5 is the upper limit for patient eligibility for a DMT - for an explanation of the EDSS see Appendix 3).

2.3 Critique of the company's definition of the decision problem

Population

The population specified in the company's decision problem is adults with RRMS. This is based on the pivotal trials that form the basis of the clinical effectiveness evidence provided in the CS, which included predominantly patients with RRMS. While the population is appropriate for the NHS, it is narrower than that specified in the NICE scope (people with relapsing forms of MS), since patients with SPMS who experience relapses are not included. We also note that, although it is not explicit in the decision problem (CS Table 1), the CS excludes patients aged over 55 years, as these were not included in the pivotal ocrelizumab trials (nor in most of the trials on the comparators). Clinical experts advising the ERG stated that patients aged over 55 years would (infrequently) be started on stronger DMTs such as ocrelizumab and the experts all agreed that it would be preferable to have clinical evidence for effectiveness and safety in patients up to age 65.

Intervention

In accordance with the NICE scope, the intervention described in the company's decision problem is ocrelizumab (brand name Ocrevus).

The CS provides an appropriate overview of the mechanism of action of ocrelizumab in relation to the pathophysiology of MS (CS section B.1.3). In summary, ocrelizumab is a recombinant humanised monoclonal antibody that selectively depletes CD20+ B cells, which are thought to be implicated in the pathophysiology of MS through their role in antigen presentation, cytokine production, autoantibody production and development of ectopic lymphoid follicle-like structures in the CNS. Through its mode of action, ocrelizumab reduces the frequency of inflammatory episodes in the CNS (i.e. relapses).

Ocrelizumab is administered as an intravenous infusion and the outlined use in the CS is:

- First dose 600 mg, administered as two 300 mg infusions two weeks apart
- Subsequent doses single 600 mg infusions, administered every six months, with a minimum interval of five months between each subsequent dose.

Two pre-medications must be administered prior to each ocrelizumab infusion to reduce the frequency and severity of infusion related reactions (IRRs):

- 100 mg intravenous methylprednisolone (or an equivalent), approximately 30 minutes prior to each ocrelizumab infusion
- Antihistamine, approximately 30–60 minutes prior to each ocrelizumab infusion

An antipyretic (e.g. paracetamol) as pre-medication may be considered approximately 30-60 minutes prior to each ocrelizumab infusion.

Safety issues

The draft summary of product characteristics (SmPC) recommends that all patients are screened for hepatitis B virus (HBV) prior to initiation of treatment with ocrelizumab, as the safety and efficacy of ocrelizumab in patients with hepatic impairment has not been formally studied. The SmPC does state that a change in dose is not expected to be required for patients with renal impairment.[18] Ocrelizumab must be withheld if progressive multifocal leukoencephalopathy (PML) is suspected and evaluation including MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebrospinal fluid (CSF) testing for John Cunningham (JC) viral DNA, and repeat neurological assessments should be considered. The SmPC states that a risk of PML cannot be ruled out since JC virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies. An increased number of malignancies (including breast cancers) have been observed in clinical trials in patients treated with ocrelizumab compared to control groups, but the SmPC noted that the incidence was within the background rate expected for an MS population.

The Committee for Medicinal Products for Human Use (CHMP) recommended in November 2017 the granting of a marketing authorisation for ocrelizumab (granted 08/01/2018).[18] Ocrelizumab is intended for the treatment of RRMS (with active disease defined by clinical or imaging features) and also in PPMS (i.e. the marketing authorisation is wider than the proposed population for this technology appraisal).

The intervention described in the decision problem is appropriate for the National Health Service (NHS) and reflects its intended licensed indication.

Comparators

Eight comparators of interest are listed in the NICE scope. As shown in Table 9, these are all included in the company's decision problem, although there are some differences in the comparator listings for the RRMS and SPMS patient groups when compared to the NICE scope. Differences include:

- *Daclizumab* is indicated for 'patients who have had an inadequate response to at least two DMTs and cannot be treated with other DMTs'.[19] As mentioned above, daclizumab use is currently restricted by an EMA alert regarding its safety (specifically liver toxicity).[16] The company state that, therefore, they do not consider daclizumab to be a relevant comparator. As such, it has been excluded from the company's economic analysis, although daclizumab is included in the company's mixed treatment comparisons (MTCs). Experts advising the ERG suggested that daclizumab it is unlikely to be used in the NHS until the safety concerns can be resolved.
- *Natalizumab and fingolimod*: In contrast to the NICE scope, the company decision problem includes natalizumab and fingolimod as comparators for the overall RRMS patient group. The CS notes that these two DMTs are only recommended for the HA and/or RES subgroups of RRMS, as per the NICE scope, but the company justifies their wider inclusion due to limitations in the subgroup MTC analyses (see Section 3.1.7 for more detail). The company has included natalizumab and fingolimod in their MTC and economic analyses, but also conducted a sensitivity analysis that excludes these comparators (CS Appendix D.1.4).
- *Comparators in the relapsing SPMS patient group:* The NICE scope includes best supportive care as a comparator for patients with relapsing SPMS. The company states that there is no available subgroup data for patients with relapsing SPMS in the company's pivotal trials. This comparator is therefore not included in the company's decision problem. The ERG's clinical experts agreed that this seems reasonable since separate data for SPMS and RRMS patients are not usually collected in clinical trials, and relapses in RRMS and SPMS should respond in the same way to immunotherapy (although relapses are rarer in SPMS and generally not managed as aggressively as in RRMS).

Table 9 Comparators included the NICE scope and the company's decision problem

Patient disease group	Final NICE scope comparators and restrictions	Company decision problem comparators
RRMS	• Alemtuzumab • dimethyl fumarate • Teriflunomide • Beta-interferon • Glatiramer acetate • Daclizumab *(only if the disease has been previously treated with disease-modifying therapy, and alemtuzumab is contraindicated or otherwise unsuitable)*	• Alemtuzumab • Dimethyl fumarate • Teriflunomide • Beta-interferon • Glatiramer acetate • Daclizumab • Natalizumab • Fingolimod
RES RRMS	• Alemtuzumab • Natalizumab • Daclizumab *(only if alemtuzumab is contraindicated or otherwise unsuitable*)	• Alemtuzumab • Natalizumab • Daclizumab
HA RRMS despite previous treatment	• Alemtuzumab • Fingolimod • Daclizumab *(only if alemtuzumab is contraindicated or otherwise unsuitable)*	• Alemtuzumab • Fingolimod • Daclizumab
SPMS with active disease, evidenced by relapses	• Best supportive care	

HA, Highly active; RES, Rapidly evolving severe; RRMS, Relapsing-remitting multiple sclerosis; SPMS, Secondary progressive multiple sclerosis.

The comparators are diverse in terms of their dosing regimens, which include oral tablets, intravenous infusions, subcutaneous injections and intramuscular injections, with administration timing and frequency varying considerably (summarised in Appendix 1).

Patients receiving intravenous infusions require attendance at hospital clinics whereas oral tablets, subcutaneous injections and intramuscular injections can be self-administered by the patient after an initial instruction clinic visit for injections. The ERG's clinical experts noted that Fingolimod (oral tablet) requires attendance for a day (6 hours admission) at hospital for first dose monitoring.

Outcomes

The outcomes are appropriate to the decision problem and conform with EMA guidance on the outcomes that should be assessed in clinical trials of MS therapies[20] (further details on the ERG's appraisal of the outcomes are given in section 3.1.5). The key outcomes specified in the NICE scope are relapse rate, severity of relapse, disability, symptoms, freedom from disease activity, mortality and adverse events.

The ERG has identified the following differences between the outcomes reported in the CS and the NICE scope:

- Severity of relapse, specified in the NICE scope, is not reported in the CS; this seems reasonable, as relapse severity was not an outcome in the pivotal clinical trials;
- Expanded disability status scale (EDSS) score, specified in the NICE scope, is reported only at baseline in the CS and trial publication;
- Four patient-reported outcomes that are either directly or indirectly relevant to the NICE scope are not reported in the CS or trial publication; these are quality of life as assessed by the EQ-5D, and three instruments that assessed depression and fatigue (all were exploratory outcomes).

Where possible, the ERG has obtained these missing outcomes from the clinical study reports (CSR) or, in the case of the EQ-5D data, via a clarification request to the company (clarification A8). Full details of the ERG's interpretation and appraisal of the outcomes are given in section 3.1.5.

Economic analysis

The company's economic evaluation is appropriate for the NHS and is consistent with the structure of established models for RRMS. Full details of the ERG's appraisal of the company model are given in section 4.3.

Other relevant factors

Subgroups

In addition to the aforementioned MS subgroups (RRMS, RES, and HA) the NICE scope specifies that the following subgroups should be considered if the evidence allows:

- people whose disease has responded inadequately to previous treatment
- people who could not tolerate previous treatment
- people in whom alemtuzumab is contraindicated or otherwise unsuitable

The CS does not report subgroup comparisons that precisely match these, but does report results of pre-specified analyses for the following subgroups that are closely related (CS Appendix E):

- analyses for treatment-naïve and treatment-experienced patients;
- analyses according to the subgroups ‘active inadequate responders’, ‘active treatment naïve’, highly active inadequate responders’ and ‘ highly active treatment naïve’ patients (reflecting regulatory definitions).

The CS also reports analyses of subgroups for a range of patient baseline demographic characteristics and disease variables (CS Appendix E).

Issues of validity and equality

The CS states that there are no obvious issues related to equity or equality in the decision problem and the ERG concurs. The ERG’s clinical experts commented that travelling to an MS clinic for infusions does put some people off, particularly if living far away. But ocrelizumab treatment is only four infusions per year so would be less of an issue than with more frequently-administered DMTs, and patients would usually be attending hospital every six months for clinic visits anyway.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to systematic review

This section summarises the company's search strategy, the ERG's critique, and updated searches that were conducted by the ERG.

3.1.1 Description of the company's search strategy

The company submission (CS) reports four systematic searches:

- Clinical evidence: last updated in July 2017
- Cost effectiveness: last updated in March 2017
- Health related quality of life: last updated in March 2017
- Cost and healthcare resource identification, measurement and valuation: last updated in February 2017

3.1.1.1 ERG's critique of the company's searches

All four search strategies were thorough and well documented. The databases selected were relevant (including Medline, Embase, the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and Health Technology Assessment database). The strategies contained a good range of controlled vocabulary terms, free text terms and application of appropriate search filters. The search syntax was apposite and the sets were correctly combined apart from a possible typographic error in the recording of the Cochrane Library clinical effectiveness search in line 53 which should have recorded a combination of lines 6-52 rather than 2-52; however, this would not have led to missing results.

Pertinent conferences were searched including: European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Americas Committee for Treatment and Research in Multiple Sclerosis conference (ACTRIMS), Consortium of Multiple Sclerosis Centers Annual meeting (CMCS), European Academy of Neurology (EAN), European Neurological Society (ENS), European Federation of Neurological Sciences (EFNS), American Academy of Neurology (AAN), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Relevant websites were additionally searched for supplementary grey literature.

The CS does not explicitly mention searching for any systematic reviews or meta-analyses of clinical effectiveness pertinent to the NICE scope bus as noted above the company did search the CDSR. A network meta-analysis by Tolley et al.[21] is briefly mentioned (CS section B.2.9) and seven systematic reviews and meta-analyses are among the excluded studies which are listed in Table 8 of the CS Appendices. Annotations in Table 8 of the CS Appendices appear to imply that the company checked two of these systematic reviews for references.[22, 23]

The company mentions that searches were conducted to inform a review of efficacy and safety (CS Appendix D.1.1). However, a systematic evaluation of studies reporting the safety of ocrelizumab (which ideally would consider non-randomised studies) is not provided. Instead, the company have obtained safety data primarily from the OPERA I and OPERA II trials (CS section B.2.10) and also from previous NICE technology appraisals for daclizumab and alemtuzumab (CS section B.3.4.4). Although a more systematic and transparent process for sourcing data on the safety of ocrelizumab would have been preferable, clinical experts advising the ERG did not identify any key issues pertaining to ocrelizumab safety that are not covered in the CS.

In summary, the searches were extensive, well recorded, reproducible and considered to be fit for purpose, with the main limitations being: (1) that they were 4-10 months out of date when the CS was received by the ERG; (2) systematic reviews and meta-analyses do not appear to have been sought or checked consistently as a source of references; and (3) a systematic search for data on safety of ocrelizumab (e.g. in non-randomised studies) was not conducted.

3.1.1.2 ERG updated searches: methods

We conducted the following additional searches to check whether the company had identified all relevant clinical effectiveness studies for inclusion in their analyses:

- All four searches were updated (restricted to Medline and Embase and to the year 2017 onwards);
- An internet search was conducted for relevant systematic reviews and meta-analyses (using free text terms for each comparator drug combined with terms referring to evidence synthesis, applied in Google, not limited by date);
- We checked all trials that were included in direct and indirect comparisons in the previous technology appraisals for the comparators listed in the NICE scope (alemtuzumab [TA312], beta-interferon and glatiramer acetate [TA32], cladribine

[TA493], daclizumab [TA 441], dimethyl fumarate [TA320], fingolimod [TA254], natalizumab [TA127] and teriflunomide [TA303]);

- Documents relating to technology appraisals of ocrelizumab in the USA[24] and Canada[25] were also checked for relevant references.

In these searches we sought randomised controlled trials (RCTs) that had compared any of the DMTs specified in the NICE scope either in head-to-head comparisons or against placebo, in patients who had RRMS.

3.1.1.3 ERG updated searches: results

After deduplication, the ERG's updated clinical effectiveness search identified 799 references published in 2017-2018, which included some references already identified by the company. It was not feasible for the ERG to screen all of these in duplicate and so we adopted a pragmatic approach which was to exclude conference abstracts (n=503) as these would be unlikely to contain sufficient information to enable inclusion the company's direct or indirect analyses. The remaining 296 references were screened by one reviewer. From these, any relevant RCTs of ocrelizumab or comparators that were not already included by the company, and any relevant systematic reviews and meta-analyses, were retrieved and checked.

Internet searches identified over 40 potentially relevant published systematic reviews and meta-analyses in RRMS. It was not feasible to check the reference lists of all these in detail and so we adopted a pragmatic approach in which one reviewer checked only those published from 2015 onwards (n=18).[21-23, 26-40] Additionally, we contacted the authors of three ongoing systematic reviews and meta-analyses[41-43] but were informed that the results of these were not available.

Our updated searches in Medline and Embase, together with checks of the reference lists of the aforementioned systematic reviews and meta-analyses and scrutiny of the studies included in the comparator NICE appraisals confirmed that the company had identified all relevant published RCTs of ocrelizumab and comparator DMTs.

Searches for ongoing trials

The CS reports searching for ongoing trials in 2 registries: clinical trials.gov and the International Trials Registry Platform (WHO ICTRP).

To check that no ongoing trials had been missed we re-ran the searches in these two registries and additionally searched the UK Clinical Trials Gateway (UKCTG), EU Clinical Trials Register (EUDRACT), ISRCTN Registry, and Centerwatch (ongoing studies are summarised in section 3.1.3.3).

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The company provides a clear description of the inclusion and exclusion criteria for the systematic literature review (SLR) of clinical effectiveness studies (CS Appendix D). The CS states that the search strategy was designed with the requirements of multiple countries in mind and is therefore more comprehensive than the NICE scope; and that the search included comparators licensed by the Food and Drug Administration (FDA) or EMA, or those expected to be licensed at the time of ocrelizumab launch.

Population

The population specified in the company's SLR was limited to adults with the relapsing forms of MS. Trials with mixed populations containing >75% relapsing form of MS were included but those containing >25% SPMS (without relapses), PPMS and/or primary relapsing MS were excluded. The ERG and the clinical experts advising us consider this to be appropriate.

Intervention

Studies on ocrelizumab 600mg q6m (i.e. every 6 months) were included, which is consistent with the intended indication.

Comparators

The SLR eligibility criteria (listed under 'Intervention' in CS Appendix Table 3) include the eight comparators listed in the NICE scope, as well as cladribine and placebo. As a consequence of the broad nature of the searches, the comparators are not limited to UK-relevant dosing regimes (e.g. teriflunomide 7mg per day is listed as well as the recommended 14 mg per day).

Outcomes

To be included, trials had to assess at least one of the following outcomes:

- annualised relapse rate
- relapse free proportion

- disability progression (12-week or 24-week confirmed)
- gadolinium-enhancing T1 lesions (number) and T2 lesions (volume)
- proportion of patients with no evidence of disease activity (NEDA) including definition of NEDA
- adverse events (AE) and serious AEs
- discontinuations due to AEs and all-cause discontinuation
- mortality
- infections
- malignancies
- SF-36 and EQ-5D

We note that the SLR eligibility criteria do not include the following outcomes that are specified in the NICE scope (and which, as noted above in section 2.3, are missing from the company's decision problem):

- severity of relapses
- disability (e.g. Expanded Disability Status Scale [EDSS])
- symptoms of MS such as fatigue, cognition and visual disturbance (other than those captured within the generic SF-36 and EQ-5D)

The ERG's clinical experts commented that as far as they are aware, no data on the severity of relapses have been collected in clinical trials of MS and so the omission of this outcome from the company's SLR would appear to be appropriate.

Study design

The design of studies specified in the SLR eligibility criteria was limited to randomised controlled trials (RCTs), but there was no limit based on the quality of the RCTs. Setting was not specified as an inclusion or exclusion criterion.

The CS provides a flow diagram illustrating the number of records identified and included/excluded at each stage of the SLR (Figure 1 in CS Appendix D.1.1). Reasons for the exclusion of studies at the full-text stage are provided with listed references in Appendix D (Table 7 in CS Appendix D.1.1), but not recorded in the flow diagram.

The CS does not report how many reviewers conducted the eligibility screening step of the SLR. The company explained in response to a clarification request from the ERG (clarification A1) that for each systematic review (including those for cost effectiveness, HRQoL and resource use, as well as the SLR of clinical effectiveness), two reviewers independently checked titles, abstracts and full-text records and any disagreements were resolved by a third reviewer. This is appropriate practice to minimise the risk of introducing errors and bias during screening.

Given that the company's SLR eligibility criteria were broader than the decision problem, the ERG enquired whether the eligibility criteria were refined during the screening process. The company explained (clarification A4) that the same eligibility criteria were applied to screening titles, abstracts and full-text articles, but that the scope of the SLR was narrowed down at a "feasibility assessment" stage. The CS implies that the feasibility assessment was part of the process for determining the eligibility of studies for the company's MTC analyses (text immediately above CS Appendix Table 9), but does not explain the rationale for why certain studies included in the SLR were considered ineligible for the MTC analyses. In response to a request from the ERG, the company further clarified the feasibility assessment and study selection process for the MTC (clarification A14); this is discussed further in section 3.1.7.

3.1.3 Identified studies

The SLR included a total of 46 RCTs, of which three are direct head-to-head comparisons of ocrelizumab against relevant comparators, and 43 were RCTs that did not include an ocrelizumab arm but had at least one relevant comparator arm that could be used in the MTC. The ERG agrees that all 46 of the identified RCTs are relevant to the NICE scope and the company's decision problem and, as noted above (section 3.1.1), we agree that the company has identified all relevant trials. The company has not included any studies which do not meet the inclusion criteria.

3.1.3.1 Ocrelizumab RCTs

The 43 comparator RCTs are discussed further in the MTC section of this report (section 3.1.7). Here, we summarise the characteristics of the three ocrelizumab studies.

The three ocrelizumab studies all included ocrelizumab as an intravenous infusion. These were:

- Two identical phase III pivotal two-arm RCTs (OPERA I and OPERA II) that compared ocrelizumab (600 mg) against subcutaneous interferon β-1a (Rebif®, 44 µg) over a 96-week treatment period.
- One phase II four-arm study that consisted of an initial randomized treatment comparison period (weeks 0 to 24), followed by a non-comparative period (weeks 24 to 96) in which all patients were switched to ocrelizumab. The four arms compared in the randomised period were ocrelizumab 600 mg, ocrelizumab 2000 mg, placebo, and intramuscular interferon β-1a (Avonex®, 30 µg).[44] At week 24, all patients apart from those receiving ocrelizumab 2000 mg switched over to receive ocrelizumab 600 mg until week 96. The ocrelizumab 2000 mg group switched to ocrelizumab 1000 mg at week 24 and then to ocrelizumab 600 mg at week 72. This high-dose group is outside of the current licensed indication for ocrelizumab and is not considered further in the present report.

The OPERA trials were followed by a non-comparative open-label extension (OLE) study in which, following a screening period to determine eligibility, patients from both the ocrelizumab and interferon β-1a arms of each trial could receive ocrelizumab 600 mg for up to a further 96 weeks (summarised in CS Figure 2). The OLE study is currently ongoing.

Results of the phase II trial are not presented or discussed in the CS (although details of the methods are given). The company's justification for this is that the assessment of the primary endpoint (total number of T1 gadolinium-enhancing lesions on MRI scans) was shorter than 48 weeks and disease progression was not an endpoint (CS section B.2.2). The NICE scope and the company's decision problem do not specify study duration as being a criterion to consider, but the ERG agrees that the duration of the randomised period of the phase II trial is very short relative to the chronic nature of MS.

The ERG considers that, provided eligibility criteria relating to study duration are applied consistently across all the studies (considered further in discussing the MTC eligibility criteria in section 3.1.7), it is reasonable to exclude clinical effectiveness evidence from the phase II trial for the following reasons:

- The duration of the randomised phase (24 weeks) was considerably shorter than the OPERA trials (96 weeks);
- EMA guidance on the conduct of clinical trials in MS suggests that study duration should be in the order of years rather than months[20];

- Clinical experts advising the ERG concurred that it would be appropriate to exclude the phase II trial given its short duration;
- The sample size (54-55 patients per arm) was considerably smaller than in the OPERA trials (>400 per arm);
- Phase II trial relapse rate and disability progression outcomes are likely to be underpowered, hindering any comparisons with those in the OPERA trials.
- Different interferon β-1a comparators were used in the phase II trial (Avonex: 30µg intramuscular injection) and OPERA trials (Rebif: 44µg subcutaneous injection) and so the ocrelizumab-interferon comparisons in the trials are not identical.

For these reasons, the ERG has not included full clinical effectiveness results from the phase II trial in the present report, but we comment on their consistency with results of the key outcomes assessed in the OPERA trials. Given that safety is a concern with DMTs, and adverse events could occur at any time on treatment, we have presented safety results from both the OPERA trials and their OLE study, and the phase II trial (see section 3.3.9).

The OPERA I and OPERA II trials were identical, double-blind, double-dummy RCTs, with identical inclusion and exclusion criteria and statistical analysis plans (Table 10). The initial 24-week randomised period of the phase II trial consisted of an RCT in which investigators were double-blinded to group assignment except for the interferon β-1a group, which was an open label arm described in the CS as being a 'rater-masked control group'. The phase II trial inclusion criteria were similar to those of the OPERA trials.

The CS provides a CONSORT flow chart that combines details of the populations of both OPERA trials, without stating the reasons for discontinuations (Figure 3 in CS Appendix D.1.2), but separate flow charts with reasons for discontinuation are given in the trial publication appendix.[45] Information about all three studies, such as design, population, countries and study centres are summarised (CS Table 6). However, details of key inclusion/exclusion criteria (CS Table 7), baseline demographics and disease characteristics (CS Table 8), statistical analyses (CS Table 9) and outcomes (CS Tables 11 to 15), are summarised for the OPERA trials only.

Table 10 Characteristics of the ocrelizumab RCTs

Study	OPERA I	OPERA II	Phase II trial
Key inclusion criteria	• Aged 18–55 years at screening; • Diagnosis of MS, in accordance with the revised McDonald criteria;[8] • At least 2 documented clinical attacks within the last 2 years prior to screening; • Or one clinical attack in the year prior to screening (but not within 30 days prior to screening); • Neurological stability for ≥30 days prior to both screening and baseline; • EDSS from 0 to 5.5, inclusive at screening; • Documented MRI of brain with abnormalities consistent with MS prior to screening.		• Aged 18–55 years • Diagnosis of RRMS • ≥2 documented relapses within 3 years before screening, ≥1 of which occurred within the past year; • EDSS sore of 1–6 points at baseline; • Evidence of previous MS inflammatory disease activity with six T2 lesions or more per MRI, or 2 relapses in the year before screening.
Key exclusion criteria	• Primary progressive MS; • Previous B-cell targeted therapies (i.e. rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab); • Disease duration >10 years in combination with EDSS ≤2.0 at screening; • Any concomitant disease requiring chronic treatment with systemic corticosteroids or immunosuppressants during the study; • History of or active primary or secondary immunodeficiency; • Congestive heart failure; • Known active bacterial, viral, fungal, mycobacterial infection or other infection, excluding fungal infection of nail beds; • Infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks or oral antibiotics within 2 weeks prior to baseline visit; • History or known presence of recurrent or chronic infection (e.g. HIV, syphilis, tuberculosis); • History of progressive multifocal leukoencephalopathy; • Contraindication to or incompatibility with IFNβ-1a; • Any previous treatment with alemtuzumab (Campath), anti-CD4, cladribine, mitoxantrone, daclizumab, teriflunomide, laquinimod, total body irradiation, or bone marrow transplantation; • Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, or natalizumab within 24 months prior to screening (exexpt if previous natalizumab treatment <1 year); • Treatment with fingolimod or other sphingosine-1-phosphate receptor modulator within 24 weeks prior to screening (except if T lymphocyte count ≥lower limit of normal).		• Secondary or primary progressive MS; • Disease duration >15 years in patients with an EDSS of ≤2; • Known history or presence of other neurological or systemic autoimmune disorders; • Treatment with rituximab or lymphocyte-depleting therapies; • Use of lymphocyte trafficking blockers within previous 24 weeks; • Use of β interferons, glatiramer acetate, intravenous immunoglobulin, plasmapheresis, and immunosuppresive treatments within previous 12 weeks; • Use of systemic glucocorticoids within previous 4 weeks; • Intolerance to interferon β-1a.

Table 10 continued

Study	OPERA I	OPERA II	Phase II trial
Countries (study centres)	32 countries (114 sites, UK n=2)	24 countries (166 sites, UK n=4)	20 countries (100 sites, UK n=4)
Intervention(s)	Ocrelizumab 600 mg **(n=410)**	Ocrelizumab 600 mg **(n=417)**	• Ocrelizumab 600 mg **(n=55)**: First treatment cycle 300 mg on days 1 & 15; subsequent cycles (weeks 24, 48 and 72) 600 mg • Ocrelizumab *2000 mg* (**n=56**): Not relevant to the current technology appraisal and not discussed further in this report.
	• First dose: two of two 300 mg OCR/placebo IV infusions 14 days apart • Subsequent doses consisted of one 600 mg OCR/placebo IV infusion • Maximum 4 doses		
Comparator(s)	• IFNβ-1a (Rebif®) 44 µg **(n=411)**	• IFNβ-1a (Rebif®) 44 µg **(n=418)**	• Intravenous placebo (**n=54**) • IFNβ-1a (Avonex®) 30 µg (**n=54**) once a week open-label treatment
	Injections 3x weekly during double-blind treatment period		Week 0-24 – switched to ocrelizumab weeks 24-48
Primary outcome	• Annualised relapse rate - ARR		• Total number of gadolinium-enhancing T1 lesions
Secondary outcomes	• % with confirmed disability progression – CDP • % with confirmed disability improvement – CDI • % with no evidence of disease activity – NEDA • Number of gadolinium-enhancing T1 lesions • Number of T2 hyperintense lesion • Number of T1 hypointense lesions • Brain volume change • Multiple Sclerosis Functional Composite score – MSFC • SF-36 Physical Component Summary score		• Annualised relapse rate – ARR • % relapse-free • Number of new gadolinium-enhancing T1 lesions • Change in volume of T2 lesions • Number of new or enlarging T2 lesions

Based on CS Tables 6 &7 and the phase II trial publication[44]

The CS, publications and CSRs do not specify how many of the patients in the OPERA trials and phase II trial were in each country, other than that 26-27% of patients in the OPERA trials were in the USA. The number of UK centres was very small, with only 2/114 sites (1.8%) in OPERA I, 4/166 sites (2.4%) in OPERA II and 4/100 sites (4%) in the phase II trial being in the UK (Table 11).

All three studies were sponsored by F. Hoffmann-La Roche.

The CS states that the demographic and disease characteristics at baseline were similar between OPERA I and OPERA II, and the ERG concurs. The OPERA trials did not collect disease type (RRMS/SPMS) at baseline, but the company estimate that based on a post-hoc analysis using 'disease progression unrelated to relapses' as a proxy for SPMS (CS section

B1.1), more than 90% of patients in the trials could be considered to have RRMS. The phase II trial differed from the OPERA trials in having a higher frequency of previous DMT use in the ocrelizumab 600 mg arm; and slightly higher mean EDSS score (possibly indicating slightly greater disability, although the difference is small) (Table 11).

The CS does not discuss any differences in patient baseline characteristics between the arms within each study, although these appear to be fairly similar in the OPERA trials. In response to a clarification request from the ERG, the company stated that in the phase II trial there were slight numerical differences for duration of MS and gadolinium-T1 lesions between the treatment arms (clarification 7b). As can be seen in Table 11, there are also differences in previous DMT use, which was higher in the ocrelizumab 600 mg arm compared to the interferon β-1a and placebo arms.

Table 11 Baseline demographic and disease characteristics of included trials

Characteristics	OPERA I Trial		OPERA II Trial		Phase II trial		
	OCR (n=410)	IFNβ-1a (n=411)	OCR (n=417)	IFNβ-1a (n=418)	OCR[a] (n=55)	IFNβ-1a (n=54)	Placebo (n=54)
Mean age, years (SD)	37.1 (9.3)	36.9 (9.3)	37.2 (9.1)	37.4 (9.0)	35.6 (8.5)	38.1 (9.3)	38.0 (8.8)
Female, n (%)	270 (65.9)	272 (66.2)	271 (65.0)	280 (67.0)	35 (64%)	32 (59%)	36 (67%)
Geographic region, n (%) United States Rest of the world	 105 (25.6) 305 (74.4)	 105 (25.5) 306 (74.5)	 112 (26.9) 305 (73.1)	 114 (27.3) 304 (72.7)	NR	NR	NR
Race, White n (%) [a]	NR	NR	NR	NR	51 (93%)	53 (98%)	52 (96%)
Mean time since symptom onset, years (SD) [min-max]	6.74 (6.37)	6.25 (5.98)	6.72 (6.10)	6.68 (6.13)	6.5 [0.5–20.5]	5.3 [0.8–35.2]	4.8 [0.6–26.2]
Mean time since diagnosis, years (SD) [min-max]	3.82 (4.80)	3.71 (4.63)	4.15 (4.95)	4.13 (5.07)	3.6 [0.1–16.5]	3.3 [0.1–20.2]	2.7 [0.1–19.2]
Mean no. of relapses in previous 12 months (SD)	1.31 (0.65)	1.33 (0.64)	1.32 (0.69)	1.34 (0.73)	NR	NR	NR
Relapses in past 3 years 1 2 3 ≥4	NR	NR	NR	NR	 1 (2%) 28 (51%) 16 (29%) 10 (18%)	 0 30 (56%) 21 (39%) 3 (6%)	 4 (7%) 26 (48%) 15 (28%) 9 (17%)
Without previous DMT, n (%)	n=408 301 (73.8)	n=409 292 (71.4)	n=417 304 (72.9)	n=417 314 (75.3)	26 (47)	37 (69)	38 (70)
With previous DMT, n (%)	n=408 107 (26.2)	n=409 117 (28.6)	n=417 113 (27.1)	n=417 103 (24.7)	29 (53)	17 (31)	16 (30)
Interferon	81 (19.9)	86 (21.0)	80 (19.2)	75 (18.0)	NR	NR	NR
Glatiramer acetate	38 (9.3)	37 (9.0)	39 (9.4)	44 (10.6)	NR	NR	NR
Natalizumab	0	1 (0.2)	1 (0.2)	0	NR	NR	NR
Fingolimod	1 (0.2)	0	4 (1.0)	0	NR	NR	NR
Dimethyl fumarate	1 (0.2)	0	0	0	NR	NR	NR
Other	2 (0.5)	3 (0.7)	1 (0.2)	1 (0.2)	NR	NR	NR

Table 11 continued

Characteristics	OPERA I Trial		OPERA II Trial		Phase II trial		
	OCR (n=410)	IFNβ-1a (n=411)	OCR (n=417)	IFNβ-1a (n=418)	OCR[a] (n=55)	IFNβ-1a (n=54)	Placebo (n=54)
Mean EDSS score (SD); median [min-max]	2.86 (1.24)	2.75 (1.29)	2.78 (1.30)	2.84 (1.38)	3.5 (1.5); 3.5 [1.0–6.0]	3.1 (1.5); 2.8 [1.0–6.0]	3.2 (1.4); 3.0 [1.0–6.0]
Gd-enhancing T1 lesions, mean (SD), median [min-max]; (IQR)	NR	NR	NR	NR	3.9 (9.88), 1 [0–46]; (0–3)	2.3 (5.26), 0 [0–24]; (0–1)	1.6 (4.05), 0 [0–25]; (0–1)
No. of Gd-enhancing T1 lesion (OPERA trials: lesions on T1-weighted MRI), n (%) 0	n=405 233 (57.5)	n=407 252 (61.9)	n=413 252 (61.0)	n=415 243 (58.6)	25 (49)	33 (66)	26 (55)
1	64 (15.8)	52 (12.8)	58 (14.0)	62 (14.9)	6 (12)	7 (14)	11 (23)
2	30 (7.4)	30 (7.4)	33 (8.0)	38 (9.2)	6 (12)	2 (4)	2 (4)
3	20 (4.9)	16 (3.9)	15 (3.6)	14 (3.4)	6 (12)	0	2 (4)
≥4	58 (14.3)	57 (14.0)	55 (13.3)	58 (14.0)	8 (16)	8 (16)	6 (13)
Mean no. of lesions on T2-weighted MRI, (SD)	51.04 (39.00)	51.06 (39.90)	49.26 (38.59)	51.01 (35.69)	NR	NR	NR
Mean volume of lesions on T2-weighted MRI, cm^3 (SD), median [min-max] [b]	10.84 (13.90)	9.74 (11.28)	10.73 (14.28)	10.61 (12.30)	13.97 (19.93), 6.69 [0.01–93.78]	13.21 (17.21), 8.25 [0.02–102.91]	8.95 (9.78), 4.77 [0.05-39.92]
Normalised brain volume, cm^3 (SD)	1500.93 (84.10)	1499.18 (87.68)	1503.90 (92.63)	1501.12 (90.98)	NR	NR	NR

From CS Table 8 and the phase II trial publication[44] NR: not reported.

[a] Phase II trial: conducted mainly in white individuals; others were mostly black (n=6) and Chinese (n=2).

[b] Phase II trial: reported in mm^3 converted to cm^3 by ERG.

Missing data in the OPERA trials:

- Number of relapses within the previous 12 months: OPERA I: IFNβ-1a group: n=1; OPERA II: OCR n=1, IFNβ-1a n=1.
- Number and volume of lesions on T2-weighted MRI: OPERA I: OCR n=2, IFNβ-1a n=3; OPERA II: OCR n=3, IFNβ-1a n=2.
- Normalised brain volume: OPERA I: OCR n=4, IFNβ-1a n=7; OCR n=3, IFNβ-1a n=4.
- Mean EDSS score: OPERA I: IFNβ-1a n=1

Baseline characteristics for disease activity subgroups

The company's economic analysis utilises data from two subgroups of OPERA trial patients: those with HA disease and those with RES disease (definitions of these subgroups are provided in section 3.1.6.4). On request from the ERG, the company provided baseline characteristics for patients in these subgroups (clarification A9c). Baseline characteristics which differed between the subgroups are summarised in Table 12.

Table 12 Baseline characteristics of disease activity subgroups in the OPERA trials

Range across both arms of both OPERA trials	HA subgroup	RES subgroup	Non-HA, non-RES subgroup
Mean age (years)	37 to 38	34 to 36	37 to 38
% from USA	32 to 38	15 to 31	26
% with previous DMT	100	21 to 31	10 to 14
Mean years since symptom onset	8.4 to 9.6	5.2 to 5.9	6.0 to 6.6
Mean years since diagnosis	6.2 to 7.0	2.9 to 4.0	3.3 to 3.9
Mean relapses in previous 12 months	1.2 to 1.4	2.2 to 2.4	1.1 to 1.2
% with no enhancing T1 lesions	49 to 69	19 to 30	65 to 69
Mean number of T2 lesions	53 to 65	53 to 56	47 to 49
Mean normalised brain volume, cm^3	1483 to 1499	1505 to 1509	1500 to 1503

Source: Tables 27 to 29 in company's clarification response

The post-hoc selection of these disease activity subgroups led to small imbalances in patients' mean age and geographical location, although it is unlikely these would influence clinical interpretation. As might be expected from the subgroup definitions (section 3.1.6.4), the proportion of patients with previous DMT, the time since symptom onset, the time since diagnosis and the proportion with enhancing T1 lesions were greater in the HA group than the RES group; whilst the mean number of relapses in the previous 12 months was higher in the RES group (Table 12).

There are larger baseline differences between trial arms within the subgroups (i.e. greater baseline clinical heterogeneity) than in the ITT population (Tables 27 to 29 in the company's clarification response; not reproduced here). However, the selection of the subgroups does not appear to have introduced any systematic imbalances between the ocrelizumab and interferon β-1a arms for any of the reported baseline characteristics.

3.1.3.2 Non-randomised ocrelizumab studies

The company did not search for non-randomised studies of ocrelizumab and no non-randomised clinical effectiveness studies were included in the CS.

The ERG agrees that focusing on RCTs for comparisons of ocrelizumab clinical effectiveness against other DMTs is appropriate, as there is relatively good availability of RCT clinical effectiveness evidence. Well-conducted RCTs are preferable to non-randomised studies for minimising risks of bias, and RCTs are required for the company's mixed-treatment comparison. However, we do not agree that non-randomised studies should have been entirely ignored, since these may be sources of safety data. As noted above (section 3.1.1), the company does not explicitly discuss any searches, or a systematic selection process, for identifying safety data, although clinical experts advising the ERG did not identify any further safety concerns beyond those reported in the CS.

3.1.3.3 Ongoing studies

The CS refers to the OLE study for OPERA I and II as ongoing and states that there are no other additional studies which are likely to be available in the next 12 months (CS section B.2.11). The ERG's search for ongoing studies identified eight ocrelizumab studies currently underway which are due to complete during 2018 or 2019 but these are either single-arm studies and/or do not report interventions or outcomes relevant to the current NICE scope.

3.1.4 Description and critique of the approach to validity assessment

The company has provided a risk of bias assessment for the three ocrelizumab trials: OPERA I, OPERA II and the phase II trial (Table 13 in CS Appendix D.1.3). The company's risk of bias assessment consists of yes/no/unclear answers to the standard NICE risk of bias questions, but without any explanatory supporting text. The company's and ERG's risk of bias assessments for the ocrelizumab studies are shown in Appendix 2. The ERG's risk of bias assessment was conducted by one reviewer and checked by a second reviewer.

In all three studies randomisation appears to have been conducted appropriately, the allocation sequences were concealed and the study arms had similar baseline characteristics, which are together indicative of a low risk of selection bias. The double-dummy and double-blind design of OPERA I and OPERA II indicates that these trials would be at low risk of performance bias. However, there is a risk of performance bias in the phase II trial since blinding was not applied

to the interferon β-1a arm. Slight differences in dropout rates between the ocrelizumab and comparator arms occurred in the trials, but the risk of attrition bias appears to be low for the ARR and CDP outcomes because the reasons for dropout were not unexpected, the analyses were by ITT, and missing data appear to have been appropriately analysed. Note, however, that missing data may not have been appropriately analysed for other secondary outcomes (section 3.1.6).

Overall, the ERG broadly agrees with the company's assessment that the three ocrelizumab studies generally are at low risk of bias (Appendix 2). However, several patient-reported outcomes which were measured in the OPERA trials (EDSS scores, EQ-5D scores, and fatigue scores) are not reported in the CS or trial publications. Although these were exploratory outcomes they are relevant to the NICE scope.

3.1.5 Description and critique of the company's outcome selection

Outcomes employed in clinical trials of MS can be divided into those which assess relapses (such as the annualised relapse rate – ARR), those which assess disability (such as time to confirmed disability progression – CDP), and those which provide supporting clinical information (including MRI scans of MS lesions or brain volume).[20, 46, 47] ARR is considered acceptable as a primary outcome in trials on efficacy of MS therapies, but cannot be taken as a surrogate for disability progression. The EMA guidance on conduct of clinical trials on MS therefore recommends that progression of disability should be assessed in addition to ARR, e.g. as a key secondary outcome.[20] So far, MRI scan parameters have not been considered reliable as a surrogate endpoints for the clinical outcomes and are not recommended as primary endpoints in pivotal trials evaluating new MS agents. However, MRI is considered a useful tool in pivotal MS trials to evaluate the consistency of clinical effects.[20] The ERG agrees that outcomes reported by the company are consistent with these considerations and are appropriate for trials assessing the effectiveness and safety of MS therapies.

The following sections summarise the key features of each of the outcomes that were assessed in the ocrelizumab trials, noting any limitations to their interpretation. EDSS scores are a component of several of the outcome measures; an explanation of the EDSS is provided in Appendix 3.

3.1.5.1 Relapses

A relapse is typically defined in MS trials as new or worsening neurological symptoms that are objectified on neurological examination in the absence of fever and last for more than 24 hours, and have been preceded by a period of clinical stability of at least 30 days, with no other explanation than MS.[47]

Relapses were protocol-defined in the OPERA trials as new or worsening neurologic symptoms that met the following criteria: were attributable to MS only in the absence of fever or infection (or injury or adverse reactions to medications); persisted for over 24 hours; were immediately preceded by a stable or improving neurologic state for at least 30 days; and were accompanied by objective neurologic worsening consistent with an increase of at least half a step on the EDSS, 2 points in one EDSS functional system score, or 1 point in each of two or more EDSS functional system scores (pyramidal, ambulation, cerebellar, brainstem, sensory, or visual). Protocol-defined relapses were confirmed to have met the pre-specified criteria defined in the protocol by a computerised algorithm that was written before database closure and unblinding of the data.[45]

Several caveats have been noted concerning the use of relapses as an outcome measure, including that: identification of relapses is subjective and therefore perfect treatment blinding is essential; patient reporting of new or worsening symptoms at scheduled clinic visits may underestimate the total number of relapses experienced; and regression to the mean may be an issue in cases where trial inclusion criteria require high relapse rates.[47]

3.1.5.2 Annualised relapse rate (ARR)

The ARR (primary outcome) was calculated in the OPERA trials as the total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment. Since a protocol-defined relapse required a relatively stable or improving neurological state of least 30 days, the theoretical maximum number of relapses per patient per year is up to 12.[45]

3.1.5.3 Confirmed disability progression (CDP)

Confirmed disability progression was defined in the OPERA trials as 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 (CDP-12) or for at least 24 weeks (CDP-24).[45]

Guidance of the EMA on the conduct of MS clinical trials[20] emphasises that disease progression should be confirmed by two consecutive examinations of the patient by the same physician at least six months apart, meaning that CDP-24 is preferable to CDP-12 as a measure of disease progression.

3.1.5.4 Confirmed disability improvement (CDI-12 or CDI-24)

Confirmed disability improvement in the OPERA trials was defined as a reduction 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 (or 24 weeks), restricted to patients with a baseline EDSS score of at least 2.0.

3.1.5.5 No evidence of disease activity (NEDA)

No evidence of disease activity was defined in the OPERA trials as: no relapse, no disability progression as confirmed at 12 weeks or at 24 weeks, no new or newly-enlarged lesions on T2-weighted MRI, and no gadolinium-enhancing lesions on T1-weighted MRI by the study end point (96 weeks), restricted to patients with a baseline EDSS score of at least 2.0.

NEDA assessments at 2 years have been found to be predictive of longer-term absence of disease progression (e.g. over 7 years) and NEDA-like outcome models are used in clinical practice to identify responders and non-responders to treatment.[47]

3.1.6 Description and critique of the company's approach to trial statistics

Relatively limited information on statistical analyses is reported in the CS and trial publications and the information provided mainly refers to the primary outcomes. Below we summarise the overall analysis approach, sample size estimation, analysis populations, statistical tests employed, methods for handling missing data, and the reporting of analyses in the OPERA trials based on information presented in the CS, trial publications and CSRs.

3.1.6.1 Statistical analysis strategy

The OPERA trials measured one primary efficacy outcome (ARR) and ten secondary outcomes. Statistical testing of the primary and secondary outcomes in the OPERA trials followed a protocol-specified fixed hierarchical testing sequence (Figure 2). This is a means of controlling type I errors (i.e. the rate of false positives), whereby the pre-specification of the order of outcomes to be tested prevents the possibility of favourable results from being selectively

'cherry picked' from among multiple outcome analyses.[48] In the hierarchical analysis, each secondary outcome was to be analysed statistically at the α=0.05 level only if the outcome immediately preceding it in the sequence was statistically significant at the α=0.05 level. Thus, secondary outcomes would only be analysed if the primary outcome (ARR) was statistically significant in both OPERA trials. Only outcomes that reached statistical significance could be considered confirmatory of clinical effectiveness. Outcomes that did not reach statistical significance were considered to be non-confirmatory, i.e. they provide descriptive information only.

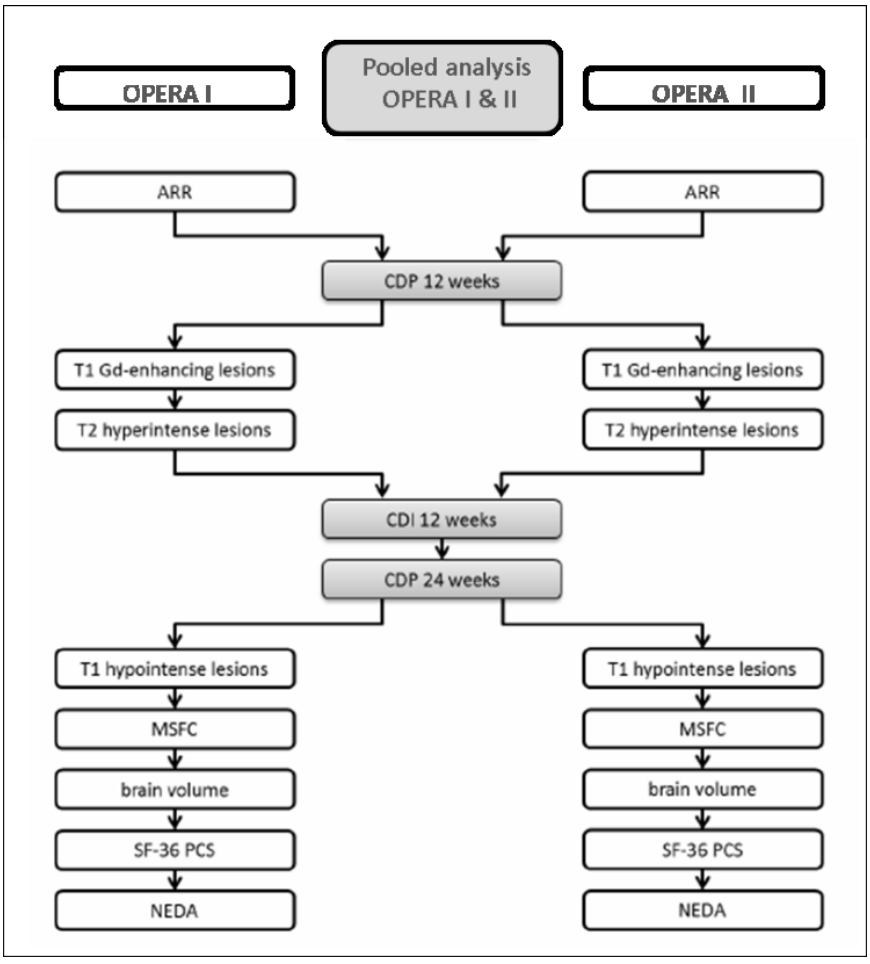


Figure 2 Hierarchical order of testing effectiveness outcomes in the OPERA trials (from CS Figure 3)

The first, fourth and fifth secondary outcomes in the sequence (CDP-12, CDI-12 and CDP-24) (grey panels in Figure 2) were tested only on the pooled data set from OPERA I and OPERA II to ensure adequate statistical power to detect treatment differences. The company provides a

justification in the trial publication appendix[45] that the characteristics and results of the two OPERA trials were similar enough for their results to be pooled, which the ERG agrees is reasonable. The primary efficacy outcome (ARR) and the remaining secondary outcomes had to be statistically significant in both OPERA trials in order for testing to proceed further in the hierarchy. For these outcomes the CS states that there was sufficient statistical power within each OPERA trial to detect relevant treatment differences, without needing to combine data from the two trials. However, a calculation justifying the statistical power is provided only for the primary outcome (see sample size estimation below).

The hierarchical approach was based on clinical meaning (referring to the importance to treating physicians and patients), regulatory requirements, and likelihood of positive outcome (CS section B.2.4). The CS further states that established endpoints were generally given higher priority over novel endpoints within the hierarchy. According to the OPERA CSRs, in situations where outcomes have similar clinical relevance, those with a greater chance of achieving a statistically significant treatment difference are listed higher in the hierarchy. The ERG agrees that the company's hierarchical testing approach and the rationale for the sequence of the outcomes to be tested are appropriate, and are in line with guidance on addressing multiplicity in statistical testing in clinical trials.[48]

3.1.6.2 Sample size estimation

The trial protocol states that the sample size was estimated based on data from previous RRMS trials. According to the trial publication,[45] the sample size for each OPERA trial was based on an estimated ARR of 0.165 in the ocrelizumab group and 0.33 in the interferon β-1a group. Based on a 2-sided t-test, it was estimated that 400 patients per arm would provide the trials with 84% statistical power to maintain a type I error rate of 0.05 and to detect a 50% lower rate with ocrelizumab than with interferon β-1a, assuming a withdrawal rate of approximately 20%.

3.1.6.3 Analysis populations

According to the CS and trial publication,[45] efficacy analyses were performed in the ITT population. This was defined as all randomised patients, including those who prematurely withdrew from the study for any reason and for whom an assessment was not performed for whatever reason. If patients received an incorrect therapy from that intended then they were summarised according to their randomized treatment. Exceptions are the NEDA and CDI-12 outcomes, for which the analysis was restricted to a subgroup of patients who had a baseline

EDSS score ≥2 (referred to as a modified ITT population). The ERG requested clarification from the company on why this subgroup was analysed rather than the ITT population, but the company's answer was not clear (clarification A12). The company did, however, provide the results of a post-hoc ITT analysis of NEDA in their clarification response.

The per protocol population was used in sensitivity analyses for ARR and CDP, although these are not reported in the CS. The per protocol population included all patients in the ITT population provided they did not have any major protocol violations that had been deemed to have the potential to affect the efficacy of the study treatment.

The safety population was used for all summaries of safety data and included all patients who received any study drug.

Although the wording of the CS and the trial publication implies that the secondary efficacy outcomes were analysed in the ITT population, the sample sizes reported in CS Table 11 for the secondary outcomes that were analysed separately in OPERA I and OPERA II are smaller than the numbers randomised. The proportions of observations missing relative to the ITT population are summarised in Table 13 and range from around 5% to 38% across the outcomes.

Table 13 Number (%) of missing observations (relative to ITT) for secondary and exploratory outcomes in the OPERA trials

	OPERA I		OPERA II	
Outcome (data from CS Table 11 unless stated otherwise)	**OCR N=410**	**IFNβ-1a N=411**	**OCR N=417**	**IFNβ-1a N=418**
Gadolinium-enhancing T1 lesions	22 (5.4)	34 (8.3)	28 (6.7)	43 (10.3)
New and/or enlarged T2 lesions	20 (4.9)	33 (8.0)	27 (6.5)	42 (10.0)
New hypointense T1 lesions	22 (5.4)	34 (8.3)	28 (6.7)	43 (10.3)
Brain volume	129 (31.5)	144 (35.0)	130 (31.2)	159 (38.0)
NEDA (baseline EDSS ≥2)	121 (29.5)	120 (29.2)	128 (30.7)	148 (35.4)
MSFC	88 (21.4)	103 (25.1)	109 (26.1)	149 (35.6)
SF-36 PCS	79 (19.3)	102 (24.8)	102 (24.5)	142 (34.0)

The largest proportions of missing observations are for the NEDA outcome (which was restricted to a subgroup with EDSS ≥2 at baseline), for the change in brain volume (which was analysed for weeks 24-96 rather than weeks 0-96) and for the patient-reported outcomes of

MSFC and SF-36 PCS (which reflect that not all patients had both baseline and follow-up measurements).

As can be seen in Table 13, the proportion of missing observations relative to the ITT population is consistently higher in the interferon β-1a arm in each trial than the ocrelizumab arm; and the proportion missing per outcome and per arm is in most cases higher in the OPERA II trial than in OPERA I. The company clarified (in their ERG report factual inaccuracy check response) that the imbalance between treatment arms is a result of the higher proportion of patients in the IFNβ-1a arm who withdrew from treatment.

3.1.6.4 Population subgroups

Subgroups of RRMS patients can be identified who have highly active (HA) and rapidly evolving severe (RES) disease (section 2.2).The CS reports (section B.2.7) that analyses of ARR, CDP-12 and CDP-24 were conducted in HA and RES subgroups of patients from the OPERA trials (the HA subgroup was pre-specified and the RES subgroup specified post-hoc). These subgroups were defined as shown in Table 14.

Table 14 HA and RES subgroup analysis population definitions

Highly active RRMS group	Rapidly evolving severe RRMS group
Treated with interferon or glatiramer acetate for ≥1 year and had: • ≥1 relapse in the previous year; • ≥1 gadolinium-enhancing T1 lesion at baseline • ≥9 hyperintense T2 lesions at baseline	• ≥2 relapses in the previous year, and • ≥1 gadolinium-enhancing T1 lesion at baseline, or • an increase in hyperintense T2 lesions at baseline (changing from 0-5 to 6-9, >9 lesions or 6-9 lesions to >9 lesions) compared to previous MRI

In response to a clarification request from the ERG (clarification A9), the company stated that the definitions of the HA and RES subgroups both relate to disease activity as measured by relapses or MRI activity, and are not mutually exclusive. The company also commented in their response that the key difference in the definitions of HA and RES subgroups is in the specification of the line of therapy. HA disease occurs in pre-treated patients only whilst the definition of the RES subgroup is not restricted to a line of therapy. As such, there is a small degree of overlap between the two subgroups in pre-treated patients, and in the OPERA trials

14% of HA or RES patients could be defined as having both HA and RES disease (clarification A9).

As noted above (section 2.3), further, pre-specified, subgroup analyses are presented by the company (CS Appendix E) according to:

- analyses for treatment-naïve and treatment-experienced patients;
- analyses according to the subgroups 'active inadequate responders',
- 'active treatment naïve', highly active inadequate responders' and ' highly active treatment naïve' patients (reflecting regulatory definitions);
- a range of patient baseline demographic and disease variables.

Most of the subgroups have reasonable sample sizes since they are based on the pooled OPERA trials data. However, the subgroup analyses should be interpreted with caution because the large number of comparisons presented in CS Appendix E risks inflating the type I error rate, as it is easy to selectively 'cherry pick' from among the presented comparisons. Note that these subgroups reported in the CS do not precisely match those specified in the NICE scope (i.e. people whose disease has responded inadequately to previous treatment, and people who could not tolerate previous treatment).

3.1.6.5 Statistical tests

Primary outcome (ARR)

The analysis of ARR employed a negative binomial model to test for treatment differences between ocrelizumab and interferon β-1a, with adjustment according to geographic region (USA versus rest of the world) and baseline EDSS score (< 4.0 versus ≥ 4.0) (CS Table 10). Log-transformed exposure time was included in the model as an offset variable for appropriate computation of relapse rate. This is a standard approach for modelling event-rate data. In response to a clarification request from the ERG, the company explained (clarification A11) that stratification by country or region is consistent with the EMA guidance on adjustment for baseline covariates in clinical trials,[49] although they did not explain how the stratification regions would be expected to influence clinical outcomes, as is recommended by the EMA.[49] The company also clarified that the EDSS cut-off of 4 was included as a stratification factor since EDSS ≥4 is known to be a strong prognostic factor for future disability progression in RRMS patients (citing Healy et al. 2013[50]), which the ERG agrees is reasonable.

The trial publication appendix[45] presents results of per-protocol analyses for ARR but does not explicitly discuss how these differ from the ITT analyses. According to the OPERA CSRs, several further sensitivity and robustness checks were performed on the primary outcome, although these are not reported in the CS or trial publication. These included: presentation of the unadjusted ARR, adjustment according to additional covariates (number of relapses occurring within 2 years prior to study entry, baseline presence/absence of gadolinium-enhancing T1 lesions, prior MS treatment, and age [<40, ≥ 40]); running the analyses with a Poisson model instead of negative binomial; and using multiple imputation to explore the potential influence of informative dropouts on the results of the primary efficacy analyses.

Secondary and exploratory outcomes

The hazard ratio for the time to confirmed disability progression (CDP-12 and CDP-24) in the trial arms was estimated using Cox regression and the treatment effect on the outcome was tested using a two-sided log-rank test stratified by the same covariates as the primary outcome (CS Table 10). Cox regression assumes proportional hazards in the survival functions under comparison, but the CS and trial publication do not provide any evidence to support this assumption. In response to a clarification request, the company provided log cumulative hazard plots from the OPERA I and OPERA II trials comparing ocrelizumab against interferon β-1a for CDP-12 and CDP-24 (clarification A17). The company argues that the curves are reasonably parallel from around 3 months onwards, suggesting the proportional hazards assumption was not violated for the comparison of ocrelizumab against interferon β-1a and the ERG agrees with this interpretation.

According to the trial publication appendix,[45] numbers of lesions on MRI scans were analysed using negative binomial regression, which is a standard approach. The CS and trial publication do not specify the statistical analysis methods employed for the remaining secondary outcomes or the exploratory outcomes which are relevant to the NICE scope although further information is reported in the OPERA CSRs. The ERG agrees that the methods appear appropriate and are consistent with the trial Statistical Analysis Plans.

The OPERA CSRs report eight sensitivity analyses for each of the CDP-12 and CDP-24 outcomes in which the population (ITT or per protocol), data imputation approach, and/or analysis stratification factors were varied in different combinations. Results of these sensitivity

analyses are not reported in the CS, but are briefly summarised in the current report (section 3.3.2.1).

3.1.6.6 Methods for handling missing data

The CS does not describe any approaches for handling missing outcomes data in the OPERA trials to support an ITT analysis. The trial publication appendix[45] briefly mentions a sensitivity analysis was conducted for missing relapse observations and that, for CDP analysis, patients with an initial disability progression during the trial who discontinued the treatment early and did not have subsequent visits with EDSS measurements were censored. The OPERA CSRs report more detailed descriptions of how missing data were analysed for each outcome, including a range of sensitivity analyses that were undertaken to test the impacts of missing data. Guidance of the EMA on the conduct of MS clinical trials[20] stresses the importance of sensitivity analyses for evaluating the impact of missing data on effectiveness outcomes. Where available, we have briefly summarised results of the sensitivity analyses in section 3.3.

3.1.6.7 Analysis reporting

Test statistics and variance estimates are generally reported clearly and appropriately for the comparisons of trial outcomes, both for the individual OPERA trials and the pooled analyses across trials. Treatment effects on the ARR are reported as rate ratios whilst effects on CDP are reported as hazard ratios, which is appropriate. Kaplan-Meier curves are also presented for the time to CDP. The sample size, mean, standard deviation, 95% confidence interval and p-value are consistently reported (CS Table 11).

3.1.6.8 Summary

The analysis methods reported in the CS and trial publication are generally consistent with those specified in the Statistical Analysis Plan for each trial and we have not identified any serious deviations. However, we note the following limitations in the statistical analysis approach as reported in the CS and trial publication:

- Several secondary outcomes in the OPERA trials (MSFC, SF-36, NEDA, and MRI outcomes) were stated to have been analysed according to the intention-to-treat (ITT) principle but the reported sample sizes for these analyses are smaller than the ITT population, with some systematic differences in missing data evident both between trial arms and between trials that are not discussed by the company;

- A range of methods was employed for handling missing data in the trials, including a variety of sensitivity analyses to test the impact of missing data on outcomes, but results of these are not presented in the CS or trial publication.

3.1.7 Description and critique of the company's approach to the evidence synthesis

The CS provides a narrative synthesis of clinical effectiveness evidence, focusing on the OPERA I and II trials. The characteristics and results of the OPERA trials are presented in tables and figures and described with accompanying text. The results of the two trials are presented individually by trial, with results for the CDP and CDI outcomes pooled across the two trials (described to be a "pre-specified pooled analysis" in CS section B.2.6, though it is not stated where this pre-specification was originally documented e.g. whether in the trial protocol). The rationale for pooling was to maintain sufficient power to detect relevant treatment differences in these secondary outcomes. The CS states that the OPERA trials were identical in terms of endpoints, inclusion and exclusion criteria, comparator, and statistical analysis plan (CS section B.2.3). Pooling the results for these outcomes is therefore a reasonable approach in the ERG's opinion.

As the OPERA trials only compared ocrelizumab with interferon β-1a 44 µg it was necessary for the company to conduct MTC analyses to facilitate indirect comparisons with the other DMTs specified in the scope of the appraisal. CS section B.2.9 and CS Appendix sections D.1.1 to D.1.4 report the methods for, and results of, the MTCs. In the following sub-sections below we summarise and critique the methods used to produce the MTCs. The ERG's critical appraisal checklist for the MTC analyses is given in Appendix 4.

3.1.7.1 Mixed treatment comparisons (MTC) overview

The CS reports a total of 23 separate MTC networks, which vary according to the patient population (ITT or subgroup), exclusion of comparators not in the NICE scope (restricted networks), investigation of the impact of trial duration (meta-regression), and inclusion of an outlier study. The network analyses conducted were as follows:

- ITT population (4 MTCs);
- MS patient subgroups: HA (3 MTCs) and RES (3 MTCs);

- Restricted network 1 (ITT population) (4 MTCs);
- Restricted network 2 (ITT population) (4 MTCs);
- Meta-regression on trial follow-up duration (ITT population) (4 MTCs);
- Inclusion of the INCOMIN trial for the CDP-24 outcome (1 MTC).

ITT population MTCs

MTCs were conducted for four outcomes: ARR, CDP-12, CDP-24 and all-cause discontinuation, which all inform the company's economic model (CDP-12 is used in the base case economic model, and CDP-24 is used in a sensitivity analysis) (section 4.3.4). Due to a lack of published data, the all cause-discontinuation outcome was not analysed for the HA or RES subgroups of RRMS. In the economic model, therefore, ITT MTC results for all-cause discontinuation were applied for the HA and RES subgroups (section 4.3.4.3). The CS states that MTCs were also conducted for the outcomes of relapse free proportion, proportion of patients with serious adverse events, and discontinuation due to adverse events, but these outcomes are not reported in the CS as they are not considered relevant to the economic evaluation (CS Appendix D.1.1). As such, ocrelizumab has not been compared against DMTs (apart from interferon β-1a 44 µg in the direct comparison in the OPERA trials) for the remaining outcomes in the NICE scope: freedom of disease activity; MS symptoms (e.g. fatigue, cognition and visual disturbance); adverse effects; HRQoL; and mortality.

Sensitivity analyses were conducted for the ITT population MTCs to explore the impact of variations to base case assumptions, using alternative prior distributions and a fixed effects rather than a random effects model.

Subgroup MTCs

MTCs were constructed using subgroup data from the included trials to estimate effects for the two subgroups of relevance to the NICE scope, i.e., HA and RES RRMS. The ERG and the CS (CS section B.2.9.1) both urge caution in the interpretation of these analyses for reasons discussed below, including the sparsity of the data, the post-hoc nature of the subgroups in the trials, lack of consistency in the definitions of the subgroups across trials, and the observational nature of the subgroup data.

Restricted network MTCs

The SLR of clinical effectiveness was conducted to support HTA submissions in a number of countries, and it therefore included some comparators that are not within the NICE scope. The two restricted network MTCs assess the impact of excluding these comparators. The CS does not explicitly define the difference between what they refer to as restricted networks 1 and 2. Footnotes to CS Appendix Figure 8 show that restricted network 1 excludes cladribine and 7mg teriflunomide, and restricted network 2 excludes cladribine, 7mg teriflunomide, daclizumab, fingolimod, and natalizumab. The ERG presumes that daclizumab is excluded as it is permitted in the NICE scope only if the disease has been previously treated with disease-modifying therapy, and alemtuzumab is contraindicated or otherwise unsuitable. Of the two networks, restricted network 2 most closely adheres to the NICE scope. The CS concludes that inclusion of comparators outside of the NICE scope [redacted]. Based on this analysis (results are summarised below in section 3.3.8.2), the ERG agrees that the ITT population MTCs are appropriate to inform the assessment of clinical effectiveness and cost effectiveness.

Meta-regression

The MTCs synthesise results from different time points, and the analysis methods assume that the results are not time dependent (see section 3.1.7.4 below). Network meta-regression was therefore conducted to validate this assumption.

Inclusion of the INCOMIN trial

The base case MTC for CDP-24 excluded the INCOMIN trial,[51] which compared interferon β-1b to interferon β-1a, as this was considered to be an outlier by clinical experts (CS section B.2.9). The CS cites a meta-analysis comparing studies of interferon-β products in RRMS, of which two (one being the INCOMIN trial) found significant differences in clinical efficacy between interferon-β products, whereas the remaining five studies showed equal clinical efficacy between products.[52] The MTC in the CS found inconsistency between CDP-12 and CDP-24 MTC inputs for interferon β-1b (with INCOMIN being the only trial of interferon β-1b informing CDP-24). The CS reports that a separate published MTC[21] also excluded the INCOMIN trial, on grounds of inconsistent results between ARR and CDP-24. CS Appendix section D.1.4 (Figure 19) provides a forest plot showing the CDP-24 results for of the base case analyses, and a sensitivity analysis in which the INCOMIN trial was included. Based on the results of this analysis (summarised in section 3.3.8.2), the ERG concludes that

[redacted] (though the CS does not comment on this).

3.1.7.2 Trials included in the MTC analyses

A total of 46 eligible studies were identified from the company's SLR of clinical effectiveness (section 3.1.3), of which 33 provided data for inclusion in the ITT networks (CS Table 16) and 16 of these contributed HA and/or RES subgroup data (CS Table 17) (NB: CS Table 17 shows that 14 rather than 16 trials contributed data to these subgroups). The numbers of trials and DMTs included in the company's MTC analyses are summarised in Table 15 and further details of the trials that contributed data to each analysis are provided in Appendix 5. As explained below, in order to enable MTC networks to be formed for the HA and RES subgroup analyses, the company linked the trials providing subgroup data via trials that provided ITT data for the 'ABCR' DMTs (see 'Inclusion/exclusion criteria' below). For the subgroup analyses the number of trials that provided subgroup data (as shown in CS Table 17) is therefore a subset of the total number of trials in the network.

Table 15 Number of treatments and trials included in MTC networks

Analysis network		Outcome			
		ARR	**CDP-12**	**CDP-24**	**All-cause discontinuation**
ITT and meta-regression on trial duration	Trials, n	30	22	21	26
	DMTs, n	17	17	15	17
HA subgroup	Trials, n	8 (21 [a])	9 (16 [a])	9 (15 [a])	NA
	DMTs, n	7 (10 [a])	7 (10 [a])	8 (9 [a])	NA
RES subgroup	Trials, n	9 (22 [a])	9 (16 [a])	4 (10 [a])	NA
	DMTs, n	8 (11 [a])	10 (13 [a])	5 (7 [a])	NA
Restricted (ITT) network 1	Trials, n	Not reported	Not reported	Not reported	Not reported
	DMTs, n	14	14	12	14
Restricted (ITT) network 2	Trials, n	Not reported	Not reported	Not reported	Not reported
	DMTs, n	11	11	9	11

NA: Not applicable (subgroups were not analysed for this outcome).

[a] Numbers in brackets are the total number in the network, including the linking trials that provided ITT ABCR data (details in Appendix 5).

Inclusion/exclusion criteria

CS Appendix Table 3 describes the inclusion and exclusion criteria for the company's systematic review of clinical effectiveness. As reported above, 46 trials met the inclusion criteria. A post hoc feasibility assessment was conducted in which additional inclusion criteria for the MTC were applied (CS Appendix D.1.1 Table 9), resulting in the exclusion of 13 trials from the ITT MTC.

The ERG asked the company to clarify the rationale for the post hoc feasibility assessment given that a systematic review inclusion/exclusion process had been followed (clarification A14d). The company responded that certain requirements for building an MTC network (e.g. knowing which outcomes have been measured) can only be informed following a systematic review of the available evidence. This was necessary to inform the decision on an appropriate trial duration cut-off (i.e. 48 weeks) since it became apparent from the systematic review that there was large variation in follow-up duration across the trials (12 to 240 weeks). The ERG agrees that, in principle, the feasibility of building an MTC network needs to be informed by a systematic assessment of the available evidence. We also agree that additional inclusion/exclusion criteria can be applied providing there is a sound clinical rationale (and not based on knowledge of the results of the trials). However, the potential use of such a feasibility assessment should be described a priori in a systematic review protocol. No such protocol is cited in the CS but, as we did not identify any additional relevant studies from an update search (see section 3.1.1), the MTC is unlikely to have omitted relevant evidence.

Following the company's feasibility assessment, 13 trials were excluded, for the following reasons (CS Appendix Table 9):

- 11 trials were excluded as they had a controlled treatment duration of less than 48 weeks;
- Two trials were excluded as having doses or regimens which are not approved or are 'ineligible' (presumably according to EMA licensing, although this is not specified);
- Specific arms of six further trials were excluded as having ineligible regimens, but this did not result in these trials being fully excluded as they contained other eligible arms.

Based on further information provided by the company (clarification A14), the ERG agrees that the study designs of the 13 excluded trials match the exclusion criteria specified by the company in CS Appendix Table 9.

The CS states that studies with a randomised controlled treatment duration period of less than 48 weeks were not considered sufficiently robust to demonstrate treatment effect on disability progression in a chronic disese characterised by periods of exacerbetions and remissions (CS section B.2.9). Excluding trials of duration less than 48 weeks resulted in exclusion of the ocrelizumab phase II trial, which had a randomised comparison duration of 24 weeks.

The ERG agrees that excluding trials that had a controlled comparison duration of less than 48 weeks (i.e. also excluding the ocrelizumab phase II trial) is appropriate, for several reasons (as stated above in section 3.1.3.1). In summary:

- 48 weeks is a short time relative to the chronic course of RRMS (of the 11 trials excluded on having a short duration we note that none had a controlled comparison period exceeding 36 weeks);
- EMA guidance on the conduct of MS trials[20] recommends that outcomes should be assessed over periods of years rather than weeks or months;
- Clinical experts advising the ERG concurred that longer-term clinical data are likely to be more reliable, given heterogeneity in the frequency and timing of relapses and remissions among patients with RRMS; as such, excluding trials less than 48 weeks in duration would be reasonable, since numerous longer-term studies are available;
- The clinical experts also pointed out that phase II trials in MS typically have MRI outcomes as their primary endpoint; since MRI outcomes do not inform the company's economic analysis, these are less likely to be directly informative than phase III trials.

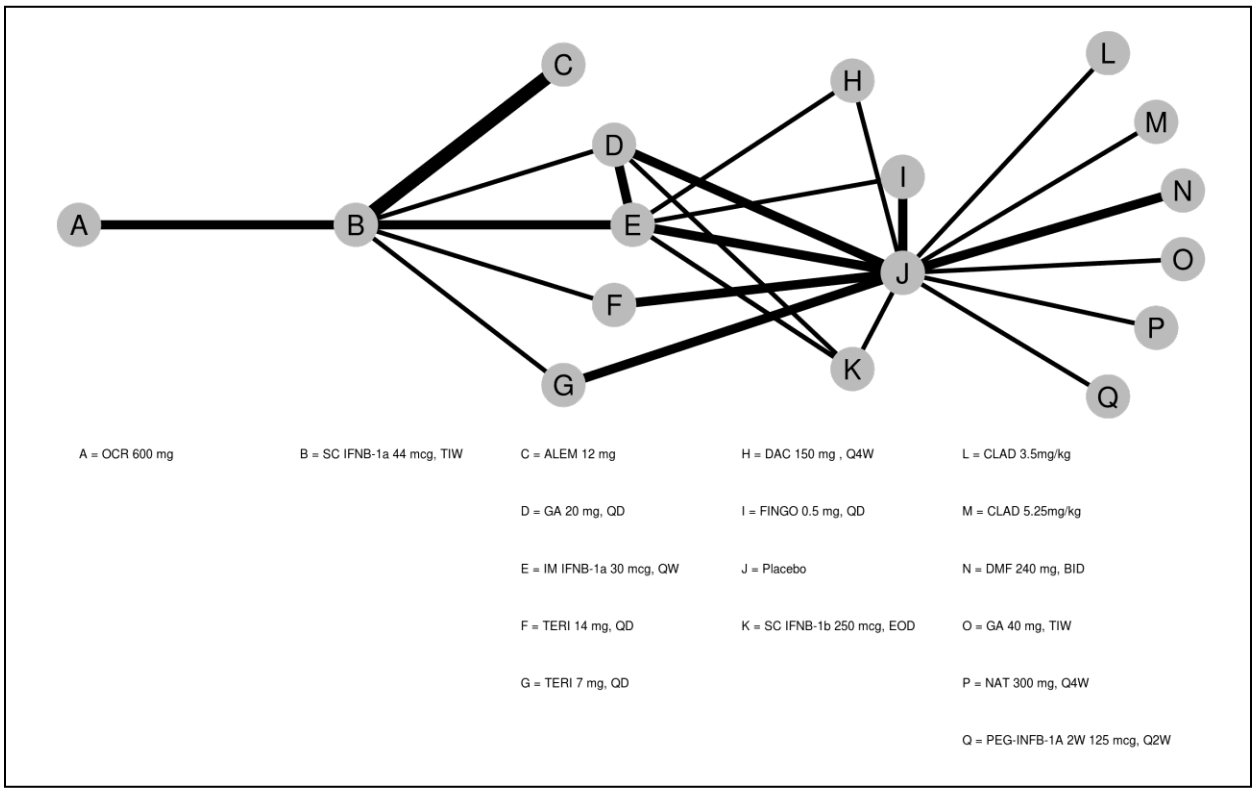
Note that the above considerations refer to clinical effectiveness outcomes, not safety outcomes (adverse events were not analysed in MTCs but are reported separately in the CS, including for the ocrelizumab phase II trial; for details see section 3.3.9 below).

The company mentioned in their clarification letter that the Etemadefir 2006 trial was excluded from MTC analyses of ARR but do not provide a clear justification (clarification A14).

Network structure

Figure 3 illustrates the network structure for the MTC, using the outcome of ARR in the ITT population as an example (the CS provides network diagrams for the other outcomes).

Ocrelizumab is connected to the network via interferon β-1a 44 µg (the comparator treatment in the OPERA trials), and then to a set of treatments including teriflunomide, glatiramer acetate, alemtuzumab (the CS refers to this as 'jump no. 1', with each jump representing the distance from ocrelizumab), and in turn to a second set of treatments including daclizumab, fingolimod, placebo and subcutaneous interferon-β 1b (jump no. 2), and to a final set of treatments including cladrabine, natalizumab, dimethyl fumarate, glatiramer acetate 40mg, and pegylated interferon β (jump no. 3).



NB. The edge width of the lines is proportional to the number of inputs for each comparison.

Figure 3 Example MTC network diagram for ARR ITT (CS Figure 7)

As can be seen from Figure 3 the network includes a number of pairwise comparisons, and some closed loops (i.e. where each comparison has both direct and indirect evidence). For the ARR ITT network the company confirmed that there were 13 pairwise comparisons that were informed by at least two trials, and 14 comparisons informed by only one trial (clarification A20a). Corresponding figures for the CDP-12 ITT network were 7 and 17, respectively, for CDP-24 ITT the figures were 6 and 12 respectively, and for all-cause discontinuations ITT the figures were 8 and 20, respectively. The majority of comparisons across the ITT MTCs (63/97; 65%)

were, therefore, informed by a single trial. The ERG notes that the maximum number of trials included in any of the pairwise comparisons was three.

The MTC network structure varies in size and shape according to different outcomes and subgroups, with the highest number of jumps being three and the lowest two. Of note, the CS reports that due to sparsity of data it was not possible to connect the networks for the HA and RES subgroups. To connect these networks the company used ITT data from 'ABCR' treatments (IFNβ-1a [Avonex], IFNβ-1b [Betaferon], glatiramer acetate [Copaxone], and IFNβ-1a [Rebif]). The underlying assumption is that, for these treatments, the treatment effect observed in the ITT population would be the same as the treatment effects in the subgroup populations (CS section B.2.9). The CS states that in the OPERA trials the results for the ITT population and the subgroups were consistent with each other for CDP outcomes, but not for ARR (for the OPERA trials subgroup results see section 3.3). The ERG suggests caution in the interpretation of the results of the subgroup analyses as the assumption of consistency in effects between ITT populations and subgroups is not fully supported.

Data sources used in the MTC analyses

Although the CS provides information about the MTC networks, it does not report which trials contributed to each specific MTC analysis and does not report the MTC input data that were used from each trial. The company clarified which trials were included in the ITT and subgroup analyses for each outcome, and the data that were used from these trials, in Tables 30 to 39 of their clarification response. Based on this information, we have summarised the trials that contributed to each MTC analysis in Appendix 5. For the ITT analyses of each outcome the company used individual trials as input data for their MTCs, but for the HA and RES subgroup analyses data from several trials were pooled. The CS does not provide a justification for pooling trials, but the company commented that "most inputs to the subgroup MTCs were as pooled estimates as no individual data were available" (clarification A20b).

For the ITT analysis of CDP-12, the company mentions that results for alemtuzumab from the CARE MS-I and CARE MS-II trials were unavailable and so the CDP-12 was instead obtained from an MTC reported in a reimbursement dossier of the Haute Autorité de Santé (HAS) which combined the CARE MS-I, CARE MS-II and CAMS223 trials (stated in the paragraph preceding Table 10 in CS Appendix D). The company has not provided a reference for the HAS dossier and does not provide any details or critique of the MTC that it contains. The ERG has been

unable to locate the dossier and therefore we cannot comment on the robustness of the HAS MTC results that the company has used.

Note that CS Table 17 states (in a footnote) “IFN + GA summed” which refers to the ARR and CDP-24 outcomes of the CARE MS-II trial and the CDP-12 outcome of the pooled FREEDOMS and FREEDOMS II trials. We assume this to be an error, since these trials did not include both interferon and glatiramer acetate arms.

Risk of bias in the trials

The company conducted a risk of bias assessment on the 46 trials identified in their SLR of clinical effectiveness (i.e. including the 13 trials that were subsequently excluded from MTC analyses). Judgements are summarised in CS section B.2.9.1 and also presented in a colour coded table (CS Appendix D.1.3, Table 13), although the CS does not provide any text justifying each judgement. The CS states that the Cochrane risk of bias criteria were used; however, the ERG notes that the criteria used are the quality assessment criteria recommended by NICE in the user guide for company evidence submissions (though these cover similar aspects of bias to the Cochrane tool). It is not stated whether risk of bias judgements for each trial were made by a single person or by more than one person. The CS notes that, where details were reported, trials were considered adequate in terms of randomisation procedures, concealment of treatment allocation and balance of prognostic variables at baseline. However, there is some risk of bias due to lack of double blinding, unexpected drop-outs or missing/inappropriate ITT analyses. The CS also notes that risk of bias assessment was limited by the availability of information for each of the trials.

We note that, based on CS Appendix Table 13, the item with the greatest number of unclear judgements was concealment of treatment allocation (reflecting information in the trials). This therefore raises the possibility of selection bias in a number of the trials, though it should be noted that most of the trials were judged to be balanced in prognostic factors at baseline between randomised study groups.

It was not feasible for the ERG to independently assess and check the risks of bias in all of the comparator trials listed in CS Appendix Table 13 within the timescale available for this technology appraisal (for our assessment of bias risk in the ocrelizumab trials see section 3.1.4). However, we noted that for up to 31 of the 46 trials included in the company’s SLR

independent ERG reports are available from previous NICE DMT technology appraisals which provide assessments of the risks of bias. We compared these independent risk of bias judgements from other ERG reports against the company's judgements in CS Appendix Table 13 to provide an indication of whether the company's risk of bias judgements are likely to be generally appropriate (further details are given in Appendix 6). This comparison indicated good agreement between the company's and the independent ERG assessments of risk of bias relating to the different sources of selection bias as as determined by the first 3 questions in CS Appendix Table 13 (randomisation, allocation concealment and balance of prognostic factors). It was not possible to compare independent ERG and company assessments of the risk of performance bias due to lack of blinding (question 4) since the ERG reports differed in how they addressed this question. For the remaining questions about imbalances in dropouts (question 5), selective reporting of outcomes (question 6) and use of ITT analysis (question 7) there was moderate agreement between the company's risk of bias of bias judgements and those provided by independent ERGs (Appendix 6). Overall, these findings give confidence that the company's judgements about the risk of selection bias in the comparator trials (including the large number of 'unclear' judgements for allocation concealment) are likely to be appropriate; there was less consistency between the company and independent ERGs in the judgements about the risks of other types of bias.

3.1.7.3 Populations represented in the MTCs

The CS tabulates characteristics of the populations included in the MTC analyses (CS Appendix Table 12) but does not comment on how reflective these are of patients with RRMS in NHS clinical practice. The company also does not explicitly discuss whether there are any imbalances in prognostic variables across the trials included in the MTCs (this is important when considering the similary assumption of MTC analysis – see section 3.1.7.5 below). According to the literature,[9, 10] patient characteristics which confer a poorer MS prognosis include (among others) older age, male sex, African American or non-White race, multifocal lesion onset, high lesion load at baseline, more than one functional system affected, early cortical involvement, and onset with motor, cerebellar, or bladder/bowel symptoms. Not all of these characteristics are reported by the company but we have summarised here the patient population characteristics that are given, as reported in CS Appendix D (most of the data are from CS Appendix Table 12).

Proportion of patients with RRMS and SPMS

The company state that the scope of their SLR was patients with relapsing forms of MS, but the eligibility criteria of the SLR allowed mixed populations of MS (i.e. RRMS and SPMS) to be included as long as at least 75% had RRMS (CS Appendix D). The company does not comment on whether the ≥75% cutoff could be applied reliably, given that the proportions with RRMS and SPMS were not always reported in the trials. Of the 33 trials included in the company's MTC analyses, 26 (79%) specified relapsing MS or RRMS as an inclusion crierion (without specifying any additional MS types in the inclusion criteria), and 15 (45%) specified progressive forms of MS as an exclusion criterion (12 trials specified the type of MS in both inclusion and exclusion criteria) (CS Appendix Table 11). However, only four trials explicitly stated that SPMS was an exclusion criterion. The company acknowledges that there may be heterogeneity in the trial populations included in the MTCs in terms of the proportions with RRMS and SPMS. The eligibility criteria indicate that patients with PPMS were not eligible for any of the included trials.

Age

According to the trial eligibility criteria, the majority of the 33 trials included in the company's MTCs were on patients aged 18-55 years (18 trials), with some covering the range 18-45 years (1 trial), 18-50 years (7 trials), 18-60 years (2 trials) or 18-65 years (1 trial). The trial by Bornstein (1987) had a younger population than all other trials (age 20-35 years) whilst two trials did not clearly report the age range. The mean age (reported in 30 trials) ranged from 31.1 to 40.6 years (CS Table 12). The MTC population therefore appears broadly representative of adults who would be treated with DMTs. As noted above, experts advising the ERG suggested that some patients aged up to 65 would receive the stronger DMTs including ocrelizumab, but only one trial included patients up to this age.

Sex

All trials had a majority of female patients, which reflects the differential disease prevalence between the sexes. The proportion male (reported in all 33 trials) ranged from 19% to 44%.

Treatment experience

The company does not explicitly define treatment naïve or treatment experienced, although they refer to patients as being 'purely naïve' (clarification A22). From the information reported in CS Appendix Table 12 it appears that patients classed as treatment-naïve could have received treatment with corticosteroids but not with DMTs or immunosuppressants. Of the 33 trials

included in MTC analyses, 24 (73%) are listed in CS Appendix Table 12 as including treatment-experienced patients. However, the company clarified that 13 of these 24 trials (including OPERA I & II) actually included mixed populations of both treatment-naïve and treatment-experienced patients (clarification A22). In these 13 mixed-population trials, the proportion of patients who were treatment-experienced at baseline ranged from 6% in the BRAVO trial to 74% in the FREEDOMS II trial. Within each of these mixed-population trials the proportions of patients who were treatment-experienced were similar across the trial arms, except in the TENERE trial where there were 12.3% more treatment-experienced patients in the interferon β-1a arm than the teriflunomide 14mg arm (clarification A22). The ERG notes that a further trial (Calabrese 2012) which is not mentioned in the company's clarification, also included a mixed population, whereby a treatment-experienced 'reference' placebo group was compared against three treatment-naïve DMT arms (CS Appendix Table 12). The company does not discuss the implications of these within-trial imbalances for interpretation of the MTC results (i.e. whether they could have introduced bias due to the within-trial comparison being confounded with the proportion treatment-experienced). However, we note that according to CS Appendix Table 30 the placebo arm of the Calabrese 2012 trial does not appear to have been included in the ARR MTC, although no explanation is provided.

The company consider the mixed treatment experience populations in the MTCs to be appropriate since the anticipated licence for ocrelizumab covers both treatment-naïve and treatment-experienced patients, and the treatment effect of ocrelizumab compared to interferon β-1a was observed in both treatment-naïve and treatment-experienced patients (clarification A22). The ERG considers that this is a reasonable justification from the perspective of the ocrelizumab-interferon comparison; however, the company does not provide a justification that the relative effectiveness of other DMTs in the MTC networks would also be independent of patients' treatment experience.

Relapse rates

The mean number of relapses in the previous 2 years before study entry (reported in 23 trials) ranged from 1.38 to 3.6. The mean number of relapses in the previous year before study entry (reported in 19 trials) ranged from 1.15 to 1.8 (CS Appendix Table 12). These rates generally reflect the trials' eligibility criteria which usually specified that patients had to have had at least one relapse in the previous year or at least two in the previous 2 years before study entry (CS Appendix Table 11).

EDSS scores

Although the EDSS is an ordinal scale, the company has preferentially reported mean EDSS scores from the trials. The mean EDSS score at baseline (reported in 31 trials) ranged from 1.3 to 3.0. Where reported, median EDSS scores were in the range 2.0-2.5. These scores reflect a range from minimal disability in one functional system (EDSS 2.0) to moderate disability in one functional system, or mild disability in three or four functional systems, with no impairment to walking (EDSS 3.0) (Appendix 3).

Time since first symptoms

The CS does not report the time since diagnosis but instead provides the time since first symptoms. It is unclear how this was defined and we assume that is is likely to be quite a variable measure, given that MS can present with a range of symptoms of variable intensity and patients might not accurately recall the time of onset. The mean time since first symptoms (measured in years) was reported in 22 trials (CS Appendix Table 12). In 21 of these trials the range was from 1 to 10.6 years. The remaining trial (Stępień 2013) is an outlier, with time since symptom onset in the two trial arms being 19.1 and 23 years.

3.1.7.4 MTC statistical approach

The statistical method used for conducting the MTC analyses was a standard Bayesian random effects model, based on methods specified in NICE Decision Support Unit Technical Support Document 2.[53] The JAGS and R statistical software programmes were used to conduct the analysis and the company provided the programming code on request from the ERG (clarification A13). CS appendix D 1.1.1 describes the statistical procedures used. The CS does not report procedures for checking model convergence (number of chains) and burn in. The NICE DSU Technical Support Document 2[53] states that the number of iterations for burn-in and posterior sampling should be reported. The statistical models used varied according to the outcome measure, as follows:

- Poisson model for ARR. A generalized linear model with a log link and Poisson likelihood, with a rate ratio reported as the chosen outcome statistic. The Poisson model accounts for the length of the observation period and assumes that the relapse rate is constant over time (given that the MTC synthesises results from different time points).
- Survival model for CDP-12 and CDP-24. A generalized linear model with identity link and normal likelihood was used, with a hazard ratio as the chosen outcome statistic.

- Binomial model for all-cause discontinuation. A generalized linear model with a logit link and binomial likelihood was used, with an odds ratio as the chosen outcome statistic.

The survival model for the CDP outcomes assumes that hazards are proportional (CS section B.2.9.1). The ERG requested clarification from the company on the justification for this assumption (clarification A17). The company provided log-cumulative-hazard plots for the OPERA I and II trials for CDP-12 and CDP-24 and state that the curves are "reasonably parallel from around 3 months onwards. The company suggests that, on this basis, it is reasonable to assume that proportional hazards assumption will also hold for other trials included in the MTC. However, whilst the ERG agrees that the proportional hazards assumption appears reasonable for the comparison of ocrelizumab against interferon β-1a (section 3.1.6.5), it is unclear whether such an assumption is appropriate for the other DMT comparisons in the MTCs.

The random effects binomial models and survival models used an informative prior distribution for the between-study variance, selected from a study which devised a novel set of predictive distributions for the degree of heterogeneity for use as prior distributions for heterogeneity in meta-analyses.[54] The choice of prior was explored by using a vague prior in sensitivity analysis. For the Poisson model (ARR) the CS reports that a good informative prior was not available for the between-study variance, and hence for the base case a vague prior was used (CS Appendix D 1.1). An alternative vague prior was compared in a sensitivity analysis. The CS reports model fit data showing the deviance information criterion (DIC) values for the priors considered in the base case and the sensitivity analyses. The base case random prior distributions used are those with the lowest DIC values. The DIC is commonly used to compare the fit of Bayesian statistical models, whereby the model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed.[55] The ERG considers that the company has clearly reported and justified their choice of prior distributions and have appropriately explored alternatives in sensitivity analyses.

The company provided additional information on the statistical procedures used in the network meta-regression (clarification A19). For each outcome measure the MTC model was extended to incorporate follow-up time as a continuous covariate, based on NICE Decision Support Unit (DSU) Technical Support Document 3,[56] which the ERG agrees is an acceptable standard approach. The regression covariate was centred on the mean trial duration, with the 'same interaction effect for all treatments' model used (defined as in the NICE Technical Support

Document[56]), and placebo as the reference treatment. The company state this was a pragmatic decision based on the available data; they acknowledge that this requires assumptions to be made on the form of the treatment and study duration interaction but do not discuss the assumptions or their plausibility. The CS reports that the meta-regression provided similar DIC values to the base case (ITT) MTC for the outcome of CDP-12, but for the remaining three outcomes the meta-regression did not provide a better fit (the meta-regression increased the DIC values by more than three units). The company provided forest plots comparing the results of the meta-regression with the standard MTC (clarification A19) which show similar results. The company's conclusion is that the differences in study duration had negligible impact on results and supported the base case. The ERG agrees with this interpretation based on the forest plots provided.

Definitions of outcomes included in the MTC analyses

ARR

The ERG noted that the trials included in the MTCs used different definitions of relapse when estimating the ARR (e.g. any relapses, confirmed relapses, protocol-defined relapses, qualifying relapses) but the CS does not discuss this. We therefore requested clarification from the company on whether this variation in definitions might influence interpretation of the MTC results. The company provided a table showing the definitions ARR and relapse that were used for each of the trials included in the MTCs (clarification A16d and Table 40 in the clarification response). The company also provided a table showing the absolute ARR and the ARR rate ratio for the comparison of ARR between DMTs both for protocol-defined relapses and for all relapses (Table 15 in the clarification response). The ERG agrees with the company's assertion that the two definitions of relapse affected the absolute ARR but had only a small impact on the rate ratio. For example, absolute ARR estimates in the CombiRx trial varied from 0.16 to 0.32 in the interferon β-1a arm and from 0.11 to 0.23 in the glatiramer acetate arm depending upon the ARR definition, whilst the corresponding difference in the ARR rate ratio was only 0.03.

In addition to the comparison of ARR based on protocol/non-protocol defined relapses mentioned above, the company reported that a sensitivity analysis had been conducted within the TENERE trial that compared definitions of ARR based on confirmed relapses and all relapses (i.e. both confirmed and non-confirmed) (clarification A16b). Results of the sensitivity analysis (Table 13 in the clarification response) show that these different definitions of ARR had negligible impact on the absolute ARR and the ARR rate ratios.

The ERG agrees that, based on the results of these sensitivity analyses, the different definitions of ARR would appear to have relatively limited impact on the ARR ratios which are used in the company's MTC analyses. A caveat is that these sensitivity analyses did not capture the full range of definitions of ARR used in the trials and so it is unclear how representative they are.

CDP

The CS does not explicitly state how CDP was defined in the trials that were included in the MTC analyses and the ERG requested clarification on this. The company provided tables showing the definitions of CDP-12 and CDP-24 for each of the trials included in the MTCs (clarification A18 and Tables 41 and 42 in the clarification response). The company commented that the trials used two key definitions of CDP, which differed in the values of the EDSS score that they used, as follows:

- an increase of ≥1.5 EDSS points from a baseline score of 0 or an increase of 1 point from a baseline score of 1 (referred to as the more stringent definition);
- a 1-point increase in EDSS (referred to as the less stringent definition, as used in the OPERA trials).

The company provided a sensitivity analysis comparing the impact of each definition on the CDP-12 and CDP-24 outcomes using data from the pooled OPERA trials (Table 16 in the clarification response). The proportion of patients with CDP-12 varied by 0.5 in the interferon β-1a arm and 0.8 in the ocrelizumab arm whilst the proportion with CDP-24 varied by 0.4 and 0.7 in these arms respectively. Differences in the corresponding hazard ratios were 0.03 for CDP-12 and 0.04 for CDP-24. The company concluded that there is limited impact of the CDP definition on MTC results and the ERG agrees.

Adjustment of outcomes included the in MTC analyses

The ERG noted that the clinical trials included in the company's MTC analyses varied according to whether their ARR estimates were adjusted for baseline covariates and according to which covariates were adjusted for. We requested clarification from the company on whether this variation in the adjustment of ARR outcomes would influence interpretation of the MTC results. The company provided a table showing the covariates adjusted for in the trials (clarification A16b and Table 14 in the clarification response). Adjusted values of ARR were reported in 20 of the 33 trials included in the company's MTC analyses, of which three (AFFIRM, OPERA I and

OPERA II) reported both adjusted and unadjusted ARR. The results presented by the company show that most of these trials adjusted the ARR according to baseline EDSS score, region, prior relapses and/or age. Some covariates such as EDSS score were adjusted for either as continuous or dichotomous variables, and the cutoff values used for dichotomous covariates varied across the trials, meaning that overall there was little consistency in how ARR outcomes had been adjusted.

The company provided a comparison of the adjusted and unadjusted ARR in the three trials where this comparison was possible (Table 13 in the clarification response). The difference in adjusted and unadjusted ARR across all the arms of these three trials ranges from 0.017 to 0.09, whilst the difference in the rate ratios range from 0.01 to 0.04. These results suggest that for the trials included in the company's MTC analyses the method of adjusting ARR, or whether adjustment was used, is unlikely to have substantially influenced the MTC results.

3.1.7.5 Assumptions of similarity, heterogeneity and consistency

Similarity

One of the key assumptions of an MTC, often referred to as the similarity assumption, is that the distribution of interactions between relative treatment effects and covariates is balanced across trials that are comparing different sets of inteventions.[57] In order to satisfy the similarity assumption, and hence avoid bias in the MTC outcome estimate, the trials in the MTC should all be balanced in terms of any variables that could act as effect modifiers. Examples of effect modifiers are patient characteristics, the way in which the outcomes are defined and/or measured, protocol requirements such as allowed co-treatment, and the length of follow up.[57] The CS does not provide an explicit statement of whether the similarity assumption is likely to hold across the trials.

A challenge when assessing the similarity of trials included in an MTC is that not all potential effect modifiers may be reported. Where available, characteristics of the trial populations, including some prognostic factors for MS progression, which could potentially act as effect modifiers if unbalanced across trials, have been summarised above (section 3.1.7.3). Differences in the definitions of trial outcomes, and differences in the methods of adjusting outcome estimates, which also have potential to be effect modifiers if unbalanced across the trials, are also summarised above (section 3.1.7.4).

As discussed above (section 3.1.7.3), there was some variation across the trials in the baseline proportions of patients who had RRMS and SPMS, in patients' age, the proportion who were male, in relapse rates in the years before study entry, and in EDSS scores, but there is no evidence to suggest any major imbalances in any of these variables that would clearly violate the similarity assumption. The balance of treatment-naïve and treatment-experienced patients across the trials was more variable, ranging from 0% (in treatment-naïve patients) to 74% in one one of the trials that included treatment-experienced patients. We also noted an imbalance in treatment-naïve/experienced patients between arms within the Calabrese 2012 trial, but it is unclear whether all arms of this trial were included in MTC analyses. The time since first symptoms was also rather variable across the trials, ranging from 1 to 10.6 years, with a single outlier trial (Stępień 2013) that included patients at 19.1 and 23 years since symptom onset.

Although the trials varied in how they defined ARR and CDP outcomes, and how they adjusted ARR outcomes for baseline covariates, the company provided sensitivity analyses which suggested that these differences are likely to have only a small or negligible effect on MTC outcomes (section 3.1.7.4). A caveat is that the sensitivity analyses on ARR definitions only covered some of the different definitions used in the trials.

In summary, most of the available baseline characteristics of the trials included in the MTC analyses, and the ways in which outcomes were defined and adjusted, appear to be adequately balanced across the trials. However, there is uncertainty as to whether the similarity assumption can be supported, due to notable variation across the trials in the proportions of patients who were treatment-naïve/experienced, and in patients' time since onset of symptoms, both of which could plausibly be considered as being potential effect modifiers.

Heterogeneity

The CS provides results of assessments of statistical heterogeneity for the head-to-head pairwise comparisons included in the MTCs, colour coded according to categorisations of low heterogeneity (I^2 = 0% to 25%), low to moderate (I^2 = 25% to 50%), moderate to high (I^2 = 50% to 75%) and high heterogeneity (I^2 = 75% to 100%) (CS Appendix D Table 27 - the ERG assumes this is for the ITT base case MTCs rather than for the subgroup MTCs). The majority of comparisons produced low heterogeneity estimates, with seven (21%) of the 34 comparisons classified as moderate to high, and none classified as high. For the seven moderate to high comparisons the CS provides forest plots (with tau-squared and p values for statistical

heterogeneity) and a discussion, in varying detail across comparisons, of potential sources of heterogeneity. The company speculate that reasons for heterogeneity might include differences in trial durations and differences in overall rates of discontinuation between trials, or unknown reasons. The company also noted an imbalance in the dropout rate between the arms within the CONFIRM trial which they suggest might have contributed to heterogeneity. However, the CS does not provide a detailed discussion of heterogeneity in the evidence base as a whole, apart from noting that there may be heterogeneity in terms of the proportion of patients included in the trials with forms of MS other than RRMS (as we have discussed above in relation to similarity).

As stated above, a random effects model was used in the base case MTC analysis, which is recommended where heterogeneity is identified or suspected.[57] Overall, the ERG considers that the results of the MTCs are unlikely to be compromised by heterogeneity given the relatively low I^2 values reported, the use of a random effects model, and the inclusion of a meta-regression on trial duration.

Consistency

The CS assesses the consistency between direct and indirect evidence by conducting a consistency assessment (CS Appendix Table 28). In response to a clarification question (clarification A20c) the company stated that they investigated inconsistency using an inconsistency model approach as recommended in NICE DSU Technical Support Document 4.[58] The inconsistency model provides results that are equivalent to having separate, unrelated, meta-analyses for every pair-wise comparison but with a common variance parameter in random effects models.[58]

The company re-ran each MTC model without assuming consistency, and the DIC values were compared with those from the standard MTC (which assumes consistency). The CS notes that a DIC for the inconsistency model that is higher than the consistency model by three units suggests potential inconsistency. The standard MTC (consistency) model had a lower DIC compared to the inconsistency model for three of the four outcome measures. The exception was the CDP-24 outcome where the consistency model had a higher DIC than the inconsistency model but this did not exceed three units, and the CS therefore regards this as unimportant.

The ERG notes that the approach taken by the company is regarded by the NICE DSU as suitable for complex networks,[58] and the networks included in the CS could indeed be regarded as complex. Other methods for investigating inconsistency are available but the company has not provided a justification for the use of their chosen method over any other. The NICE DSU also suggests that "inconsistency assessments are inherently underpowered and will often fail to detect it. Investigators must therefore also ask whether, if inconsistency is not detected, conclusions from combining direct and indirect evidence can be relied upon" (page 4).[58] However, the CS does not discuss this.

The company provided forest plots for all pairwise comparisons following an ERG request (clarification A20). The ERG cross-checked the results of the company's pairwise meta-analyses (direct comparisons) against the results of the base case ITT MTC (direct and indirect comparisons) for the four outcome measures. In the majority of cases the results of the two sets of analyses were similar, suggesting overall consistency in results. In a minority of cases the ERG noted small differences between the width of confidence intervals from the pairwise meta-analyses and the MTC credible intervals, where intervals crossed 1 (for ARR and all cause discontinuations).

3.1.7.6 MTC summary

- A total of 23 MTC networks are reported in the CS, varying in composition according to patient population, subgroups and comparators included.
- A total of 33 RCTs provided data to inform the MTCs, based on the company's systematic review of clinical effectiveness, with a smaller number informing the subgroup MTCs. The ERG did not identify any additional relevant studies from an update search undertaken for this report.
- A Bayesian random effects model was used, with sensitivity analysis using alternative prior distributions and fixed effects. The statistical procedures were based on methods recommended by the NICE DSU and are reported clearly, though certain procedures (e.g. assessing model convergence) are not described.
- The networks have a complex structure with ocrelizumab (OPERA trials) connected to comparator treatments via second-order and third-order groups of treatments ('jumps'). The MTCs directly inform the company's economic model. The majority of comparisons across the networks were informed by a single trial which can be considered a limitation.

- Heterogeneity assessments undertaken by the company showed that the majority of pairwise comparisons were considered to have low heterogeneity. The CS does not provide a detailed discussion of heterogeneity in the evidence base as a whole, but the ERG considers the results are unlikely to be compromised by potential heterogeneity.
- The statistical consistency assessment used by the company did not suggest the presence of inconsistency between direct and indirect evidence. The ERG's cross-check of the results of the direct and indirect evidence found that results were similar. The CS does not explicitly discuss the similarity assumption across the trials.

Limitations identified in the MTCs include:

- The subgroup MTCs should be interpreted with caution due to sparsity of data, the fact that they are post hoc subgroups extracted from the trials, and the observational nature of the data.
- The MTC analyses of CDP-12 and CDP-24 assume proportional hazards. The company provided evidence to suggest that this assumption is supported for the comparison of ocrelizumab against interferon β-1a, but it is unclear whether the assumption would be supported for comparisons among other DMTs.
- To enable MTC networks to be formed for HA and RES disease severity subgroups, the company utilised ITT data from trials of 'ABCR' comparators (types of interferon β and glatiramer acetate). The underlying assumption is that, for these treatments, the treatment effect observed in the ITT population would be the same as the treatment effects in the subgroup populations. However, the company has not clearly justified that this assumption is supported. Overall, given the limitations of the subgroup analyses, including that they post-hoc and potentially at risk of selection bias, both the company and ERG consider the MTC results for these subgroups to be unreliable.
- There are marked differences between trials included in the MTCs in the proportions of patients who were treatment-naïve and treatment-experienced, and also in the time since onset of symptoms. The the ERG is therefore uncertain whether the consistency assumption of MTC analysis is supported.
- There is uncertainty around some individual input data for the MTCs. (i) An independent MTC which the company used to provide ITT CDP-12 outcomes for some comparisons against alemtuzumab, obtained by the company from the 'HAS Reimbursement dossier' has not been critiqued by the company and the ERG is unable to locate the dossier to check it. (ii) It is unclear whether the placebo arm in the Calbrese 2012 trial was included

in MTC analysis. (iii) The company does not adequately justify why the Etemadefir 2006 trial was excluded from MTC analyses of ARR.

- The company did not conduct any sensitivity analyses to investigate whether MTC outcomes were sensitive to the inclusion of trials that were judged to be at high risk of bias.

3.2 Summary statement of the company's approach

Overall, the company's approach to the synthesis of clinical effectiveness and safety data meets the CRD's quality criteria (Table 16).

Table 16 ERG's quality assessment of the CS review (CRD criteria)

CRD Quality Item	ERG comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. The company's SLR was designed with multiple countries' requirements in mind and was therefore broader than the NICE scope. A feasibility assessment was conducted to determine which of the identified studies were to be included in MTC analyses, but the feasibility assessment process is not clearly reported and the CS does not report how many reviewers conducted screening (further information was provided in clarification responses).
2. Is there evidence of a substantial effort to search for all relevant research? (i.e. all studies identified)	Yes for the clinical effectiveness evidence. However, sourcing of safety data did not appear to follow a systematic process. Non-randomised studies (which might provide safety data) were not sought. The company did not initially provide the ERG with all relevant references (these were provided in a clarification response).
3. Is the validity of included studies adequately assessed?	Yes, risk of bias was assessed according to standard NICE criteria, for the two OPERA trials and the phase II trial, and for 23 RCTs of comparators that informed the company's MTC (narrative justification of the company's risk of bias judgements was not provided).
4. Is sufficient detail of the individual studies presented?	Yes for the two OPERA trials. The CS does not report clinical effectiveness results for the phase II trial (these were provided in a clarification response).
5. Are the primary studies summarised appropriately?	Yes, the information provided in the CS and Appendices is generally well-structured and clear. The CS does not report baseline characteristics of disease activity subgroups in the OPERA trials (these were provided in a clarification response), and does not report exploratory outcomes in the OPERA trials that are relevant to the NICE scope.

The CS and Appendices are generally well-presented and easy to follow. The main limitations are that the feasibility assessment process for including/excluding trials in the MTC analyses

was not clearly explained (but was subsequently clarified); safety data were not searched for systematically (although no key safety issues appear to have been missed); clinical effectiveness results of the phase II trial are not included in the CS; some exploratory outcomes measured in the OPERA trials which are specified in the NICE scope are not mentioned in the CS.

The company provided electronic copies of the CSRs for both OPERA trials, but not for the phase II trial, although a study publication was provided.[44] The CSR for the phase II trial, the ocrelizumab draft summary of product characteristics (SmPC), and most other references which were missing from the submission were subsequently provided by the company on request from the ERG (clarifications A5 and A7a). However, a reference for the HAS meta-analysis was not provided to the ERG and we have been unable to locate this document.

3.3 Summary of the submitted evidence

The clinical effectiveness results presented in this section are from the pivotal OPERA I and OPERA II trials which compared ocrelizumab (600mg IV infusion) against interferon β-1a (Rebif 44 µg subcutaneous injection) over 96 weeks.

The company did not include the results of the identified ocrelizumab phase II trial comparing ocrelizumab (600 mg or 2000 mg IV infusion) with interferon β-1a (Avonex 30 µg intramuscular injection) or placebo in their submission (but provided information on methods and results in clarification A7). We have not presented full clinical effectiveness results of the phase II trial here, for the reasons explained above (section 3.1.3.1). We do, however, briefly comment on the consistency of findings from the phase II trial and OPERA trials for those outcomes that were assessed in both; and we have included the phase II trial as a source of adverse events data (section 3.3.9 below).

Results are presented below in an order which broadly matches the categories of outcomes specified in the NICE scope, i.e. relapse rate (section 3.3.1), disability progression (section 3.3.2), disability improvement (3.3.3), symptoms and quality of life (section 3.3.4), and freedom from disease activity (section 3.3.5). All-cause discontinuation, which is not specified in the NICE scope, is an outcome that informs the company's economic analysis and is reported in section 3.3.6. Outcomes relating to brain lesions and brain volume, which are not explicitly mentioned in the NICE scope, are reported under 'MRI outcomes' (section 3.3.7). Mortality,

which is listed as an outcome in the NICE scope, is reported under adverse events (section 3.3.9).

The first seven of the 11 outcomes tested in the company's hierarchical sequence (Figure 2 above) were statistically significant, supporting the company's hypothesis of the superior clinical effectiveness of ocrelizumab compared to interferon β-1a for these outcomes (CS Table 12). The eighth outcome in the sequence (MSFC) was statistically significant only in the OPERA II trial. In line with the pre-specified analysis plan, the company therefore interpreted MSFC and the remaining three outcomes below it in the sequence (brain volume, SF-36 PCS, and NEDA) as being non-confirmatory of clinical effectiveness (i.e. providing descriptive information only).

3.3.1 Relapse rate

Results from analyses of the ARR (the primary outcome in the OPERA trials) are presented here for the ITT population (section 3.3.1.1) and for the subgroup analysis of ARR according to disease activity and disease progression (section 3.3.1.2). The HA and RES subgroups are defined in Table 14 above; note that these are not mutually exclusive since in the OPERA trials 14% of patients could be defined as having both HA and RES types of MS (indicated by the company in clarification A9).

3.3.1.1 ITT population

The OPERA I and OPERA II trials both met their primary endpoint, with the ARR over 96 weeks analysed in the ITT population reduced significantly in the ocrelizumab arms compared to interferon β-1a (Table 17). The ARR for each trial arm and the rate ratios for the comparisons were almost identical in the two trials; the rate of relapse was around 46% lower with ocrelizumab than with interferon β-1a.

Table 17 Annualised relapse rate at 96 weeks

Trial	Ocrelizumab		Interferon β-1a		Rate ratio (95% CI) [a]
	N	ARR	N	ARR	
OPERA I (data cut-off 02/04/2015)	410	0.156	411	0.292	0.536 (0.400 to 0.719); p<0.0001
OPERA II (data cut-off 12/05/2015)	417	0.155	418	0.290	0.532 (0.397 to 0.714); p<0.0001

[a] Adjusted by study, baseline EDSS score (<4.0 vs ≥4.0) and geographical region (US vs rest of world).

The rate ratio for the pooled analysis was 0.535 (95% CI 0.435 to 0.659) (CS Table 13). The trial publication supplementary appendix[45] reports results from a per-protocol analysis of ARR per trial that was not part of the hierarchical testing procedure. This yielded almost identical results to the ITT analysis for both OPERA trials. Further sensitivity analyses were conducted, using a Poisson model, 50% and 100% imputation of missing data, and variation of the adjustment covariates (summarised in the Canadian Agency for Drugs and Technologies in Health (CADTH) appraisal of ocrelizumab[25]), and these all yielded results consistent with the ITT analysis.

ARR was a secondary outcome in the ocrelizumab phase II trial. Results of the phase II trial over 24 weeks were consistent with those of the OPERA trials over 96 weeks in showing ocrelizumab to be effective in reducing the rate of relapses in patients with RRMS. According to the phase II trial publication,[44] ARR over 24 weeks in the ocrelizumab arm was 0.13 (95% CI 0.53 to 0.29), which was 80% lower than in the placebo arm (0.64 (95% CI 0.43 to 0.94); p=0.0005) and 64% lower than in the interferon β-1a (Avonex) arm (0.36 (95% CI 0.22 to 0.60); p=0.03).

3.3.1.2 Disease activity and treatment experience subgroups

ARR in disease activity subgroups

In both the HA and RES subgroups ocrelizumab significantly reduced the ARR compared to interferon β-1a, which is consistent with the results for the ITT population (

Table 18). In the ocrelizumab arm the subgroup ARR were similar to or lower than those in the ITT population; whilst in the interferon β-1a arm, the subgroup ARR were higher than in the ITT population. As such, the rate ratios for the disease activity subgroups (HA 0.32; RES 0.38) are lower than for the ITT population (0.54).

Table 18 Annualised relapse rate in disease activity subgroups at 96 weeks (pooled OPERA trials analysis)

Analysis group	Ocrelizumab			Interferon β-1a			Rate ratio (95% CI)	Interaction test p-value
	N	Events	ARR	N	Events	ARR		
HA	143	23	0.099	140	64	0.313	0.317 (0.181 to 0.556); p<0.0001	0.0346
RES	150	40	0.151	140	78	0.394	0.384 (0.243 to 0.607); p<0.0001	0.0811
Non-HA/RES	567	189	0.250	556	137	0.173	0.691 (0.538 to 0.888); p=0.0038	-
ITT	827	194	0.156	829	334	0.291	0.535 (0.435 to 0.659); p<0.0001	-

Based on CS Table 13 and clarification A9
ARR, annualised relapse rate; CI, confidence interval, HA, highly active; ITT, Intention-to-treat; RES, rapidly evolving severe.

ARR in treatment experience subgroups

Based on data from the pooled OPERA I and OPERA II trials, the ARR was compared in subgroups of treatment-experienced and treatment-naïve patients, in a post-hoc analysis (as requested by the EMA) (CS Appendix E). Treatment-experienced patients were defined very broadly, as having had treatment with any medication for MS in the 2 years before randomisation. The ARR is not reported for each subgroup, but the rate ratios for ocrelizumab versus interferon β-1a (not reported whether adjusted) were statistically significant for both the treatment-naïve subgroup (0.567; 95% CI 0.445 to 0.772; p<0.0001) and the treatment-experienced subgroup (0.462; 95% CI 0.310 to 0.688; p=0.0001), indicating that clinical effectiveness of ocrelizumab at reducing relapse rates was independent of patients' (broadly-defined) treatment experience.

3.3.2 Disability progression

Results from analyses of the time to confirmed disability progression are presented here for the ITT population (section 3.3.2.1) and for the subgroup analysis of CDP according to disease activity and treatment experience (section 3.3.2.2).

3.3.2.1 ITT population

The proportion of patients with 12-week confirmed disability progression was significantly lower in the ocrelizumab arm compared to the interferon β-1a arm in both OPERA trials and in the pooled analysis (Table 19). The reduction in risk of CDP-12 for those receiving ocrelizumab was 40% in the pooled analysis (HR 0.60 (95% CI 0.45 to 0.81); p=0.0006).

Table 19 Proportion of patients with 12-week confirmed disability progression (CDP-12) at 96 weeks

Trial	Ocrelizumab		Interferon β-1a		Hazard ratio (95% CI) [a]
	N	Proportion (%) with CDP-12	N	Proportion (%) with CDP-12	
OPERA I	410	7.6 [b]	411	12.2 [b]	0.57 (0.37–0.90); p=0.0139
OPERA II	417	10.6 [b]	418	15.1 [b]	0.63 (0.42–0.92); p=0.0169
Pooled OPERA I + II	827	9.1 [c]	829	13.6 [c]	0.60 (0.45–0.81); p=0.0006

[a] Adjusted by study, baseline EDSS score (<4.0 vs ≥4.0) and geographical region (US vs rest of world).
[b] From trial publication (not reported in CS)
[c] Data are from the trial publication; they differ slightly from those in CS Table 11 and the CSR.

The proportion of patients with 24-week confirmed disability progression was also significantly lower in the ocrelizumab arm compared to the interferon β-1a arm in both OPERA trials and in the pooled analysis (Table 20). The hazard ratios are almost identical for 24-week CDP and 12-week CDP, both for each OPERA trial and for the pooled analysis. The reduction in risk of CDP-24 for those receiving ocrelizumab was 40% in the pooled analysis (HR 0.60 (95% CI 0.43 to 0.84); p=0.0025).

Table 20 Proportion of patients with 24-week confirmed disability progression (CDP-24) at 96 weeks

Trial	Ocrelizumab		Interferon β-1a		Hazard ratio (95% CI) [a]
	N	Proportion (%) with CDP-24	N	Proportion (%) with CDP-24	
OPERA I	410	5.9 [b]	411	9.5 [b]	0.57 (0.34–0.95); p=0.0278
OPERA II	417	7.9 [b]	418	11.5 [b]	0.63 (0.40–0.98); p=0.0370
Pooled OPERA I + II	827	6.9 [c]	829	10.5 [c]	0.60 (0.43–0.84); p=0.0025

[a] Adjusted by study, baseline EDSS score (<4.0 vs ≥4.0) and geographical region (US vs rest of world).
[b] From trial publication (not reported in CS).
[c] Data are from the trial publication; they differ slightly from those in CS Table 11 and the CSR.

For both the CDP-12 and CDP-24 outcomes, there was a slight difference between the trials: the proportion of patients with an event was 2-3% lower in OPERA I than OPERA II and the corresponding hazard ratio was 6% lower in OPERA I than OPERA II.

The CSRs for OPERA I and OPERA II present eight sensitivity analyses for each of the CDP-12 and CDP-24 outcomes (not mentioned in the CS), in which the population (ITT or per protocol), data imputation (with or without), and/or analysis stratification factors were varied in different combinations. For the proportion of patients with CDP-12, the hazard ratios ranged from [redacted] in OPERA I and [redacted] in OPERA II. For the proportion with CDP-24 the hazard ratios ranged from [redacted] in OPERA I and [redacted] in OPERA II. [redacted].

3.3.2.2 Disease activity and treatment experience subgroups

CDP-12 and CDP-24 in disease activity subgroups

In both the HA and RES subgroups the proportion of patients with disability progression was consistently lower in the ocrelizumab arm than the interferon β-1a arm, both for progression confirmed at 12 weeks and progression confirmed at 24 weeks (

Table 21). The CS concludes that the effect of ocrelizumab at reducing progression in the subgroups is consistent with that in the ITT population. For both CDP-12 and CDP-24 outcomes the RES subgroup hazard ratios were similar to the ITT population hazard ratios (all were in the range 0.60 to 0.65), whilst the HA subgroup hazard ratios were smaller (range 0.47 to 0.50). However, only the hazard ratio for CDP-12 assessed in the HA subgroup was statistically significant (the CS does not comment on these differences).

Table 21 CDP-12 and CDP-24 in disease activity subgroups at 96 weeks (pooled OPERA trials analysis)

Analysis group	Ocrelizumab			Interferon β-1a			Hazard ratio (95% CI)	Inter-action test p-value
	N	Events	% events	N	Events	% events		
CDP-12								
HA	143	12	8.4	140	22	15.7	0.47 (0.23 to 0.95); p=0.0311	0.5109
RES	150	15	10.0	140	20	14.3	0.65 (0.33 to 1.29); p=0.2163	0.8490
Non-HA/RES	567	74	13.1	556	49	8.8	0.61 (0.42 to 0.87); p=0.0065	-
ITT	827	75	9.1	829	113	13.6	0.60 (0.45 to 0.81); p=0.0006	-
CDP-24								
HA	143	10	7.0	140	17	12.1	0.50 (0.23 to 1.09); p=0.0763	0.6898
RES	150	14	9.3	140	20	14.3	0.61 (0.31 to 1.22); p=0.1566	0.9853
Non-HA/RES	567	53	9.3	556	34	6.1	0.60 (0.39 to 0.92); p=0.0169	-
ITT	827	57	6.9	829	87	10.5	0.60 (0.43 to 0.84); p=0.0025	-

Based on CS Tables 14 and 15 and clarification A9

CDP-12 and CDP-24 in treatment experience subgroups

Based on data from the pooled OPERA I and OPERA II trials, CDP-12 and CDP 24 were compared in subgroups of treatment-experienced and treatment-naïve patients, in a post-hoc analysis (as requested by the EMA) (CS Appendix E). As previously stated, treatment-experienced patients were defined very broadly, as having had treatment with any medication for MS in the 2 years before randomisation.

The proportions of patients with CDP-12 in the ocrelizumab and interferon β-1a groups, and the corresponding hazard ratios, were very similar for the treatment-naïve and treatment-experienced patient subgroups, and the ITT population (Table 22). Similar results were found for CDP-24, except that the proportions of patients achieving an event were more variable across the analysis groups for the ocrelizumab arm (Table 23). However, the hazard ratios for the treatment experienced groups for both outcomes were not statistically significant. The company suggest (CS Appendix E) that the lack of statistical significance is likely driven by the low number of events and lack of statistical power.

Table 22 CDP-12 in treatment naïve/experienced subgroups at 96 weeks

Analysis group (pooled OPERA trials)	Ocrelizumab		Interferon β-1a		Hazard ratio (95% CI) [b]
	N	Proportion (%) with CDP-12 [a]	N	Proportion (%) with CDP-12 [a]	
Treatment naive	604	8.8	605	13.6	0.60 (0.42 to 0.85); p=0.0037
Treatment experienced	223	9.9	223	13.9	0.61 (0.35 to 1.06); p=0.0797
ITT population	827	9.1	829	13.6	0.60 (0.45–0.81); p=0.0006

Source: CS Appendix E
[a] calculated by ERG.
[b] ITT analysis adjusted by baseline EDSS score and region; not reported whether subgroup analyses adjusted.

Table 23 CDP-24 in treatment naïve/experienced subgroups at 96 weeks

Analysis group (pooled OPERA trials)	Ocrelizumab		Interferon β-1a		Hazard ratio (95% CI) [b]
	N	Proportion (%) with CDP-24 [a]	N	Proportion (%) with CDP-24 [a]	
Treatment naive	604	6.5	605	10.6	0.57 (0.38 to 0.85); p=0.0056
Treatment experienced	223	8.1	223	10.3	0.67 (0.36 to 1.24); p=0.2039
ITT population	827	6.9	829	10.5	0.60 (0.43–0.84); p=0.0028

Source: CS Appendix E
[a] calculated by ERG.
[b] ITT analysis adjusted by baseline EDSS score and region; not reported whether subgroup analyses adjusted.

3.3.3 Disability improvement

Both CDI-12 and CDI-24 were measured in the OPERA trials, although only CDI-12 was specified in the statistical testing hierarchy (Figure 2 above) and reported in the CS and trial publication.

Proportion with CDI-12

The pooled analysis of CDI-12 demonstrated that ocrelizumab was associated with a statistically significant increase in the proportion of patients with CDI-12 by week 96 compared to interferon β-1a (

Table 24).

Table 24 Proportion of patients with 12-week confirmed disability improvement (CDI-12) at 96 weeks

Trial	Ocrelizumab		Interferon β-1a		Risk ratio (95% CI) [b]
	N	Proportion (%) with CDI-12 (95% CI) [a]	N	Proportion (%) with CDI-12 (95% CI) [a]	
Pooled OPERA I + II	628	20.70 (17.60 to 24.08)	614	15.64 (12.85 to 18.75)	1.33 (1.05 to 1.68); p=0.0194

[a] For subgroup of patients with baseline EDSS score ≥ 2.0; Kaplan-Meier estimate.
[b] Adjusted by study, baseline EDSS score (<4.0 vs ≥4.0) and geographical region (US vs rest of world).

Proportion with CDI-24

The analysis of CDI-24, reported in the CSRs for OPERA I and OPERA II, demonstrated that ocrelizumab was associated with a [redacted] in the proportion of patients with CDI compared to interferon β-1a in OPERA I, but the difference in OPERA II was [redacted] (Table 25). [redacted].

Table 25 Proportion of patients with 24-week confirmed disability improvement (CDI-24) at 96 weeks

Trial	Ocrelizumab		Interferon β-1a		Risk ratio (95% CI) [b]
	N	Proportion (%) with CDI-24 (95% CI) [a]	N	Proportion (%) with CDI-24 (95% CI) [a]	
OPERA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OPERA II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] For subgroup of patients with baseline EDSS score ≥ 2.0; Kaplan-Meier estimate.
[b] Adjusted by study, baseline EDSS score (<4.0 vs ≥4.0) and geographical region (US vs rest of world).

3.3.4 Symptoms and health related quality of life

The CS reports two instruments that assessed patients' functional ability (MSFC) and health-related quality of life (SF-36). A further four scales which assessed patients' disability (EDSS), health-related quality of life (EQ-5D), fatigue (MFIS) and depression (CES-D) are not reported in the CS or trial publication but are summarised briefly below. Apart from EQ-5D, these scales do not provide input data to the company's economic analysis but have relevance to interpreting patients' quality of life and disease burden and as such provide supporting information. Note that some of these outcomes were exploratory and/or suffer from missing data which were unbalanced between the study arms (see Table 13 above).

3.3.4.1 Outcomes reported in the CS

Change in Multiple Sclerosis Functional Composite (MSFC) over 96 weeks

The MSFC is appropriate as a patient reported outcome measure for MS trials since it captures upper limb function and cognitive impairment which are not addressed by the EDSS.[20] Ambulatory function is assessed with the timed 25-foot walk test; hand function with the nine-hole peg test; and cognitive function with the paced auditory serial addition task (PASAT). The results of the tests that assess these domains are presented on interval scales (either seconds or number of correct responses) and are converted to a z-score based on the values of a reference population. Changes in MSFC scores are not an explicit outcome in the NICE scope but are a secondary outcome reported in the CS. This outcome failed the hierarchical testing procedure and therefore provides descriptive information only. Changes in z-scores in both OPERA trials were positive in direction, indicative of improvement through time, but statistically significant only in OPERA II. The clinical significance of the change is uncertain because there is no validated minimal clinically important difference for MSFC scores[25] (clinical significance is not discussed by the company) and the company does not specify the reference population used to calculate the scores.

Change in SF-36 Physical Component Summary (SF-36 PCS) over 96 weeks

The SF-36 is a generic measure of quality of life which is relevant to the NICE scope, and changes in SF-36 PCS from baseline are reported in the CS as a secondary outcome. However, this outcome failed the hierarchical testing procedure and therefore provides descriptive information only. In both OPERA trials the mean SF-36 PCS scores for patients in the ocrelizumab groups showed a slight increase from baseline whereas the mean scores in the interferon β-1a groups decreased from baseline, but the difference was statistically significant only in OPERA II. Absolute SF-36 PCS scores are not reported. The ERG understands that no minimum clinically important difference has been established for the SF-36 PCS specifically in MS patients,[25] but the changes were all less than 1.0 point (on a scale of 0-100) which is less than the accepted minimum clinically important difference for SF-36 PCS in general use (2.0 points)[59] (clinical significance is not discussed by the company).

3.3.4.2 Outcomes not reported in the CS

Change in EDSS score over 96 weeks

A description of the EDSS instrument is given in Appendix 3. The EDSS [60] quantifies disability in MS and is an important component in the definitions of the ARR, CDP, and NEDA outcomes. EDSS is specified as a relevant outcome in the NICE scope but only baseline scores are reported in the CS and trial publication. According to the CSRs, the median EDSS was [redacted] in both trial arms in OPERA I and OPERA II and [redacted] (a score of 2.5 on the EDSS scale indicates mild disability in one functional system or minimal disability in two functional systems). A statistically significant improvement in the mean EDSS score [redacted] is reported in the CSRs. However, since EDSS has an ordinal scale the mean is not a reliable statistic for this outcome. Clinical experts advising the ERG commented that it is reasonable to expect a stable EDSS score over 96 weeks in RRMS patients receiving ocrelizumab and interferon β-1a.

Change in EQ-5D over 96 weeks

EQ-5D is a generic measure of quality of life which is relevant to the NICE scope. Pooled EQ-5D scores from OPERA I and OPERA II provided health utility values in the company's economic model (section 4.3.4.4). EQ-5D scores are not reported in the CS, trial publication and OPERA CSRs and were requested from the company (clarification A8). The mean EQ-5D scores pooled from both OPERA trials were [redacted] in the ocrelizumab and interferon β-1a arms at baseline, 48 weeks and 96 weeks, ranging from [redacted]. The company stated that EQ-5D was measured for the purposes of economic modelling, and a comparison of EQ-5D across treatment arms was not planned as no significant differences were expected over the trial duration (clarification A8).

Change in MFIS fatigue scores over 96 weeks

Fatigue is specified as an outcome in the NICE scope and the company capture fatigue in their economic analysis as an adverse event. The ERG notes that fatigue was also assessed in the OPERA trials using the MFIS instrument, although this was an exploratory outcome and is not mentioned in the CS or trial publication. MFIS measures the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. A minimum clinically important difference in MFIS scores has not been established.[61] According to MFIS scores reported in the CSRs, the degree of fatigue experienced by patients in the OPERA trials [redacted] between the

ocrelizumab and interferon β-1a arms and [redacted] over the 96-weel trial period (on a scale of 0=best to 84=worst fatigue, scores ranged from [redacted] in both arms).

Change in CES-D depression scores over 96 weeks

Depression is not specified as an outcome in the NICE scope but is relevant in comparisons of DMTs. The company capture depression in their economic analysis as an adverse event. The ERG notes that depression was also assessed in the OPERA trials using the CES-D instrument, although this was an exploratory outcome and is not mentioned in the CS or trial publication. A minimum clinically important difference for CES-D has not been established.[62] According to CES-D scores reported in the CSRs, the degree of depressive symptoms experienced by patients in the OPERA trials [redacted] between the ocrelizumab and interferon β-1a arms and [redacted] over the 96-weel trial period (on a scale of 0=best to 60=worst depressive symptoms, scores ranged [redacted] in the ocrelizumab arms and [redacted] in the interferon β-1a arms).

3.3.5 Freedom from disease activity

Two outcomes relating to freedom from disease activity were measured in the OPERA trials:

- proportion of patients with no evidence of disease activity (NEDA)
- proportion of patients who remained relapse-free

Of these, only NEDA is reported in the CS. The proportion relapse-free is provided in the OPERA CSRs (and summarised in the CADTH appraisal of ocrelizumab[25]).

Proportion with NEDA

The statistical testing hierarchy had been stopped before the evaluation of no evidence of disease activity (NEDA) in both OPERA trials and so this outcome should be interpreted as being descriptive. The results presented in the CS are differ slightly from those given in the trial publication for this outcome, with the results presented in the CS being based on a smaller sample size, although an explanation is not provided. Both sets of data show that a greater proportion of patients treated with ocrelizumab than with interferon β-1a achieved NEDA at week 96 in both OPERA trials (Table 26).

Table 26 Proportion of patients with no evidence of disease activity (NEDA) by week 96

Trial	Data source	Ocrelizumab		Interferon β-1a		Mean difference (MD) or relative risk (RR) (95% CI) [b]
		N [a]	Proportion (%) (95% CI) with NEDA	N [a]	Proportion (%) (95% CI) with NEDA	
OPERA I	Publication[45]	382	47.9	384	29.2	MD 64 (36 to 98); p<0.001 [c]
	CS Table 11	289	47.4 (41.5 to 53.3)	291	27.1 (22.1 to 32.6)	RR 1.74 (1.39 to 2.17); P<0.0001 [c]
OPERA II	Publication[45]	379	47.5	375	25.1	MD 89 (54 to 132); p<0.001 [c]
	CS Table 11	289	43.9 (38.1 to 49.9)	270	24.1 (19.1 to 29.6)	RR 1.81 (1.41 to 2.32); P<0.0001 [c]

[a] Subgroup with baseline EDSS >2; trial publication states that the analysis excluded patients who were withdrawn for reasons other than efficacy failure or death and who did not have clinical disease activity at the time of treatment discontinuation in the trial.
[b] Adjusted by baseline EDSS score (<4.0 vs ≥4.0) and geographical region (US vs rest of world).
[c] P-value is descriptive only, as preceding outcome in the testing hierarchy was not statistically significant.

The CADTH appraisal of ocrelizumab[25] reports that a pooled analysis of NEDA across both the OPERA trials and a sensitivity analysis in the ITT population both demonstrated consistent results with those reported for the EDSS >2.0 subgroup (these analyses are not referred to in the CS).

Proportion relapse-free

The proportion of patients who remained free of relapses at 96 weeks is not reported in the CS or trial publication. According to the CADTH appraisal of ocrelizumab,[25] the proportion was higher in the ocrelizumab group than in the interferon β-1a group in both trials (OPERA I: 80.4% versus 66.7%; OPERA II: 78.9% versus 64.3%). Relative risks were 1.20 (95% CI 1.10 to 1.31) in OPERA I and 1.23 (95% CI 1.12 to 1.35) in OPERA II (both p<0.0001).

The proportion of patients relapse-free at 24 weeks was a secondary outcome in the ocrelizumab phase II trial. According to the phase II trial publication,[44] the differences numerically favoured ocrelizumab (87%) over placebo (76%) and interferon β-1a (78%) but were not statistically significant (confirmed by the company in clarification A7b).

3.3.6 All-cause discontinuation

The NICE scope does not specify all-cause discontinuation as an outcome, but this outcome informs the company's economic model (section 4.3.4.3). A summary of all-cause discontinuation pooled across the OPERA trials is provided in Table 27, for the ITT analysis

population and also for the HA and RES disease activity subgroups (from the company's response to clarification A9). The proportion of patients who discontinued due to any cause was higher in the ocrelizumab arms than the interferon β-1a arms. This was consistent across the ITT population and disease activity subgroups, although not statistically significant in the subgroups.

Table 27 All-cause discontinuation in the pooled OPERA trials

Analysis group	Ocrelizumab			Interferon β-1a			Odds ratio (95% CI)	Inter-action test p-value
	N	Events	% events	N	Events	% events		
HA	140	28	20.0	143	18	12.6	0.58 (0.30 to 1.11); p=0.1000	0.8508
RES	140	26	18.6	150	17	11.3	0.56 (0.29 to 1.10); p=0.0913	0.8989
Non-HA/RES	567	117	20.6	556	69	12.4	0.54 (0.39 to 0.75); p=0.0003	-
ITT	829	169	20.4	827	101	12.2	0.54 (0.41 to 0.71); p<0.0001	-

From clarification A9

3.3.7 MRI outcomes

The NICE scope does not specify any MRI outcomes to be assessed and the MRI outcomes reported by the company do not inform their economic analysis. Only a brief summary of these outcomes is therefore provided here.

Four MRI outcomes were measured in the OPERA trials:

- Cumulative number of T1 enhancing lesions over 96 weeks, which indicate sites of active MS inflammation;
- Total number of new or newly-enlarged T2 hyperintense lesions over 96 weeks, which indicate areas of active or previous inflammation;
- Total number of T1 hypointense lesions over 96 weeks, which indicate areas of chronic irreversible MS damage;
- Change in brain volume, which indicates extensive structural damage resulting from MS and may be present even in the early stages of the disease.

The mean numbers of all three types of lesion were statistically significantly lower in the ocrelizumab arm than the interferon β-1a arm over 96 weeks in both OPERA trials (CS Table 11). The rate ratios (95% CI) were 0.058 (0.032 to 0.104) in OPERA I and 0.051 (0.029 to 0.089) in OPERA II for enhancing T1 lesions; 0.229 (0.174 to 0.300) in OPERA I and 0.171 (0.130 to 0.225) in OPERA II for new and/or enlarged hyperintense T2 lesions; and 0.428 (0.328 to 0.557) in OPERA I and 0.357 (0.272 to 0.470) in OPERA II for hypointense T1 lesions (all differences $p<0.0001$).

Brain volume decrease over 24 to 96 weeks was less in the ocrelizumab arm than the interferon β-1a arm, although the difference was statistically significant only in OPERA I; and this outcome was considered to be descriptive since preceding outcomes in the statistical testing hierarchy were not significant.

The ocrelizumab phase II trial reported the total number of T1 enhancing lesions (primary outcome), number of new T1 enhancing lesions, and number of new or enlarging T2 lesions (secondary outcomes). According to the study publication,[44] at 24 weeks there were fewer of all three types of lesion in the ocrelizumab arm compared to the placebo and interferon β-1a (Avonex) arms. These differences between ocrelizumab and placebo were all statistically significant, and the difference between ocrelizumab and interferon β-1a was also statistically significant for the primary outcome (not reported for the secondary outcomes).

The MRI outcomes together indicate that ocrelizumab is effective at reducing clinical disease activity compared to interferon β-1a and placebo. A caveat is that the MRI outcomes in the OPERA trials suffer from missing data which was unbalanced between the study arms (see Table 9) and the impact of this on the results is unclear.

3.3.8 Mixed Treatment Comparison results

Results of the base case (ITT) MTC analyses are summarised below in section 3.3.8.1 and the results of MTC subgroup and sensitivity analyses are summarised in section 3.3.8.2.

3.3.8.1 Base case analyses

Results of the base case (ITT) MTC analyses of ARR, CDP-12, CDP-24 and all-cause discontinuation are summarised in Table 28. Shaded cells in the table indicate where the outcome statistic (i.e., rate ratio, hazard ratio or odds ratio) is not statistically significant, i.e. where the 95% CrI crosses 1.0.

Table 28 MTC analysis results for ITT populations

OCB 600mg versus:	ARR Rate ratio (95% CrI)	CDP-12 Hazard ratio (95% CrI)	CDP-24 Hazard ratio (95% CrI)	All-cause discont. Odds ratio (95% CrI)
ALEM 12 mg	[redacted]	[redacted]	[redacted]	[redacted]
CLAD 3.5mg/kg				
CLAD 5.25mg/kg				
DAC 150 mg, q4w				
DMF 240 mg, bid				
FINGO 0.5 mg, qd				
GA 20 mg, qd				
GA 40 mg, tiw		No data	No data	No data
IM IFNβ-1a 30 µg, qw (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 22 µg, tiw (Rebif)	No data	[redacted]	No data	[redacted]
SC IFNβ-1a 44 µg, tiw (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]
SC IFNβ-1b 250 µg, eod	[redacted]	[redacted]	No data	[redacted]
PEGβ-1a 2W 125 µg, q2w	[redacted]	[redacted]	[redacted]	[redacted]
NAT 300 mg, q4w	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
TERI 7 mg, qd				
TERI 14 mg, qd				
Data sources	CS Appendices Table 14	CS Appendices Table 17	CS Appendices Table 20	CS Appendices Table 23

bid: twice per day; eod: every other day; qd: once per day; qw; once per week; q2w: every 2 weeks; q4w: every 4 weeks; tiw: three times per week
Shaded cells indicate the outcome is not statistically significant (i.e. the 95% CrI includes 1.0)

[redacted]

[redacted]. Ocrelizumab was most effective at reducing ARR, CDP-12 and CDP-24 when compared against

[redacted] (Table 28).

3.3.8.2 Subgroup and sensitivity analyses

As explained above, the company conducted several sensitivity and subgroup analyses in the MTC:

- comparison of full and restricted networks and inclusion/exclusion of the INCOMIN trial (see section 3.1.7.1);
- comparison of fixed-effect model results against random-effects models which had two different vague priors (see section 3.1.7.4);
- comparison of the ITT population and HA and RES subgroups (see section 3.1.7.1).

Full versus restricted networks

Forest plots reported in Figures 8, 13, 19 and 24 in CS Appendix D show that the company's two analyses which excluded "non-NICE comparators" from the networks [redacted] on the ARR, CDP-12, CDP-24 and all-cause discontinuation outcomes when compared to the base case ITT analysis results. Inclusion [redacted] of the INCOMIN trial [redacted] the MTC results for CDP-24 (the only relevant MTC outcome assessed in the INCOMIN trial) (Figure 19 in CS Appendix D).

Fixed versus random effects models

For each of the ARR, CDP-12, CDP-24 and all-cause discontinuation outcomes, forest plots reported in Figures 4, 9, 14 and 20 in CS Appendix D show that the two random-effects analyses with informative and vague priors [redacted]; and the fixed-effects analysis [redacted]. The differences between the fixed and random effects confidence intervals would not influence the interpretation of statistical significance given above, except perhaps for those comparisons where the random-effects 95% confidence interval barely overlaps 1.0.

HA and RES disease activity subgroups

For each of the ARR, CDP-12 and CDP-24 outcomes, forest plots reported in CS Figures 11, 16 and 21 show that the HA and RES subgroups [redacted]. The CS does not provide numeric estimates of the rate ratios and hazard ratios other than as depicted graphically in the forest plots. Due to limitations in the data the disease activity subgroups were not analysed for all-cause discontinuation. As mentioned above (section 3.1.7.6) the HA and RES subgroup results for ARR, CDP-12 and CDP-24 should be interpreted with caution due to sparsity of data, the

fact that they are post hoc subgroups extracted from the trials, and the observational nature of the data.

3.3.9 Adverse events

The CS reports adverse events in the OPERA trials in CS section B.2.10. Some additional detail is given in the trial publication[45] for infusion-related reactions, herpes infections, and neoplasms during the 96 weeks of the randomised trials. The CS does not report adverse events for the OPERA OLE study, but these were provided by the company in response to a clarification request from the ERG (clarification A28). Adverse events in the OPERA trials and OLE study are summarised below in section 3.3.9.1.

Adverse events in the phase II trial are reported up to 48 weeks in CS Appendix F and the trial publication.[44] On request from the ERG, the company provided a summary of adverse event rates in the trial up to 96 weeks (clarification A7b) which are summarised below in section 3.3.9.2.

3.3.9.1 Adverse events in the OPERA trials and OLE study

OPERA trials up to 96 weeks

In both OPERA trials the proportion of patients who experienced at least one adverse event was similar in the ocrelizumab and interferon β-1a arms, although slightly higher in OPERA II (ca 80%) than OPERA I (ca 86%). The proportion experiencing at least one serious adverse event was also similar in both arms, for both trials (range 7% to 10%). Rates of discontinuation due to adverse events were low, but half as many patients receiving ocrelizumab discontinued due to an adverse event (3%) compared to those receiving interferon β-1a (6%) (Table 29).

The main differences in adverse events between the trial arms were for infusion-related reactions (IRR) which were more frequent among patients receiving ocrelizumab; and influenza-like illness and injection site reactions which were more frequent among those receiving interferon β-1a (Table 30).

The proportion with at least one IRR ranged from 31% to 38% in the ocrelizumab arms, and from 7% to 12% in interferon β-1a arms, with the proportions being slightly higher in OPERA II than in OPERA I. The majority of IRR were mild (18% to 25% in the ocrelizumab arms; 5% to 8% in the interferon β-1a arms) and moderate (9% to 11% in the ocrelizumab arms; 2% to 3% in

the interferon β-1a arms). Only one life-threatening IRR occurred (bronchospasm), in the ocrelizumab arm of OPERA I (Table 29). Infusion-related reactions led to the withdrawal of 11 ocrelizumab-treated patients (1.2% to 1.5%) compared with no patients who received the placebo infusion, and no cases of anaphylaxis occurred in the trials.

The most commonly reported symptoms associated with IRR adverse events in the ocrelizumab arms were pruritus, rash, throat irritation, and flushing. According to the trial publication, [45] the first 300 mg dose of ocrelizumab was associated with the highest proportions of patients with an IRR (27.5%), which decreased to 4.7% following the second 300 mg infusion (day 15). For the first infusion of the full 600 mg ocrelizumab dose, 13.8% of patients had at least one IRR, and this proportion decreased for subsequent doses.

A relatively high proportion of patients in both arms of both trials had infections (53% to 60%) but this is not discussed in the CS.

Table 29 Summary of adverse events in the OPERA trials

Event, n (%)	OPERA I		OPERA II	
	Ocrelizumab (n=408)	Interferon β-1a (n=409)	Ocrelizumab (n=417)	Interferon β-1a (n=417)
Any AE	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Any serious AE	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)
AE leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction (IRR)	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Mild IRR	73 (17.9)	22 (5.4)	106 (25.4)	35 (8.4)
Moderate IRR	38 (9.3)	8 (2.0)	45 (10.8)	14 (3.4)
Severe IRR	14 (3.4)	0	6 (1.4)	1 (0.2)
Life-threatening IRR	1 (0.2)	0	0	0
Infection (MEDRA definition) [a]	232 (56.9)	222 (54.3)	251 (60.2)	219 (52.5)
System organ class infection or infestation	231 (56.6)	216 (52.8)	251 (60.2)	217 (52.0)
Herpes zoster	9 (2.2)	4 (1.0)	8 (1.9)	4 (1.0)
Oral herpes	9 (2.2)	8 (2.0)	15 (3.6)	9 (2.2)
Herpes simplex	4 (1.0)	1 (0.2)	3 (0.7)	1 (0.2)
Neoplasm	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death	0	1 (0.2)	1 (0.2)	1 (0.2)

Source: CS Table 18 and trial publication

AE, Adverse events; IFNβ-1a, Interferon β; NR, Not reported; OCR, Ocrelizumab; SOC, System organ class.

[a] Defined in the Medical Dictionary for Regulatory Activities infections system organ class “infections and infestations” or as an adverse event with pathogen information provided.

The company’s economic model utilises adverse events data for those events that occurred at a frequency of at least 5% in any trial arm (section 0). For the majority of these, the difference between trial arms in the proportion of patients affected was less than 5% (Table 24). In the pooled adverse events data across both OPERA trials, events which occurred in at least 5% of patents in any arm and also differed by at least 5% between the arms were IRRs (ocrelizumab 34%, interferon β-1a 10%), influenza-like illness (ocrelizumab 5%, interferon β-1a 21%), and injection-site erythema (ocrelizumab 0.1%, interferon β-1a 15%) (Table 24).

Table 30 Adverse events reported in ≥ 5% of patients up to 96 weeks in the OPERA trials

Event, n (%)	OPERA I & II [a]	
	Ocrelizumab (n=825)	Interferon β-1a (n=826)
Total number of patients with at least one AE occurring at relative frequency ≥5%	544 (65.9)	539 (65.3)
Infusion related reactions	283 (34.3)	80 (9.7)
Headache	93 (11.3)	124 (15.0)
Influenza-like illness	38 (4.6)	177 (21.4)
Upper respiratory tract infection	125 (15.2)	87 (10.5)
Nasopharyngitis	122 (14.8)	84 (10.2)
Urinary tract infection	96 (11.6)	100 (12.1)
Fatigue	64 (7.8)	64 (7.7)
Injection site erythema	1 (0.1)	127 (15.4)
Depression	64 (7.8)	54 (6.5)
Arthralgia	46 (5.6)	51 (6.2)
Sinusitis	46 (5.6)	45 (5.4)
Back pain	53 (6.4)	37 (4.5)
Insomnia	46 (5.6)	38 (4.6)
Bronchitis	42 (5.1)	29 (3.5)
Injection site reaction	2 (0.2)	45 (5.4)

Source: CS Table 21

The company noted that herpes virus infections were more common in patients receiving ocrelizumab, although as can be seen in Table 29 the difference in frequency between trial arms was relatively small. No cases of progressive multifocal leukoencephalopathy were reported in patients who had been treated with ocrelizumab.

Neoplasms

During the 96-week trial duration, four neoplasms occurred in the ocrelizumab arms (2 breast carcinoma, 1 renal cell carcinoma, 1 malignant melanoma) and two occurred in the interferon β-1a arms (1 mantle cell lymphoma, 1 squamous cell carcinoma). The trial publication[45] reports that between the clinical cutoff dates of the two trials (April-May 2015) and June 2016, five further cases of neoplasm were detected during the OLE study, during which all the patients received ocrelizumab. (2 breast cancer, 2 basal-cell skin carcinoma, 1 malignant melanoma). Based on an overall analysis of all the company's MS trials up to June 2016, the overall neoplasm incidence was 0.40 per 100 patient-years of exposure to ocrelizumab, compared to 0.2 per 100 patient-years in groups receiving interferon β-1a or placebo. The company concludes (CS section B.2.13) that the neoplasms observed in the OPERA I and OPERA II

trials need further investigation in terms of the epidemiology of neoplasm in the population of patients with MS and long term experience with ocrelizumab and other anti-CD20 treatments.

Mortality

The mortality rate in the OPERA trials was low, with only three deaths recorded among the 1651 trial participants, one in each arm of OPERA II and one in the interferon β-1a arm of OPERA I. The deaths were not considered to be treatment-related.

Anti-drug antibodies

The CS reports the baseline prevalence and post-baseline incidence of anti-drug antibodies (ADA) to ocrelizumab and interferon β-1a (CS Table 22). The company confirmed that the tests for ADA were conducted at 6-monthly intervals during the OPERA trials (clarification A26). The incidence of treatment-induced ocrelizumab ADA antibodies during the 96-week trial period was low (3/807 tested patients; 0.4%) and was similar to the baseline prevalence (5/798 tested patients; 0.6%). Of the three patients who had treatment-induced ADA in the ocrelizumab arm, only one tested positive for neutralizing antibodies to ocrelizumab.

Opera OLE

The CS does not report adverse events for the OLE study. In response to a request from the ERG (clarification A28) the company provided a summary of the numbers of adverse events per 100 patient-years of exposure to ocrelizumab experienced, for patients exposed to ocrelizumab in the core OPERA trials and in the OLE study up to the latest clinical data cut-off, 17th February 2017. This included 2301 patients who were exposed to any part of an ocrelizumab dose, and the mean number of doses received was 7.3.

The total (95% CI) number of events per 100 patient-years was:

- OPERA trials: 289.66 (280.95 to 298.56);
- OPERA trials + OLE study up to 20th January 2016: 241.65 (237.63 to 245.72);
- OPERA trials + OLE study up to 17th February 2017: 225.70 (222.37 to 229.07).

These data show that overall rates of adverse events declined during the OLE study. The company also provided corresponding event rates for deaths, serious adverse events, serious infections, and infusion-related reactions leading to withdrawal at the first infusion (clarification A28; not reproduced here). The company concluded in their clarification response that deaths,

serious AEs and serious infections had stable event rates during the OLE study, and showed no increase compared with the controlled treatment periods, although rates of infusion-related reactions decreased as expected. As at February 2017, no serious confirmed opportunistic infections had been reported. The ERG agrees that the company's interpretation of overall adverse event rates in the OLE study appears reasonable, although numbers of individual adverse events were not provided.

3.3.9.2 Adverse events in the phase II trial

The phase II trial consisted of an initial 24-week randomised comparison of ocrelizumab 600mg, interferon β-1a (Avonex) and placebo, after which (weeks 24 to 96) patients in these groups all received ocrelizumab 600mg.

Adverse events in the phase II trial are reported up to 48 weeks in CS Appendix F and the trial publication,[44] whilst overall adverse event rates up to 96 weeks were provided by the company upon request from the ERG (clarification A7b). These data are summarised below.

Adverse events up to 48 weeks

Adverse events are reported separately for the 0-24 weeks randomised phase and the 24-48 weeks non-comparative period.

Weeks 0 to 24

The proportion of patients with any adverse event was lower in the ocrelizumab arm (62%) than the placebo arm (70%), and the proportion with treatment-related adverse events was also lower among patients receiving ocrelizumab (31%) than those receiving placebo (46%). Two patients (4%) had to withdraw due to adverse events in the ocrelizumab arm compared to one (2%) in the interferon β-1a arm, and none in the placebo arm. A larger proportion of patients receiving ocrelizumab than interferon β-1a had at least one infection (42% versus 20%), but the rate in the ocrelizumab group was comparable with the placebo group (41%). Overall, the adverse event profile during the randomised treatment comparison is consistent with that of the OPERA trials (likely reflecting the shorter duration of the phase II study).

Weeks 24 to 48

Following the switch to ocrelizumab in the interferon β-1a and placebo arms, the proportions of patients with the various types of adverse event remained generally similar to those observed in

the ocrelizumab arm during weeks 0 to 24. As would be expected, the proportion of patients with IRR at the start of cycle 2 was higher among patients previously on interferon β-1a (30%) or placebo (42%) than those who had already received ocrelizumab (16%).

Neoplasms

The CS (Appendix F) and trial publication do not mention whether any neoplasms occurred during the overall 48 weeks of the phase II trial, although the incidence of neoplasms is captured in an analysis of the cancer risk across all of the company's trials (section 3.3.9.1 above).

Mortality

No deaths occurred in the three study arms during the overall 48 weeks of study.

Anti-drug antibodies

CS Appendix F reports the incidence of human antihuman antibodies. It is not specified whether the data provided for each trial arm are for antibodies against ocrelizumab and/or against interferon β-1a (both of which were reported for the OPERA trials above), although it seems reasonable to assume that all the data in Table 29 of CS Appendix F refer to ocrelizumab. The data show that the incidence rates of the ADA in patients who received ocrelizumab were 0% at week 12, 2.7% at week 24, and 0% at week 48, which are similar to or within the baseline prevalence rate (2%). The highest incidence of ADA (2/31 patients tested; 6.5%) was at week 24 in patients who were receiving interferon β-1a.

Adverse event rates up to 96 weeks

Total event rates were provided by the company for adverse events and serious adverse events (clarification A7b). These indicate that overall rates of adverse events generally decreased in the three study groups during 96 weeks of treatment (Table 32). Rates of serious adverse were highest in cycle 3, affecting a maximum of four patients (8%) in the group who had received interferon β-1a in cycle 1, before declining again in cycle 4. No data on frequencies of specific adverse events over 96 weeks were provided by the company. The company concluded (clarification A7b) that the adverse event profile of ocrelizumab during the open label treatment period up to week 96 was consistent with observations during the first 24 weeks. The ERG agrees is a reasonable conclusion regarding overall event rates but we would have preferred to see more detailed data on the specific types of adverse events that occurred.

Table 31 Summary of adverse events up to 48 weeks in the phase II trial

Outcome n (%) of patients with	Week	Ocrelizumab (n=55)	Interferon β-1a (Avonex) (n=54)	Placebo (n=54)
Any AE	0 to 24	34 (61.8)	30 (55.6)	38 (70.4)
	24 to 48	26 (52.0)	30 (60.0)	36 (67.9)
Serious AE	0 to 24	1 (1.8)	2 (3.7)	2 (3.7)
	24 to 48	1 (2.0)	3 (6.0)	1 (1.9)
AE leading to withdrawal	0 to 24	2 (3.6)	1 (1.9)	0
	24 to 48	0	1 (2.0)	0
Any treatment-related AE (TRAE)	0 to 24	17 (30.9)	19 (35.2)	25 (46.3)
Most common TRAE: Influenza-like illness		0	10 (18.5)	0
Headache		1 (1.8)	5 (9.3)	3 (5.6)
Urinary tract infection		3 (5.5)	1 (1.9)	5 (9.3)
Upper respiratory tract infection		4 (7.3)	0	2 (3.7)
Nasopharyngitis		1 (1.8)	3 (5.6)	2 (3.7)
Chills		1 (1.8)	3 (5.6)	0
MS relapse		1 (1.8)	0	3 (5.6)
Oral herpes		1 (1.8)	0	3 (5.6)
Any treatment-related AE (TRAE)	24 to 48	7 (14.0)	7 (14.0)	13 (24.5)
Most common TRAE: Urinary tract infection		0	0	3 (5.7)
Headache		1 (2.0)	2 (4.0)	2 (3.8)
Nausea		0	2 (4.0)	0
Upper respiratory tract infection		0	1 (2.0)	2 (3.8)
Respiratory tract infection		1 (2.0)	1 (2.0)	2 (3.8)
Any infection	0 to 24	23 (41.8)	11 (20.4)	22 (40.7)
	24 to 48	17 (34.0)	13 (26.0)	16 (30.4)
Serious infection	0 to 24	0 (0)	0 (0)	1 (1.9)
	24 to 48	1 (2.0)	1 (2.0)	1 (1.9)
Infusion-related reactions: Cycle 1 Day 1		19 (34.5)	-	5 (9.3)
Cycle 1 Day 15		2 (3.8)	-	6 (11.1)
Cycle 2 Day 1		8 (16.0)	15 (30.0)	22 (41.5)
Cycle 2 Day 15		1 (2.0)	1 (2.1)	2 (3.8)

Source: CS Appendix F

Table 32 Overall adverse event rates up to 96 weeks in the phase II trial

Assessment time	Outcome	Ocrelizumab [a]	Interferon β-1a	Placebo
Weeks 0 to 24 (cycle 1)	**Safety population**	**n=55**	**n=54**	**n=54**
	Patients with AE, n (%)	35 (63.6)	32 (59.3)	38 (70.4)
	Number of AE	116	91	117
	Patients with SAE, n (%)	1 (1.8)	2 (3.7)	2 (3.7)
Weeks 24 to 48 (cycle 2)	**Safety population**	**n=50**	**n=50**	**n=53**
	Patients with AE, n (%)	27 (54.0)	30 (60.0	38 (71.7)
	Number of AE	74	66	88
	Patients with SAE, n (%)	1 (2.0)	3 (6.0)	1 (1.9)
Weeks 48 to 72 (cycle 3)	**Safety population**	**n=49**	**n=49**	**n=50**
	Patients with AE, n (%)	24 (49.0)	19 (38.8)	25 (50.0)
	Number of AE	53	46	43
	Patients with SAE, n (%)	3 (6.1)	4 (8.2)	1 (2.0)
Weeks 72 to 96 (cycle 4)	**Safety population**	**n=46**	**n=46**	**n=49**
	Patients with AE, n (%)	21 (45.7)	16 (34.8)	24 (49.0)
	Number of AE	34	28	42
	Patients with SAE, n (%)	-	2 (4.3)	-

Source: Company clarification A7b

[a] Data for ocrelizumab 600mg (data for ocrelizumab 2000mg group not reproduced here)

In their clarification the company mentioned that following the 96 weeks of ocrelizumab in the phase II trial there was a treatment-free period of variable duration (minimum 48 weeks). Patients who completed both the main (96-week) treatment period and the treatment-free period were invited to participate in an open label extension study during which they received ocrelizumab 600 mg every 24 weeks (clarification A7b). The company stated that due to the low number of patients that entered the open-label extension study and the fact that selection bias cannot be excluded, data should be interpreted with caution. According to the company, no new safety findings were identified during the treatment-free or open-label extension periods; no increase in the rate or incidence of infections or serious infections was observed compared with the main 96-week treatment period; and the IRR profile observed during the open-label extension was consistent with the main 96-week treatment period in terms of severity and nature of symptoms. No data were provided in support of these specific conclusions.

3.3.9.3 Summary of safety issues

Overall, the safety data provided by the company suggests that the most frequent adverse events experienced by patients receiving ocrelizumab are generally similar to those experienced by patients receiving interferon β-1a (either as Rebif or Avonex), including headache, upper respiratory tract infection, nasopharyngitis, urinary tract infection and fatigue. Ocrelizumab is not associated with the influenza-like symptoms and injection-site reactions typical of interferon β-1a and slightly fewer patients on ocrelizumab seem to experience headache than those receiving the interferon β-1a. IRR are a common problem with ocrelizumab but typically decrease after the first infusion. Across the company's trials the prevalence of neoplasms among patients receiving ocrelizumab is low, but it is higher than among patients receiving interferon β-1a or placebo, which warrants further investigation in the longer term. The baseline prevalence and post-baseline incidence of anti-drug antibodies were low in the OPERA trials (<1%), although slightly higher in the phase II trial (maximum 6.5%). The ERG agrees with the company's assertion that ocrelizumab has a generally favourable safety profile compared to the β-interferons. Based on the aggregate data, no new safety issues appear to have arisen in the longer-term phases of the trials compared to the randomised comparison periods.

4 COST EFFECTIVENESS

4.1 Overview of the company's economic evaluation

The company's submission to NICE includes:

- A review of published economic evaluations of ocrelizumab compared with other DMTs or placebo for adults with RRMS (CS Section B.3.1).

- A report of an economic evaluation undertaken for the NICE STA process, comparing ocrelizumab with the following comparators in patients with RRMS: IFNβ-1a (Avonex, Rebif), IFNβ-1b, PEGβ-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, natalizumab, daclizumab (CS Section B3.2).

4.2 Company's review of published economic evaluations

The company conducted a systematic search to identify economic evaluations of DMTs for multiple sclerosis. This broad review was conducted to inform economic modelling and HTA across multiple countries. Details of the review methods are reported in CS Appendix G. It included economic evaluations (cost-utility, cost-effectiveness, cost-benefit and cost-minimisation studies) of selected disease modifying therapies (IFNβ-1a, IFNβ-1b, GA, natalizumab, fingolimod, teriflunomide, alemtuzumab or DMF) in comparison with any active treatment or placebo, for adults (age ≥ 18 years) diagnosed with multiple sclerosis, with a primary focus on RRMS, SPMS and PPMS. The search was conducted in March 2016 and updated in March 2017, and included the MEDLINE, Embase, Cochrane Library and EconLit databases, as well as supplementary searches of reference lists, conference proceedings, websites and HTA documents. In total, the initial review and update included 55 full publications, covering 53 unique economic evaluations. The PRISMA diagram is shown in Figure 42 of CS Appendix G. The company lists excluded papers but not those that were included, and no further details are given about the overall nature or quality of the included studies.

The main text of the CS (section B.3.1) reports that 33 unique studies relating to RRMS as well as 7 previous NICE appraisals were identified from the systematic review, but that none of these related to modelling the cost-effectiveness of ocrelizumab.

The ERG has identified two more recent papers reporting economic analyses of ocrelizumab compared with INFβ-1a, based on results from the OPERA I and II trials. The Yang et al. study was funded by Genentech and used a model with the same structure as the submitted model

and many of the same assumptions.[63] They reported that over a 20-year time horizon and discounted at 3% per year, ocrelizumab would yield an estimated 14.557 life years and 6.826 QALYs, compared with 14.511 life years and 6.270 QALYs with INFβ-1a: a gain of 0.046 life years and 0.556 QALYs. Ocrelizumab was estimated as cost-saving compared with IFNβ-1a, although the cost results are not relevant for this appraisal because they are based on US costs and resource use. The other study by Frasco et al., also funded by Genentech, used a different model structure and longer time horizon (30 years), yielding a larger estimate of the QALY gain: 0.84 for ocrelizumab vs. INFβ-1a.Frasco, Shih (64)

The company did report a published health technology assessment prepared by the Institute for Clinical and Economic Review for the California Technology Assessment Forum (CTAF) on DMTs for MS, including ocrelizumab for relapsing disease.[24] This included a systematic review and MTC of clinical evidence and a cost-effectiveness model. The basic structure of the CTAF HTA model was similar to the company's submitted model: with 20 basic health states, EDSS 0–9 for RRMS, EDSS 1–9 for SPMS and death. However, there were some differences in assumptions and parameter sources. For example, the CTAF HTA modelled a new-onset, treatment-naïve RRMS population from age 29 years, whereas the company model started with an older population (age 37 years), some previously-treated. The CTAF HTA model assumed second-line treatment (evenly split between other commonly-used drugs) after discontinuation of initial treatment, whereas the company assumed that patients would move directly to best supportive care. Another difference was that the CTAF HTA did not assume discontinuation of treatment following conversion to SPMS. The CTAF base case results indicated that ocrelizumab is the second most effective treatment, with 10.94 QALYs over a lifetime, following a maximum of 12.46 QALYs for alemtuzumab. The analysis was conducted from a US healthcare payer perspective and the price of ocrelizumab was not available at the time of analysis, so the cost and cost-effectiveness results are not relevant for the NICE appraisal.

In summary, there are no published analyses that provide cost-effectiveness estimates that are relevant to the current appraisal. However, the modelled estimates of QALYs from the CTAF assessment report and the analyses based on the OPERA trials by Yang et al. and Frasco et al. provide a basis to cross-check the results of the submitted model. We discuss this further in section 4.3.5 below.

4.3 Summary and critique of the company's model

4.3.1 NICE reference case

Table 33 summarises the ERG assessment of whether the CS meets the NICE reference case requirements. We conclude that it does, but note that cost-effectiveness estimates are not presented for the whole population and all patient subgroups requested by NICE. We discuss this in section 4.3.2 below.

The company does not present results for all comparators in the scope. They exclude daclizumab, arguing that it is not an appropriate comparator due to the EMA alert regarding its safety.[16] Alemtuzumab is also excluded from results for the HA and RES subgroups. The main text of the CS only presents results for the β-interferon drugs (including pegylated β-interferon) and glatiramer acetate together in a 'blended ABCR' comparator. However, results for the IFNβ-1a (Avonex an Rebif), IFNβ-1b, PEGβ -1a and GA are presented in Appendix J.1.2 of the CS, and the model does include all comparators. The CS also presents results for some out of scope indications: natalizumab and fingolimod are included in the main ITT analysis, although they are only recommended for HA and RES subgroups. We discuss comparators further on page 118 below.

In line with the NICE reference case, costs are estimated for health care funded by the NHS and social care funded by local authority personal social service departments. The model includes the facility to exclude non-medical (social care) costs and to include loss of wages (productivity costs), but these options are not used in results presented in the CS.

Table 33 NICE reference case requirements

NICE reference case requirements:	Included in the CS	Comment
Decision problem: As per the scope developed by NICE	Yes	Four subgroups not modelled: • Active SPMS • Inadequate response to previous treatment • Intolerance to previous treatment • Contraindicated to or unsuitable for alemtuzumab
Comparator: As listed in the scope developed by NICE	Yes	Separate 'ABCR' drugs in Appendix J. Daclizumab results not presented in the CS, but available in model
Perspective on costs: NHS and PSS	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	Utility loss for carers is included, as in previous appraisals of DMTs for MS
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	50 years
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life.	Yes	
Source of data for measurement of health-related quality of life: Reported directly by patients and/or carers.	Yes	
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% per year for costs and health effects	Yes	

4.3.2 Decision problem

4.3.2.1 Population

Ocrelizumab is licensed for treatment of adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features.[EMA] This matches the NICE scope for this appraisal.

The company used baseline characteristics of patients from the pooled OPERA I and II trials to define the age (mean 37), gender (34% male) and EDSS distribution of the cohort in their model (CS section B.3.3). Disease type (RRMS/SPMS) at baseline was not collected in these trials, but the company estimate that upwards of 90% of patients in the OPERA trials could be considered to have RRMS, based on a post-hoc analysis using 'disease progression unrelated to relapses' as a proxy for SPMS (CS section B1.1). They conclude that evidence of the effectiveness of ocrelizumab is only available for the RRMS population (CS section B.3.2.2). The model is therefore tailored for the RRMS population and results are not estimated for people with active SPMS.

We agree that the lack of baseline data on disease type in the OPERA trials makes it impossible to separate the clinical effects of ocrelizumab for RRMS from those for relapsing SPMS. However, it could be argued that the OPERA trials provide evidence for a mixed population of patients with relapsing forms of MS, albeit with a predominance of RRMS. Experts advising the ERG have suggested that, given its mode of action, ocrelizumab would be expected to reduce inflammatory relapses in patients with active SPMS, although it would not prevent disability progression due to neurodegeneration.

4.3.2.2 Subgroup analysis

Disease activity groups

The NICE scope distinguishes four subgroups based on disease activity:

1. Relapsing-remitting multiple sclerosis
2. Rapidly-evolving severe RRMS (RES)
3. Highly-active RRMS despite previous treatment (HA)
4. SPMS with active disease, evidenced by relapses (Active SPMS)

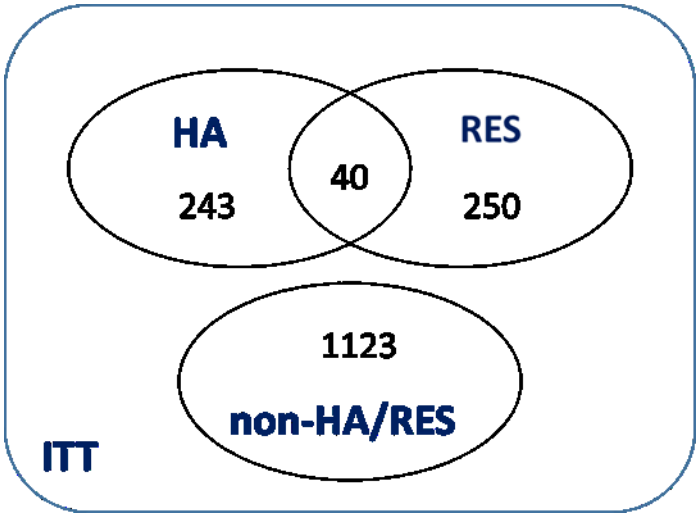
Comparators differ between groups 1 to 4 (see Table 34), so it is necessary that they are modelled separately. This suggests that, although labelled as 'relapsing-remitting multiple sclerosis', the first group should exclude people with RES or HA disease (because they are not

eligible for all of the same comparators). Group 1 above is therefore better thought of as 'non-HA/RES' RRMS.

The company reports economic analyses for three RRMS groups (CS section B.3.2.2):

- people with RRMS (labelled 'ITT' in the CS)
- people with RES RRMS
- people with HA RRMS despite previous treatment

The ITT group is modelled using clinical effectiveness results from the MTC for all randomised patients analysed by ITT, and natural history data for the whole RRMS population. It therefore incorporates the RES and HA subgroups. Despite this, the CS presents economic results for the ITT population including comparators that are not appropriate for RES or HA (interferon-beta, glatiramer acetate, teriflunomide and dimethyl fumarate). The use of ITT estimates of effect might also bias the cost-effectiveness estimates for group 1 in the scope (non-HA/RES RRMS). In response to a clarification question (A9), the company provided additional analysis of the OPERA data for patients with non-HA/RES relapsing MS (Clarification question A9). The disposition of participants between the HA, RES and non-HA/RES subgroups is shown in Figure 4 below.



Adapted from the company's response to clarification question A9. The ERG corrected the number of participants in the HA and RES subgroups in the above graph to fit the tabulated results (CS Tables 13 to 15)

Figure 4 Disposition of OPERA participants by subgroup

The results of the non-HA/RES subgroup analysis are shown in Tables 6-9 in the clarification response. The effects of ocrelizumab on rates of disability progression (CDP-12 and CDP-24) and all-cause treatment discontinuation were very similar for ITT and non-HA/RES analyses. However, the estimated effect on the rate of relapses was lower in the non-HA/RES subgroup than in the ITT analysis: rate ratio for ARR 0.535 (0.435 to 0.659) for ITT vs. 0.691 (0.538 to 0.888) for non-HA/RES. Thus the cost-effectiveness of ocrelizumab compared with IFNβ-1a is likely to be worse for patients without HA or RES than is suggested in the company's base case results. We note that this is a post hoc analysis, conducted at the request of the ERG, and should be treated with caution. The effect of excluding patients with HA or RES from the comparisons with other DMTs is uncertain.

We do not have the non-HA/RES subgroup results for other trials included in the MTC, thus it is not possible to adapt the company model to do a full comparative analysis for RRMS patients without HA or RES.

Other patient subgroups

The company do not present economic results for other subgroups in the scope:

5. People whose disease has responded inadequately to previous treatment
6. People who could not tolerate previous treatment
7. People in whom alemtuzumab is contraindicated or otherwise unsuitable

The company cite the lack of comparative data in the public domain for a MTC, as justification for not attempting economic analysis for these subgroups (CS section B.1.1). We agree that, since the clinical trial publications for the comparator DMTs did not consistently report whether trial participants were in any of these three subgroups, MTC networks would not have been feasible for these subgroups.

The company do note that there is some evidence relevant to the 'inadequate response' subgroup from the pooled OPERA data (CS Appendix E). Ocrelizumab was on average more effective for participants with active disease despite previous treatment for at least a year with interferon or glatiramer acetate, compared with the ITT results. However, the confidence intervals for this 'active inadequate responder' subgroup were wide and overlapped with those for the ITT population. There is also a lack of evidence for people with inadequate response to other comparators: as prior treatment with alemtuzumab, cladribine, daclizumab and

teriflunomide were exclusion criteria in the OPERA trials; and very few patients had been previously treated with natalizumab, fingolimod or dimethyl fumarate (CS section B.2.3). The company did not attempt subgroup analysis of the OPERA data for people who could not tolerate previous treatment or who were contraindicated or unsuitable for alemtuzumab.

In summary, the ERG accepts that separate economic analysis for the inadequate response, intolerance and contraindicated/unsuitable for alemtuzumab subgroups would not be feasible.

4.3.2.3 Comparators

The company's economic model includes all of the comparators specified in the scope for relapsing-remitting disease, see section B.3.2.3 of the CS. A summary of the availability of results for different comparators by subgroup is shown in Table 34 below.

Table 34 Treatments included in company economic analysis

Drug	*Availability of results by disease activity subgroup*			
	RRMS (ITT)	HA RRMS	RES RRMS	Active SPMS
Ocrelizumab	CS Tables 55/56	CS Table 66/67	CS Table 70/71	
Blended ABCR	CS Tables 55/56			
IFNβ-1a	Appendix J	Model only [a]	Model only [a]	
IFNβ-1b	Appendix J	Model only [a]	Model only [a]	
PEGβ -1a	Appendix J			
GA	Appendix J	Model only [a]	Model only [a]	
Teriflunomide	CS Tables 55/56			
DMF	CS Tables 55/56			
Fingolimod	CS Tables 55/56	CS Table 66/67	Model only [a]	
Alemtuzumab [b]	CS Tables 55/56	Model only [a]	Model only [a]	
Natalizumab	CS Tables 55/56		CS Table 70/71	
Daclizumab [c]	Model only [a]	Model only [a]	Model only [a]	
BSC				

Shaded cells indicate that drug is not included in scope for defined subgroup

[a] Not presented in company results, but available in model

[b] Results presented with and without alemtuzumab as comparator

[c] Additional restrictions in scope: where alemtuzumab is contraindicated to or otherwise unsuitable, and for patients with RES only if disease previously treated with DMT

Alemtuzumab

The company present their base case results including alemtuzumab (Table 56 page 127), but also report an analysis excluding alemtuzumab (Table 57, page 128). Their rationale for this is that it is important to maintain treatment choice because the "trade-offs between efficacy, safety, convenience, resource use and cost" mean that alemtuzumab will not be suitable for every patient (page 126). The CS does not report results for alemtuzumab in the HA and RES subgroups, because effects on disability progression were not available from the MTC for the CDP-12 measure, which the company use in their base case analysis (CS page 142). However, the model does allow calculation of subgroup results for alemtuzumab with the CDP-24 measure of progression, which we use as our base case.

Daclizumab

The company include daclizumab in their model but exclude it from tables of economic results. They justify this by arguing that daclizumab is no longer a relevant comparator due to an EMA safety warning that has restricted its use to 'patients who have had an inadequate response to at least two DMTs and cannot be treated with other DMTs' (CS page 10).[16] However, we present results for daclizumab below, because it is still within scope. However, to aid committee decision making, where relevant we also report incremental ICERs excluding daclizumab.

Blended ABCRs

The main text of the CS only gives results for a 'blended ABCR' comparator - a weighted mean of the interferon-beta drugs (IFNβ-1a, IFNβ-1b and PEGβ-1a) and glatiramer acetate. The company justify this by stating that these drugs are 'generally considered by clinicians to be broadly equivalent' (CS page 125). The results were pooled using weightings based on market share (page 125). The market share estimates were derived from confidential NHiS data from 92 out of 170 NHS Trusts in May-June 2017, obtained through freedom of information requests to all hospital Trusts in the UK (Clarification response, question B1). Separate results are presented for each drug in the blended ABCR comparator in Appendix J (page 180). The company argue that results are insensitive to the weighting used for the ABCR comparator. However, the pairwise ICERs comparing ocrelizumab with each drug in the ABCR comparator does show some variation (Table 62 Appendix J.1.2). We present results below with the ABCR blended comparator, but also for separate drugs comparator when relevant.

Out of scope comparators

The company report results for natalizumab and fingolimod for the broad RRMS (ITT) population, which are not in the scope (CS Tables 56-58, pages 127-128). The model also has the capacity to include some other comparators that are excluded from the scope: IFNβ-1a, IFNβ-1b, PEGβ-1a and glatiramer acetate for the HA and RES groups; and fingolimod for the RES group. We do not include any of these comparators in ERG analyses.

4.3.3 Model structure and assumptions

4.3.3.1 Overview of model structure

Key features of the model are described on pages 84-91 of the CS. The model structure is illustrated in Figure 24 (CS page 85), replicated below.

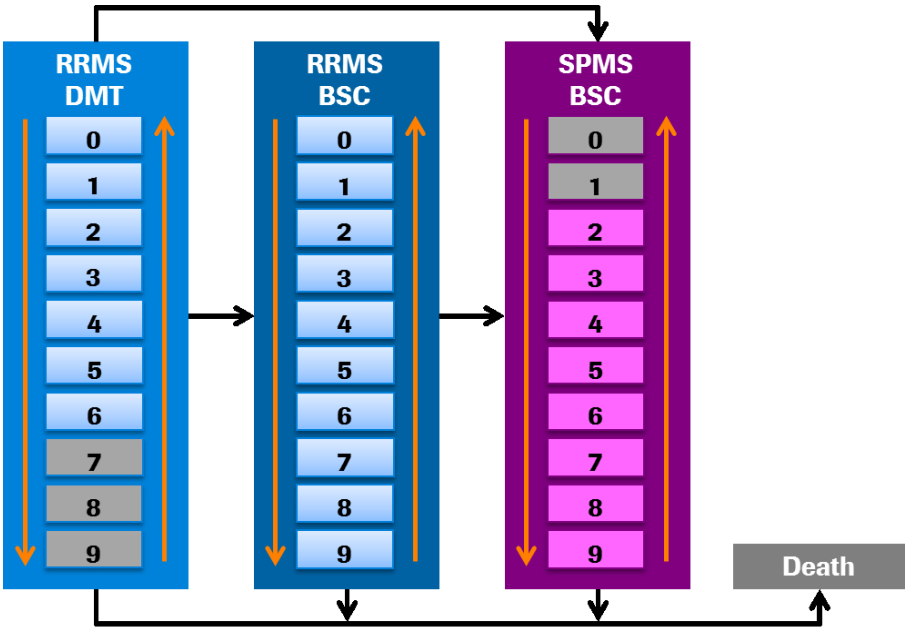


Figure 5 Illustration of model structure (copied from CS Figure 24)

The model is a cohort health state transition model of a Markov type. It uses a one-year cycle, updating the distribution of the cohort between health states, costs and outcomes annually. A 'half-cycle correction' (HCC) is used to adjust costs and QALYs for the timing of events within a year. The company argue that the HCC should not be applied for alemtuzumab, which is always administered at the beginning of a model cycle. The coding of the model makes it difficult to turn off the HCC, so instead the company apply an uplift of 5% to the price of

alemtuzumab to offset the HCC. We tested the appropriateness of this adjustment and also consider whether an adjustment should also be applied for the first of the two annual doses of ocrelizumab, which is also applied at the beginning of the model cycle (see section 4.5.1 below).

The model uses a 50-year time horizon, taking the cohort from an initial age of 37 years up to 87 years.

The ***health states*** are defined by the following characteristics:

- *Disease type*: the model starts with a cohort of people with RRMS. Over time, members of the cohort may convert to SPMS.

- *Treatment status*: patients start on ocrelizumab or one of the comparator drugs (DMT). After discontinuation of treatment, patients receive best supportive care (BSC). The model does not allow for a second line or sequencing of DMT. It is also assumed that after conversion to SPMS, patients only receive BSC.

- *Level of disability*: EDSS 0 to 9 - a higher score indicating worse disability. Although EDSS allows half point increments, the model only uses integer values. This is consistent with models in previous NICE appraisals and reported data. Due to treatment stopping rules (see below), there are no patients on DMT with EDSS greater than 6. It is also assumed that patients with SPMS cannot have an EDSS score less than 2.

The model therefore includes 31 health states, including death. However, 5 of the EDSS states are always empty (EDSS states 7 to 9 in RRMS and EDSS-0 and 1 in SPMS, shown in grey in Figure 5).

Each year, members of the cohort can make one of the following transitions:

- ***Disability progression***: The base case model uses transition probabilities between EDSS states estimated from natural history data. Due to the progressive nature of MS, disability tends to increase over time, although it can sometimes improve: thus the base case model allows transitions to higher or lower EDSS states. EDSS can change by more than one level in a year, but large jumps are unlikely. The same probabilities are assumed for transitions between EDSS states within SPMS as within RRMS. A different set of probabilities is used for the RES and HA subgroups, reflecting the more rapid progression of disability in these groups. Treatment modifies the probabilities of EDSS

progression in accordance with CDP effects from the mixed treatment comparison (ITT, RES and HA groups). In their base case, the company uses CDP-12 as the measure of progression, but CDP-24 is used in sensitivity analysis. By assumption, treatment does not affect rates of disability regression.

- ***Treatment discontinuation***: Patients on DMT may stop treatment for various reasons, including intolerance and inadequate response. The model assumes a constant annual probability of withdrawal for each drug in each subgroup (ITT, HA and RES), estimated by MTC of all-cause discontinuation. In addition, treatment is assumed to stop when patients progress beyond EDSS 6 or after conversion to SPMS. These stopping rules are based on NHS England policy and ABN guidelines.[6, 65] After discontinuation, patients are assumed to receive only BSC, with no lasting effects of DMT.

- ***Conversion to SPMS***: Each year, there is a chance that patients with RRMS may convert to SPMS, estimated from natural history data. The probability of conversion is higher for patients with worse disability (higher EDSS). The conversion probabilities by EDSS state are assumed constant over time and do not differ for the HA and RES subgroups. Treatment is assumed to modify the probability of conversion to SPMS by 50% of the effect on disability progression. By assumption, conversion to SPMS is accompanied by a one-point increase in EDSS and cessation of any DMT. SPMS is defined as a chronic state, so transition back to RRMS is not allowed.

- ***Mortality***: Death can occur from any health state. For patients without disability (EDSS 0), mortality rates are the same as in the general population (by age and sex), but increase with EDSS. The relative risks of mortality by EDSS level are the same for RRMS (ITT, HA and RES) and SPMS. Treatment does not have a direct effect on mortality, although there is an indirect effect through delay in disability progression.

In addition to state transitions the model includes two other important outcomes:

- ***Relapse rates***: Each health state is associated with a mean number of relapses per year, the ARR, estimated from natural history data. ARR tends to decrease with time since diagnosis and hence with increasing EDSS. The ARR is higher for people with more active forms of RRMS, including RES and HA, and lower in SPMS. Treatment modifies the relapse rate, reducing the mean ARR at each level of EDSS. Estimates of the relative reductions in ARR for each DMT and subgroup come from the MTC.

- ***Adverse events***: The types and incidences of AEs vary between DMT drugs. The model incorporates AEs with an occurrence of 5% or more in either arm of the pooled OPERA I and II trial data. This includes infusion-related reactions and injection site pain, a range of infections, musculoskeletal symptoms, depression, fatigue, headache and insomnia. In addition, PML was included because of its high cost and patient impact. Each of the included AEs is associated with an annual incidence for each DMT, which is assumed constant over time. Estimates of AE rates come from the pooled analysis of the OPERA data and a previous submission to NICE (Daclizumab).[66]

4.3.3.2 Treatment effects

In summary, DMTs are associated with the following benefits and harms, in comparison with best supportive care (placebo):

- Reduced rate of relapses (ARR)
- Reduced rate of disability progression (CDP)
- Reduced probability of conversion to SPMS
- Annual incidence of a range of adverse events
- Indirect reduction of mortality rates through delayed disability progression

In the base case model, these effects apply continuously regardless of treatment duration (there is no 'waning' of treatment effects), but they cease immediately on discontinuation. The impact of treatment waning is tested in two scenario analyses: one with the same waning assumptions for all DMTs (25% loss of effect in years 2-5 and 50% loss from year 6); and another with the same waning assumptions for comparators but delayed waning for ocrelizumab (25% loss for years 5-7 and 50% loss from year 8). The company justifies the latter based on persistence of effects for 4 years in the ocrelizumab open label extension study (CS pages 101-2).

4.3.3.3 Health-related quality of life

QALYs accumulate in the model as a function of the number of years that the cohort spend in the different health states and utility values associated with those states. Health state utility values are calculated from five components, shown below. The model assumes that these values do not differ by patient group or subgroup.

For patients, utility depends on:

1) their level of disability, with declining utility from EDSS 0 to 9;
2) an additional utility loss after conversion to SPMS;

3) the utility loss associated with a relapse; and

4) the utility loss associated with each type of adverse event.

For caregivers:

5) loss of utility related to the patient's level of disability (EDSS)

4.3.3.4 Health and social care costs

The model includes the following categories of cost:

1) Treatment costs: drug acquisition, administration and monitoring by DMT
2) Health state costs by EDSS state and additional cost for SPMS
3) The additional cost of care during relapses
4) The cost of care and treatment for each type of adverse event

Health state costs and the costs per relapse and per adverse event do not differ by patient subgroup or treatment.

4.3.4 Model parameters

The company model includes five sets of parameters: demographics, transition probabilities, treatment effects, utilities, and resource use and costs, as summarised in CS Table 53.

4.3.4.1 Baseline population

The OPERA I and II trials are discussed in detail in section 3.1.3.1 above. The company pooled patient-level data from these two trials to determine mean age, gender and EDSS distribution at baseline. Given the similarity between the values for the ITT population and the HA and RES subgroups (CS Table 26), the company decided to use the ITT values for the subgroups. The company tested the impact of applying baseline characteristics from the UK MS Risk Sharing Scheme (RSS) in a scenario analysis (Pickin et al 2009)[67]. It is not clear how these values from RSS were obtained, as only a graphical distribution of baseline EDSS scores is reported by Pickin et al. We present values used in the company's base case analysis and scenario analysis in Table 35. On average, the OPERA trial participants were younger with lower levels of disability than participants in the UK MS RSS.

The best source of baseline patient characteristics is not clear-cut. Although the RSS dataset is large and specific to the UK, it was collected prior to routine use of DMT (2002-2005) and might not be reflective of the current UK patient population. The OPERA trials recruited from 2011, but it appears that only a small number of patients were from UK sites (ERG Table 10) and

inclusion/ exclusion criteria would have restricted the study population. On balance, the ERG agrees with the company that the OPERA population provides a more appropriate characterisation of the baseline population than the RSS.

Table 35 Baseline patient characteristics: adapted from CS Table 26 and model

Characteristic		**Base case** OPERA pooled ITT population (n=1656)		**Scenario analysis** UK MS Risk Sharing Scheme [a] (n=3730)	
Mean age (years)		37.2		39.3	
Gender (% male)		34		25 [b]	
EDSS, n (%)	0	51	(3.1)	112	(3.0)
	1	312	(18.9)	261	(7.0)
	2	504	(30.5)	746	(20.0)
	3	389	(23.5)	727	(19.5)
	4	244	(14.7)	765	(20.5)
	5	145	(8.8)	373	(10.0)
	6	10	(0.6)	578	(15.5)
	7	0	(0.0)	168	(4.5)
	8	0	(0.0)	0	(0.0)
	9	0	(0.0)	0	(0.0)

[a] Derived from Pickin et al. 2009[67]

[b] In total number of patients recruited to start DMT for the first time (n=4871)

4.3.4.2 Natural history

The model requires parameters to describe the 'natural history' of the baseline population in the absence of DMT; that is, with only best supportive care. This includes annual probabilities for transitions: disability progression in RRMS; conversion from RRMS to SPMS; disability progression in SPMS; and mortality. In addition, annual rates of relapse are required for each health state. The company recognises the inadequacy of short term trials (OPERA I and II) and opts to use real-world longitudinal observational data where possible. The lack of a placebo arm further limits the use of the OPERA trials to explore the natural progression of MS. The ERG agrees that the company's preference for longer term data is reasonable. We discuss the company's data sources for each set of natural history parameters below.

Disability progression in RRMS

The model requires a transition matrix to define the annual probabilities of moving between RRMS EDSS states. Two sources of data to define this matrix are cited in the CS: the British Columbia and the London Ontario datasets. Previous NICE appraisals have used these data, sometimes in combination with other data sources. For emphasis, we reproduce CS Table 27,

which itemises the company's summary of major differences between the British Columbia and the London Ontario datasets (see Table 36 below).

Table 36 CS Key differences between natural history datasets: CS Table 27

British Columbia	London Ontario
Used in UK RSS and recent NICE appraisals (TA441 and ongoing ID809)	Used in older NICE appraisals (TA32, TA127, TA254, TA303, TA312, TA320)
Includes data on 898 patients	Includes data on 345 patients
Follow up period 1980 - 1995	Follow up period 1972 – 1989
Improvements in EDSS allowed	No improvements in EDSS allowed
Transitions available for all health states	No transitions available for EDSS 0 and 9 (RRMS) or EDSS 0, 1, and 9 (SPMS)
Single matrix for mixed population of RRMS and SPMS patients	Separate matrices for RRMS and SPMS patients

The London Ontario estimates of transition probabilities between the RRMS EDSS health states are reproduced (Commercial in Confidence) in Table 29 of the CS (section B.3.3). These were derived in analysis conducted for the 2002 NICE appraisal of beta-interferon and glatiramer acetate.[68, 69] The analysis was subsequently criticised for retrospective smoothing to censor improvements in EDSS states.[70] The company argues that recent evidence from experts supports health state regressions as well as progressions, as demonstrated by analysis of the British Columbia dataset (Palace et al 2014).[70]

In line with the most recent NICE appraisals (TA441 and TA320), the company uses the transition matrix derived from the British Columbia dataset (Table 37) for their base case analysis. This was based on a subset of patients from the British Columbia database age ≥ 28 years, with EDSS ≤ 6.5, at least two relapses in the previous 2 years and included some patients with SPMS (15.7%). The company explores the impact of using the London Ontario dataset in a scenario analysis. We agree with this approach.

For the RES and HA subgroups, the CS applies a transition matrix that reflects more active disease. This matrix was derived from the placebo arm in the AFFIRM phase III study for a RES subgroup, and was used in the natalizumab NICE appraisal (TA127).[15] In the absence of published data, the company uses the same matrix to reflect transition in the HA subgroup. The company uses data from the British Columbia matrix to impute data for EDSS states 7 and

above which were not available from the AFFIRM study (CS Table 30). The CS acknowledges that the transition matrix for the subgroups is less robust due to a smaller sample size.

Table 37 Disability transition matrix (British Columbia): CS Table 28

EDSS		EDSS state in following year									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Current EDSS state	0	0.6954	0.2029	0.0725	0.0217	0.0042	0.0014	0.0018	0.0001	0.0000	0.0000
	1	0.0583	0.6950	0.1578	0.0609	0.0164	0.0046	0.0064	0.0005	0.0001	0.0000
	2	0.0159	0.1213	0.6079	0.1680	0.0446	0.0185	0.0216	0.0017	0.0005	0.0000
	3	0.0059	0.0496	0.1201	0.5442	0.0911	0.0585	0.1165	0.0103	0.0036	0.0003
	4	0.0017	0.0221	0.0666	0.1152	0.4894	0.1039	0.1681	0.0258	0.0067	0.0006
	5	0.0005	0.0053	0.0294	0.0587	0.0874	0.4870	0.2731	0.0388	0.0188	0.0010
	6	0.0001	0.0013	0.0044	0.0250	0.0307	0.0408	0.7407	0.1090	0.0438	0.0042
	7	0.0000	0.0002	0.0005	0.0025	0.0073	0.0039	0.1168	0.6927	0.1606	0.0156
	8	0.0000	0.0000	0.0000	0.0003	0.0006	0.0005	0.0188	0.0557	0.9034	0.0207
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0018	0.0057	0.1741	0.8183

Source: Palace et al 2014[70]: Age at onset ≥ 28 years, RRMS and SPMS.
Underlined values adjusted so that rows sum to 1.

Conversion from RRMS to SPMS

The company relies on estimates of the annual probability of conversion from RRMS to SPMS derived from the London Ontario dataset (see Table 38). Estimates of conversion probabilities are not available from the British Colombia dataset, as this was not analysed separately for people with RRMS and SPMS. The company use the same SPMS conversion probabilities for the ITT population and the HA and RES subgroups, arguing that the conversion from RRMS to SPMS is primarily driven by EDSS state. Given the faster rate of disability progression for the RES and HA subgroups, the model will still predict that they convert to secondary-progressive disease more quickly than patients with less active disease.

Table 38 Annual probability of conversion to SPMS (London Ontario): CS Table 31

EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Probability										

Disability progression in SPMS

The company applies the same dataset from the British Columbia study for EDSS progression in SPMS as in RRMS (Table 37). They justify this by noting that the British Columbia study included both RRMS and SPMS patients. This is true, although SPMS patients represented a small proportion (16%) of the total number of patients in the cohort. We note that Yang et al. took a more conservative approach in their economic evaluation of ocrelizumab by assuming that EDSS regression was not possible in SPMS.[63] The company has included an option to apply this assumption in their model, by constraining the British Colombia disability transition matrix to prevent improvements for patients with SPMS. We apply this approach in scenario analysis.

The company applied the British Columbia transition matrix for the RES and HA subgroups after conversion to SPMS. The London Ontario dataset was tested in sensitivity analysis (CS Table 32).

Relapse rates

Annual relapse rates by EDSS states are reported in CS Tables 35 and 36. The OPERA trials lacked a placebo-controlled arm, so do not reflect the natural history of relapse. Estimates are therefore based on pre-treatment natural history data. The company base case uses estimates for the ITT population from the natalizumab appraisal (TA127).[15] See Table 38 below. These were based on two sources: the ARR by year since diagnosis reported by Patzold et al. 1982[71]; and EDSS state by year since diagnosis from the UK MS Survey (Orme et al. 2007)[72], reported TA127. Relapse rates for the HA and RES subgroups were estimated based on a relative risk of relapse of 1.98 for RES vs. ITT in the AFFIRM trial, as reported in the natalizumab CS (TA127).

Table 39 ARR by EDSS state and subgroup: CS Tables 35 and 36

EDSS	ITT		RES/HA	
	RRMS	SPMS	RRMS	SPMS
0	0.709	0	1.407	0
1	0.729	0	1.448	0
2	0.676	0.465	1.343	0.923
3	0.720	0.875	1.430	1.738
4	0.705	0.545	1.400	1.083
5	0.591	0.524	1.173	1.041
6	0.490	0.453	0.972	0.900
7	0.508	0.340	1.009	0.676
8	0.508	0.340	1.009	0.676
9	0.508	0.340	1.009	0.676

We note that as the frequencies of relapses are expected to decrease with progression, there are some estimates in Table 39 that appear anomalous (e.g. the ARR increases between EDSS levels 2 and 3, and between levels 6 and 7). This leads us to question the robustness of these estimates. Some alternative sources were reported in the economic model, based on other previous NICE appraisals, but these have similar inconsistencies. Given the lack of a more credible alternative, we agree with the company's approach, but highlight the sensitivity of results to relapse rates.

Mortality

The company's model applies mortality multipliers for MS to all-cause mortality rates derived from the most recent national life tables for England and Wales (ONS 2013-15).[73] The mortality multipliers by EDSS state are taken from estimates in the NICE appraisal of fingolimod (TA254)[13]. See Table 40. The company's model assumes that mortality per EDSS state is the same for RMSS and SPMS patients as well as for subgroups with more active disease. The CS does not model a direct treatment effect on mortality. The ERG agrees that an indirect treatment effect is reflected through treatment effects on disability progression.

Table 40 MS mortality multipliers by EDSS: CS Table 37

EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Mortality multiplier	1.00	1.43	1.60	1.64	1.67	1.84	2.27	3.10	4.45	6.45

4.3.4.3 Treatment effects

Estimates of the relative effects of treatment on relapse rates, disability progression and treatment discontinuation are based on the company's MTC meta-analysis. The company analysed separate networks of evidence for the HA and RES subgroups for the ARR and CDP outcomes. Although they question the robustness these subgroup results, due to the sparsity of the evidence base and use of post-hoc analyses, the company uses them in base case analysis, with scenarios based on ITT results for the subgroups. Due to ERG concerns about the MTC subgroup analyses (see section 3.1.6 above), we use the ITT results in our base case and additional analyses presented below.

Effects on annual relapse rate

The base case uses estimates of relative risks for the ARR outcome from the MTC (section 3.1.6 above). These relative risks are multiplied by the ARR for each EDSS state under best supportive care; the natural history rates described above.

Table 41 Treatment effects on relapse rates: relative risk vs. placebo ARR

Treatment	ITT		HA		RES	
	Median	95% CrI	Median	95% CrI	Median	95% CrI
Ocrelizumab	[redacted]		[redacted]		[redacted]	
IFNβ-1a (Avonex)	[redacted]		[redacted]		[redacted]	
IFNβ-1a (Rebif)	[redacted]		[redacted]		[redacted]	
IFNβ-1b	[redacted]		[redacted]		[redacted]	
PEGβ-1a	[redacted]					
Glatiramer acetate	[redacted]		[redacted]		[redacted]	
Alemtuzumab	[redacted]		[redacted]		[redacted]	
Daclizumab	[redacted]		[redacted]		[redacted]	
Dimethyl fumarate	[redacted]					
Fingolimod	[redacted]		[redacted]		[redacted]	
Natalizumab	[redacted]				[redacted]	
Teriflunomide	[redacted]					

Shaded cells show indications that are not included in the NICE scope

Effects on disability progression

Hazard ratios from the company's MTC (section 3.1.6 above) are used in the model as the basis of treatment effect on disease progression - see Table 42. The company conducted MTCs for the ITT population and HA and RES subgroups, which are applied to the appropriate sets of 'natural history' transition probabilities.

The company uses the measure of confirmed disability progression (CDP) at 12 weeks in their base case, reporting results at 24 weeks as a scenario analysis. They justify this on the basis that CDP-24 is less robust, due to the lower quality and quantity of trial data available in the MTC. However, it can be seen from Table 42 that CDP-24 estimates are available for all indications in the scope, with the exception of two forms of beta-interferon for the ITT group and daclizumab for RES. We believe that CDP-24 should be used in the base case when available, as it is a more robust measure of lasting disability progression. This approach has been favoured by NICE committees in recent appraisals of DMTs for MS.[14,19,74]

Table 42 Treatment effects CDP at 12 and 24 weeks: HR vs placebo

Treatment	ITT		HA		RES	
	Median	95% CrI	Median	95% CrI	Median	95% CrI
CDP-12						
Ocrelizumab						
IFNβ-1a (Avonex)						
IFNβ-1a (Rebif)						
IFNβ-1a (Rebif 22)						
IFNβ-1b						
PEGβ-1a						
Glatiramer acetate						
Alemtuzumab						
Daclizumab						
Dimethyl fumarate						
Fingolimod						
Natalizumab						
Teriflunomide						
CDP-24						
Ocrelizumab						
IFNβ-1a (Avonex)						
IFNβ-1a (Rebif)						
IFNβ-1a (Rebif 22)						
IFNβ-1b						
PEGβ-1a						
Glatiramer acetate						
Alemtuzumab						
Daclizumab						
Dimethyl fumarate						
Fingolimod						
Natalizumab						
Teriflunomide						

Shaded cells show indications that are not included in the NICE scope

Treatment discontinuation (OR all-cause discontinuation)

Section B.2.9 of the CS shows the company's network for all-cause discontinuation for 17 treatments including placebo. The results of the company's MTC, reported in CS Appendix D.1.4., capture withdrawal from treatment due to adverse events as well as lack of efficacy and are estimated as odds ratios compared with ocrelizumab - see Table 43 below. The odds ratios are converted to annual probabilities in the model, using the absolute discontinuation rate for

ocrelizumab to anchor the estimates. The company base case uses all-cause discontinuation, but the model does include the facility to calculate results using only AE-related discontinuation. Due to a paucity of data, the company did not conduct separate MTCs for treatment discontinuation in the HA or RES subgroups, hence ITT estimates were used for these analyses. As noted above, the company model assumes a constant annual withdrawal rate throughout the time horizon. We consider the method used to generate annual probabilities of treatment withdrawal and the underlying assumptions to be appropriate.

Table 43 Discontinuation: OCR vs ocrelizumab and annual probabilities: from CS Table 38 and economic model**DMT**	**All cause**				**AE-related**
	OCR vs. ocrelizumab			Annual probability	Annual probability
	Median	95% CrI			
Ocrelizumab	NA	NA	NA	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 22)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEGβ-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terifluomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA: not applicable

4.3.4.4 Health related quality of life

OPERA utility regression

EQ-5D-3L data were collected at baseline and at weeks 48 and 96 in the OPERA I and II trials, and also at week 0 and 46 of the open label extension study. Utility scores were obtained using the UK Value set.[75] These data were collected for use in regression analysis to estimate utility by EDSS and comparison between study arms was not pre-specified (Clarification A8). Mean

utility scores in the OPERA trials and OLE study were similar for the intervention and control arms (company's response to clarification question A8).

The methods used in the company's utility regression are reported in CS Appendix H.1.5 and further explanation is given in the Clarification response of 12 January. In total, 5073 observations were used for the regression, including 1177 observations at week 96. Imputation was not used for missing data. No EQ-5D observations were available for patients with EDSS 8 or 9, and only 4 were available for EDSS level 7. The model included EDSS, sex, region and relapse, and the company state that extending the model to include randomization arm did not improve the fit (p=0.9047). The analysis could not have adjusted for RRMS/SPMS disease type because this categorization was not collected in the OPERA trials.

Systematic review

The company also conducted a systematic review to identify HRQoL studies relevant to the economic evaluation (CS section B.3.4.3). Figure 25 in the CS (reproduced in Figure 6 below) plots EQ-5D utility scores by EDSS state from 7 relevant studies, in addition to the company's regression analysis of the OPERA data. The curves depict a consistent pattern of declining utility with increasing EDSS score.

The OPERA results are more conservative than most, with a less steep gradient. However, the company notes that confidence intervals overlap with those from the Orme et al. analysis[72] which represent the lowest range of utility scores in the available data sources. The company ascribed the higher utility scores in the OPERA trials to the average age of the patients at baseline (37 years) compared to patients in the MS Trust survey with an average age of 51 years. Orme et al. used data from a postal survey of 12,968 people, of whom 2708 provided data suitable for analysis. The final regression included recent relapse, SPMS, PPMS, education, years since diagnosis and gender as covariates, alongside EDSS states.

The utility scores used in the economic model are listed in Table 44 below (copied from CS Table 43). Values for RRMS states 0 to 6 were taken from the OPERA utility regression analysis described above. Values for RRMS EDSS states 7 to 9 were obtained from the RRMS EDSS state 6, adjusted using decrements (vs. EDSS 6) from Orme et al.. The Orme et al. analysis was also used to provide an estimate of the decrement associated with SPMS compared with RRMS: 0.045 (0.014 to 0.076).

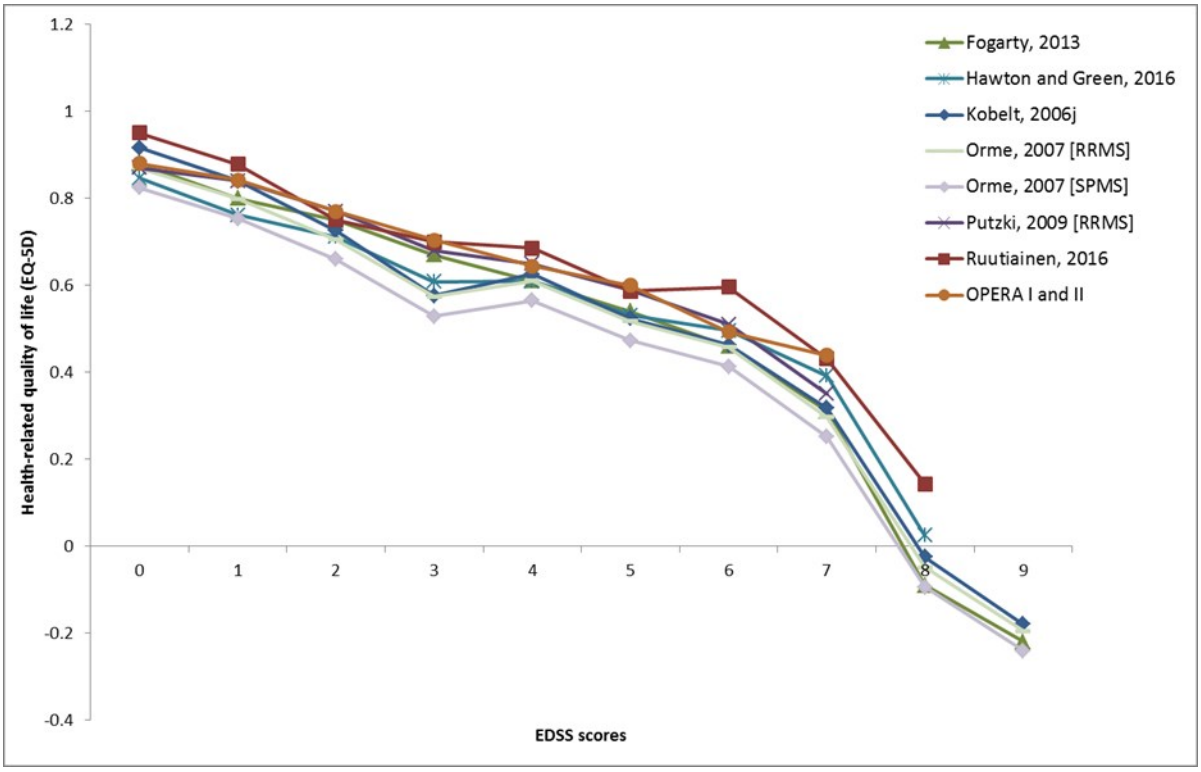


Figure 6 Consistency of EDSS-dependent utility values: CS Figure 25

Table 44 Health state utility values used in model: CS Table 43

EDSS	RRMS	SPMS
0	0.881	0.836
1	0.843	0.798
2	0.770	0.725
3	0.705	0.660
4	0.644	0.599
5	0.601	0.556
6	0.493	0.448
7	0.308	0.263
8	-0.038	-0.083
9	-0.184	-0.229

The ERG agrees with this approach, particularly as the CS also reports a scenario analysis using utility scores drawn entirely from the MS Trust survey (Orme et al.)[72]. The model uses an appropriate method to characterise uncertainty around the OPERA utility analysis coefficients and Orme et al utility decrements for PSA.

The same values are used for people with more active forms of disease (HA and RES). This is appropriate because the OPERA regressions include adjustment for utility loss associated with relapses, and the model applies separate estimates of QALY loss associated with relapses.

Relapse disutility

The company use two parameters to estimate the QALY loss per relapse:

- The disutility experienced during relapses. In the base case, the Orme et al. estimate of 0.071 (0.046 to 0.096) is used. This is similar to the estimate from the OPERA utility regression, 0.101 (0.061 to 0.140), which the company uses for scenario analysis.
- An average duration of a relapse (46 days) sourced from NICE TA32. The CS reports scenario analysis to test the impact of assuming a relapse duration of 1 or 2 months.

The estimated QALY loss attributable to relapses is therefore modest at 0.009 per relapse on BSC in the base case model; or a maximum of 0.015 per year for patients with more active forms of disease (ARR of 1.7 for RES/HA). These assumptions are consistent with previous NICE appraisals.

We note that the assumption about the duration of relapses is related to the timing of confirmation of disability progression in the natural history dataset (British Colombia in the base case) and clinical evidence base (CDP-12 vs. CDP-24).

Caregiver disutility

The company model specifies caregiver utility values used in previous NICE assessments based on estimates from (TA127).[15, 19] These estimates were based on a maximum utility decrement of 0.14 from studies in Alzheimer's disease, weighted for level of EDSS in accordance with reported time spent by caregivers in the UK MS Survey. No alternative source of caregiver disutility is reported.

Table 45 Caregiver disutility by EDSS state

0	1	2	3	4	5	6	7	8	9
0	-0.001	-0.003	-0.009	-0.009	-0.02	-0.027	-0.053	-0.107	-0.14

We note that in the NICE appraisal TA441, the manufacturer for daclizumab reports an additional set of values from the Delphi survey.

4.3.4.5 Resource use and costs

The model includes treatment costs, costs of ongoing health and social care by health state and additional costs for relapses and adverse events. In this section we discuss the sources and assumptions about treatment, health state and relapse costs. AE-related costs are discussed in the following section.

Treatment costs: drug acquisition, administration and monitoring

The company provides detailed tables itemising resource use and cost assumptions for drug acquisition (CS Table 45), drug administration (CS Table 47) and monitoring (CS Table 48). A summary, based on CS Table 49, is shown below. This includes the list price for each drug: which is confidential for ocrelizumab. The PAS price for ocrelizumab is [redacted] for each year of treatment. PAS prices for other comparators are reported in Addendum 1 to this report.

Table 46 Summary of drug treatment costs (adapted from CS Table 49)

Drug	Drug acquisition [a]		Drug administration		Monitoring cost	
	year 1	year 2+	year 1	year 2+	year 1	year 2+
Alemtuzumab	35,225	21,135	2,497	1,509	1,093	1,024
Daclizumab	19,160	19,160	172	0	374	317
Dimethyl fumerate	17,898	17,898	130	0	574	243
Fingolimod	19,163	19,163	494	0	663	231
Glatiramer acetate	6,681	6,681	172	0	347	237
IFNβ-1a (Avonex)	8,502	8,502	172	0	368	237
IFNβ-1a (Rebif)	10,572	10,572	172	0	370	237
IFNβ-1b	7,259	7,259	172	0	368	237
Natalizumab	14,690	14,690	6,422	6,422	767	451/ 597 [b]
Ocrelizumab	19,600	19,600	1,501	1,007	366	297
PEGβ-1a	8,502	8,502	172	0	368	237
Teriflunomide	13,529	13,529	0	0	381	240

[a] At list price; [b] Monitoring cost, year 2 / 3+;

Although the list price of alemtuzumab is £35,225 in year one and £21,135 in year 2+, these costs are increased by 5% in the company model to adjust for the half cycle correction (HCC). This is based on the argument that the HCC should not be applied to alemtuzumab costs, which are only incurred at the beginning of the cycle. This is correct and we agree that the 5% uplift is reasonable: the cost of alemtuzumab is £35,255 in year 1 without the HCC; £33,530 with the

HCC but no adjustment; and £35,207 with the HCC and 5% adjustment. However, we do question whether some adjustment should also be made for ocrelizumab, for which one dose is administered at the beginning of the cycle. We therefore include a 5% uplift in half the cost of ocrelizumab in the ERG base case, as well as the 5% adjustment for the whole cost of alemtuzumab.

The CS notes that although alemtuzumab is an induction treatment, retreatment is sometimes required and in certain cases patients switch to other DMTs due to treatment failure. The CS reports findings from observational studies by Tuohy et al and Willis et al to support this assumption.[76, 77] Of 87 patients observed over a median 7-year follow-up period, Tuohy and colleagues found that 52% required just two treatments. Relapses prompted re-treatments ranging from three to five treatment cycles. Willis et al found that out of 100 patients identified and followed-up for 6.1 years, 40 required additional treatment cycles. Both studies were in UK settings.

The company incorporates the assumptions from the alemtuzumab CS to account for re-treatment. These included average re-treatment rates of 19%, 16% and 14% for years 3, 4 and 5 respectively, drawn from the CARES MS I AND II follow up data (CS Table 46).[78, 79] For the year six onwards, the company uses a 13% re-treatment rate estimated from Touhy et al.[76] A treatment switching scenario as a result of failure on alemtuzumab is not explored and the company believes this would underestimate treatment costs associated with alemtuzumab. We are of the opinion that evidence does point to re-treatment in a significant number of patients who receive alemtuzumab, however the assumption of ongoing re-treatment for 13% of patients every year is not supported. The NICE Committee on daclizumab concluded that a maximum of four re-treatments should be modelled. We therefore exclude re-treatment with alemtuzumab from year 6 onwards in our base case analysis, and test the effect of this in scenario analysis.

Regarding the drug administration and monitoring costs, most of the values in CS Tables 47 and 48 are derived from the daclizumab NICE appraisal, while the remaining parameters are estimated from SmPC requirements and the opinion of the company's experts. We checked the component costs against specified sources and found most of them to be appropriate. We had concerns about certain values in CS Tables 47 and 48, such as the assumption that patients on natalizumab attended 13 day cases in the first year and 12 MS nurse visits for patients on

alemtuzumab. We note, however, that these assumptions will have negligible impact on cost-effectiveness.

Health state costs

The CS considers four sources of evidence on resource use and costs for the modelled health states, obtained from a systematic literature review (CS section B.3.5.2).[80-83] We summarise health state costs from these four studies in Table 48 (adapted from Table 51 on page 120 of the CS):

- **Hawton and Green (2016)**[80] was a UK study that used data from a prospective, longitudinal cohort to describe health and social care by EDSS category.

- **Karampampa et al. (2012)**[81] (the TRIBUNE study) analysed questionnaires completed by 1261 MS patients from 5 European countries to estimate the societal cost of MS linked to relapses and disease severity.

- **Kobelt et al. (2006)**[82] reported on the UK results from a survey across 16 European countries. The study, which was based on the UK MS Trust survey, reported costs from a societal perspective. In the three studies mentioned above, no distinction was made between costs accrued by RRMS and SPMS patient subgroups. Costs were only reported for pooled mild, moderate and severe EDSS states in the Karampampa ad Kobelt papers.

- **Tyas et al. (2007)**[83] conducted a regression analysis of the the UK MS Trust Survey data used by Kobelt et al. Tyas et al. disaggregated costs into the ten EDSS health states, which showed significant variation with patients in the most severe MS states accruing the greatest costs. Tyas et al. also differentiated costs for RRMS and SPSS subgroups. The company adjusted the Tyas et al. estimates, using an estimate from Kobelt et al. that only 25% of direct non-medical costs are publicly funded and fall within the NICE reference case.

- The manufacturer's submission to NICE on daclizumab reported health state costs from a burden of illness cost analysis, the **Biogen BOI study**.[66] This analysis appears to be related to two recently-published papers, which report results from a Biogen-funded burden of illness study in the UK and other European countries.[84, 85] However, these published sources do not provide results at the level of detail needed for the ocrelizumab

analysis. The Warwick ERG team working on the daclizumab appraisal provided a detailed comparison of the Biogen BOI results and other published estimates. The Biogen analysis estimated UK costs, including: direct medical costs; direct non-medical costs and costs of informal care from family and friends. The Warwick ERG noted uncertainty over the proportion of investment and community care costs borne by the NHS/PSS and applied estimates of 80% and 100% of community care costs (see Table 47 below).

Table 47 Health state cost estimates

	RRMS			SPMS		
	BOI@80%	BOI@100%	TA320	BOI@80%	BOI@100%	TA320
EDSS 0	[redacted]	[redacted]	£937	[redacted]	[redacted]	£1,263
EDSS 1	[redacted]	[redacted]	£974	[redacted]	[redacted]	£1,301
EDSS 2	[redacted]	[redacted]	£714	[redacted]	[redacted]	£1,040
EDSS 3	[redacted]	[redacted]	£3,906	[redacted]	[redacted]	£4,232
EDSS 4	[redacted]	[redacted]	£1,892	[redacted]	[redacted]	£2,218
EDSS 5	[redacted]	[redacted]	£3,210	[redacted]	[redacted]	£3,537
EDSS 6	[redacted]	[redacted]	£4,285	[redacted]	[redacted]	£4,611
EDSS 7	[redacted]	[redacted]	£11,279	[redacted]	[redacted]	£11,605
EDSS 8	[redacted]	[redacted]	£27,472	[redacted]	[redacted]	£27,798
EDSS 9	[redacted]	[redacted]	£21,982	[redacted]	[redacted]	£22,309

Source: ERG report on Daclizumab [19]

The NICE daclizumab Committee concluded that the Biogen BoI study as adjusted by the ERG, was appropriate as a “starting point” for making recommendations but acknowledged uncertainty over the ERG adjustments. (TA441 section 4.18)

For their base case, the company uses health-state costs from Tyas et al. (2007)[83], adjusted to 2016 using the PSSRU Hospital and Community Health Services inflation index (PSSRU).The company argues that Tyas et al. represents the most complete and robust data on MS costs in the UK. Their model also uses a cost of relapse, independently from the EDSS health state costs. As there is wide variation in costs of relapse reported in the literature, the company uses data from Tyas et al (£1,623) in the base case to maintain consistency with health state costs.

Based on the committee considerations in the daclizumab appraisal, we decided to use the updated UK MS Survey figures at 2014/15 prices cited in the Warwick addendum to their report for the daclizumab appraisal in our base case. We also conduct scenario analysis using costs

from the Biogen Burden of Illness analysis assuming 80% paid by the NHS and PSS, as cited by Warwick.

Table 48 Summary of annual health state costs by EDSS: Adapted from CS Table 51

Cost category	EDSS states and costs (£)									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Hawton[80]										
Health and social care	510	455	358	334	501	503	652	658	1660	
Karampampa [81]										
Medical	6714				8101			6059		
Non-medical	1913				10299			41242		
Kobelt 2006 [82]										
Healthcare	5400				7000			7700		
Services/ investments	400				1200			9000		
Informal care	1100				7000			25200		
Tyas et al. [83]										
Medical, RRMS	250	85	213	850	806	1419	2162	6583	10761	15121
Medical, SPMS	530	365	493	1130	1086	1699	2442	6863	11041	15401
Non-medical	2536	3462	4414	6212	4028	6333	6580	10808	15339	10161

4.3.4.6 Adverse events

Incidence of adverse events

Table 49 summarises the annual probabilities of AEs used in the economic model. Citing the approach in the CS for the daclizumab appraisal (TA441), the company only include AEs with an occurrence of 5% or more in either arm of the pooled OPERA analysis. They argue that this is conservative, as events with frequency ≥ 5% for comparators but not ocrelizumab are omitted. As in the daclizumab CS, PML is also included for natalizumab because of its high impact on patients and costs.

The AE rates for ocrelizumab were based on pooled analysis of the OPERA I and II trials (section 3.3.9.1). The proportions of events in OPERA I and II was similar, so the decision to pool the two studies is reasonable. Annual AE rates for comparators were sourced from the Biogen CS for the daclizumab appraisal (Table 79).[66] Biogen stated that they had included adverse events as an outcome in the systematic search for their MTC, but we could not determine how they had pooled data from these studies from the published submission. The model adjusts the AE rates for ocrelizumab to align with the common comparator treatment

(IFNβ-a1 Rebif) that links the AE rates in the daclizumab trial with those in OPERA I and II. This adjustment is reasonable.

Table 49 Adverse event rates (%) used in economic model

	OCR	IFNβ-1a (Rebif)	IFNβ-1a (Avonex)	DAC	PEGβ-1a	IFNβ-1b	GA	ALEM	DMF	FINGO	NAT	TERI
Infusion reaction	34	10	-	-	-	-	-	-	-	-	-	-
Headache	8	15	15	8	47	17	10	22	8	17	21	11
Influenza-like illness	3	21	24	4	-	-	-	1	-	4	-	-
Upper resp. tract infection	6	11	6	8	-	4	5	8	6	17	-	-
Nasopharyngitis	11	10	13	12	11	10	9	13	10	16	-	13
Urinary tract infection	3	12	5	5	-	5	5	10	8	6	11	4
Fatigue	12	8	10	3	11	13	8	8	6	8	15	6
Injection site pain	0	21	5	5	-	4	16	-	-	-	-	-
Depression	13	7	8	4	-	9	5	-	4	4	10	-
Arthralgia	2	6	4	3	12	7	5	-	-	4	10	-
Sinusitis	6	5	-	-	-	-	-	-	-	-	-	-
Back pain	5	4	4	4	13	6	5	-	5	5	-	5
Insomnia	6	5	-	-	-	-	-	-	-	-	-	-
Bronchitis	5	4	2	3	-	-	-	-	-	4	-	
PML	-	-	-	-	-	-	-	-	-	-	2	-

The short follow-up period in the OPERA trials could mean that certain adverse events are not captured in the economic model. The ERG considers that criteria used in deciding which adverse events are included in the model is arbitrary. Our clinical experts are also of the opinion that adverse events for some DMTs are over-emphasised in CS Table 4. However, these adverse events, such as cardiac failure and seizures, were not included in Table 40 and therefore not modelled. Our experts were of the opinion that all headache rates in CS Table 40 were over-estimated, particularly for natalizumab which had a rate of 21.2%. Other rates queried for natalizumab include UTI (10.5%), fatigue (14.5%), arthralgia (10%) and PML (2.1%) which clinicians thought were much higher than expected. Clinicians also questioned the infusion-related reaction rates reported in Table 40, specifically for alemtuzumab which they felt were under-estimated.

Despite our concerns about the face validity of the AE probabilities, only PML and depression have a sizeable cost or QALY effect (see below), so other AE rates are unlikely to influence cost-effectiveness. We therefore follow the company's approach to modelling AEs in the ERG

analysis but use scenario analysis to explore omitting PML and depression and the adjustment for ocrelizumab versus interferon.

Adverse event disutilities and costs

The company relies mainly on estimates from the daclizumab CS for TA441 for the disutilities and duration of adverse events. They supplemented missing data for a few adverse events with estimates from the alemtuzumab CS to NICE (TA312). Table 42 on page 108 of the CS summarises the assumptions about disutilities and durations of AE used in the company base case (CS Table 42). This includes an assumption that 6.9% of adverse events are serious, based on the overall proportion of SAEs in the pooled OPERA data.

The assumptions used to estimate the costs for treating adverse events in the company's base case analysis are summarised in CS Table 52. As with AE disutilities, assumptions about AE costs were sourced primarily from the daclizumab CS to NICE and weighted by assuming 6.9% of AEs are serious (pooled OPERA analysis). Costs were uprated to 2016 before use in the model.

The resulting estimates of QALY loss and cost per adverse event are shown in Table 50 below. It can be seen that the QALY loss is negligible for most types of AE. The largest loss is for PML, based on a mean utility loss of 0.3 lasting for one year (the equivalent of 4 months of healthy life). This may be an underestimate as, PML is likely to have more lasting effects including mortality. The largest AE-related costs are associated with depression with an average cost of £970 and PML with an average cost of £12,810. We note that the cost for depression assumes an average of 12 psychotherapy sessions for non-serious depression and 52 sessions for serious depression. This is number of sessions is unlikely in the NHS. The high cost for PML is related to a long-stay hospital admission, which may be reasonable given the seriousness of this condition.

Table 50 QALY loss and costs for included adverse events

Adverse events	Average per event					
	QALY loss			Cost (£)		
	Non-serious	Serious	Mean [a]	Non-serious	Serious	Mean [a]
Infusion-related reaction	0.000	0.000	0.000	0	0	0
Headache	0.004	0.033	0.006	0	210	14
Influenza-like illness	0.000	0.000	0.000	0	0	0
Upper resp. infection	0.004	0.008	0.004	65	65	65
Nasopharyngitis	0.000	0.000	0.000	0	65	4
Urinary tract infection	0.001	0.001	0.001	2	907	64
Fatigue	0.000	0.000	0.000	0	109	8
Injection site pain	0.000	0.000	0.000	0	65	4
Depression	0.034	0.560	0.070	821	2,996	971
Arthralgia	0.007	0.017	0.008	2	424	31
Sinusitis	0.000	0.000	0.000	0	0	0
Back pain	0.007	0.034	0.009	0	666	46
Insomnia	0.000	0.000	0.000	0	0	0
Bronchitis	0.000	0.000	0.000	131	131	131
PML	0.300	0.300	0.300	12,810	12,810	12,810

Source: CS Table 42 and 52

[a] Assuming that for each type of AE 6.9% are serious, based on average proportion of SAEs in OPERA trials.

4.3.5 Model validation

4.3.5.1 Internal consistency

The company describe their approach to model validation in section B.3.10 of the CS. They state that external agencies performed two separate quality checks of the model, reviewing calculations and testing extreme values. Any errors identified were corrected. The face validity of the model structure, inputs and results was considered at an advisory boards with clinical and health economic experts from the UK.

The ERG conducted a series of internal consistency checks on the company's submitted:

- We compared all model input parameters with the figures cited in the CS and in the original source. We did not identify any errors, although the natural history relapse rates cited to three decimal places in the CS (Table 35) were entered in the model with only two decimal places. We corrected this small discrepancy, which did not materially affect the results.

- We replicated all model outputs presented in the CS, including the scenario analyses which we changed manually as well as running the macros.
- Due to the size of the model we could not check every formula in the spreadsheet, but we reviewed the chain of calculations through the model, from data inputs, through parameter calculations to modelled outcomes and cost estimates. We also did a more detailed check of core model calculations used to estimated transition matrices, the Markov trace and cost and QALY calculations.
- We conducted a series of model 'stress tests', entering extreme values and checking that they have the expected impact on model results: for example that setting utility values to 1 makes QALYs equal to life years.

4.3.5.2 External consistency

The company note that comparison of economic results between NICE appraisals was complicated because of the amount of redacted information in previous submissions. They compare clinical effectiveness estimates from their MTC that are used in the submitted model with estimates from a recent analysis conducted by the Institute for Clinical and Economic Review (ICER) for the California Technology Assessment Forum (CS Table 74).[24] The CS and ICER estimates of ARR for all drugs are very similar. The CDP estimates are similar for most drugs, but do differ for some. This may be related to the timepoints for confirmation: the company present CDP-12 and CDP-24 separately, while ICER used CDP-24 when available or otherwise CDP-12.

The ICER report also compares their effectiveness estimates with those from other published network meta-analyses (Table 6 page 37 for ARR and Table 8 page 42 for CDP). There are some large discrepancies, which may relate to availability of evidence (e.g. the Cochrane review was conducted in 2014) and/or to the methods or conduct of the systematic reviews or NMAs. This suggests that there is additional uncertainty around the clinical effectiveness evidence used to drive the submitted model that is not captured in the probabilistic sensitivity analysis. In particular, we highlight that the company's one-way sensitivity analysis shows that CDP effectiveness parameters are a key source of decision uncertainty.

It is difficult to compare the modelled outcomes (QALYs and LYs) from the company model with those from other appraisals (due to redaction in previous submissions). Comparisons with outcomes from the ICER model are not straightforward because of differences in the decision

problem addressed (the ICER report considered a lifetime and sequenced approach to DMT use from MS diagnosis).

4.3.6 ERG critique of model

The company lists assumptions in CS Table 25 and makes comparisons with previous appraisals in Table 54. We summarise the company's arguments and ERG judgements in Table 51 below.

Table 51 Summary and critique of model assumptions

Assumption	Company justification	ERG comments
No impact of treatment on severity or duration of relapses	Lack of trial evidence of treatment effect on severity of relapses. May underestimate clinical benefit of 'high-efficacy' treatment like ocrelizumab	Given the lack of evidence, the base case assumption of no effect on relapse duration /severity is appropriate. However, we acknowledge that this may underestimate treatment effects.
EDSS progression measure CDP-12 in base case	The company argue that the evidence base is larger for disability progression confirmed at 12 weeks than at 24 weeks.	CDP-24 is a more robust measure of progression, because it is less likely to be confused with longer relapses. It has been preferred in previous committee considerations.
EDSS can regress as well as progress in RRMS and SPMS	In recent years it has become generally accepted that some patients with RRMS and SPMS do experience improvements in EDSS. The British Columbia cohort study that is used to provide transition probabilities for the model includes episodes of disability regression as well as progression.	We agree. This reflects advice received by the ERG from clinical experts. It is also consistent with recent NICE committee conclusions. However, we note that disability improvement is less likely in SPMS, when neurodegenerative rather than inflammatory processes start to drive disability progression.
Treatment affects EDSS progression but not regression	This is a conservative assumption that may underestimate the clinical benefit of 'high-efficacy DMTs like ocrelizumab' which have demonstrated the ability to reverse disability. (See CS Table 11, page 37)	There is some evidence of disability improvement from the OPERA trials. However, evidence is not available for comparators from MTC. We therefore agree with the company's conservative approach.

Table 51 continued

Assumption	Company justification	ERG comments
Transition from RRMS to SPMS is accompanied by a 1-point increase in EDSS	Assumption in line with previous appraisals based on London Ontario data. An increase in disability may have been partially captured in the British Columbia dataset (included 15.7% SPMS patients at baseline).	This is an assumption, not underpinned by evidence. ERG experts have suggested that the transition to secondary-progression disease is not necessarily accompanied by an increase in disability.
Partial effect of treatment on conversion to SPMS	In line with the previous appraisal of natalizumab, 50% of the treatment effect on CDP is applied to the probability of conversion from RRMS to SPMS.	This assumption is not based on evidence. A more conservative approach would be to assume no direct effect of DMTs on converstion to SPMS.
No direct effect of treatment on mortality (but indirect effect via EDSS)	Literature has demonstrated that the risk of death is primarily dependent on the level of disability (EDSS). Duration of trials too short to detect impact on mortality.	We agree.
Constant rate of all-cause treatment withdrawal	Experience with DMTs has shown that intolerance can occur either soon after start of treatment (e.g. infusion related reactions) or can develop years later (e.g. PML). Similarly, for, withdrawal due to lack of efficacy, early withdrawal in non-responders and late withdrawal after development of neutralizing antibodies / drug resistance. Assumption in line with several previous appraisals and supported by data from UK Risk Sharing Scheme.	We agree. It is difficult to assess the long-term pattern of withdrawals and we acknowledge that there are factors that might drive both early and late withdrawals.
No waning of treatment effectiveness over time Scenarios with waning are presented	Long-term waning not definitively proven nor disproven. 4-year OLE data for ocrelizumab shows sustained effect across ARR, CDP, and MRI outcomes; and ocrelizumab generates negligible neutralising antibodies, unlike other DMTs. Also, perceived reduction in clinical benefit results in switching to a therapy with different mechanism of action.	Clinical advisors to the ERG have suggested that the generation of neutralizing antibodies is unlikely to be a significant indicator of continued benefit. We acknowledge the evidence of sustained benefit from the ocrelizumab OLE study. However, in the absence of a review of long-term follow-up studies for all DMTs, we cannot draw conclusions about the relative persistence of effects for different DMTs.

Table 51 continued

Assumption	Company justification	ERG comments
Treatment discontinued when EDSS>6 or on conversion to SPMS	Some DMTs are licensed for relapsing SPMS (IFNβ-1a, daclizumab, and ocrelizumab), though the extent of use is uncertain. Patients are likely to experience a period of overlap between RRMS and relapsing SPMS when they may continue DMTs in line with the clinical guideline and NHS England Policy. After progression to non-relapsing SPMS DMT is expected to cease in line with guidance.	These are conventional stopping rules for DMT, although expert advisors have suggested that there is not a sharp division between RRMS and SPMS, and many patients will continue to experience relapses in SPMS and may well benefit form DMT.
Only AEs with incidence (≥5 %) in either arm of pooled OPERA studies were included	Due to the complexity and number of comparators in the model, the set of AEs included was based on the safety profile of ocrelizumab. This could have underestimated the impact of AEs for comparators if these weren't common in the OPERA trials. An exception was made for PML which is known to have high costs and disutilities and is relatively common with natalizumab (≥2 %). Other high-efficacy DMTs like alemtuzumab are associated with rare but severe AEs that are not included in the model.	We agree that the exclusion of common and high impact AEs for comparators would have biased results against ocrelizumab. However, our clinical experts have advised us that some estimates of AE rates for comparators seem unrealistic. They have questioned the estimate of 2% for PML with natalizumab. There is therefore uncertainty over whether the incidence and severity of AEs are accurately captured in the model.
Constant rate of AEs	The safety profiles of DMTs are complex and have evolved over time. Some AEs occur soon after the start of treatment (e.g. infusion related reactions), while others can develop after many years of continued treatment (e.g. PML). This is in line with the approach used in several previous appraisals.	We have been advised that there is considerable uncertainty over the timing of AEs. Given this, the assumptions of a constant rate over time is reasonable.

4.4 Cost effectiveness results

4.4.1 Base case

The company's base case results are reported in CS section B.3.7. Table 52 below reproduces results for the ITT population with the PAS price for ocrelizumab and list prices for all comparators.

Note that these results are not informative for comparators with a PAS (dimethyl fumerate, fingolimod and teriflunomide) because the incremental costs do not reflect prices paid in the NHS. We present results with all available PAS prices in Addendum 1 to this report.

We consider that the fingolimod and natalizumab comparisons in this analysis are also not informative. The company explains that they extended their ITT base case to include fingolimod and natalizumab, which are only recommended for subgroups with HA or RES disease respectively, because the ITT MTC is more robust than the HA and RES MTCs. We agree that there is greater uncertainty over the MTC subgroup analyses. However, cost-effectiveness results for the HA and RES subgroups are influenced by natural history parameters in addition to effectiveness parameters. Thus the ITT estimates in Table 52 are not necessarily applicable to these subgroups. The company's subgroup analyses are discussed in section 4.3.2.2 below.

Table 52 Company ITT base case (OCR PAS; list prices for comparators) Adapted from CS Table 57

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER (£/QALY)	
				Ocrelizumab vs. comparator [c]	incremental
Blended ABCRs	[redacted]	[redacted]	[redacted]	26,435	-
Alemtuzumab	[redacted]	[redacted]	[redacted]	OCR dominated	8,296
Teriflunomide [b]	[redacted]	[redacted]	[redacted]	9,832	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	-	Dominated
Dimethyl fumarate [b]	[redacted]	[redacted]	[redacted]	OCR dominant	Dominated
Fingolimod [a b]	[redacted]	[redacted]	[redacted]	OCR dominant	Dominated
Natalizumab [a]	[redacted]	[redacted]	[redacted]	OCR dominant	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Comparator not in scope for 'ITT' population; b PAS available but not included in this analysis; c pairwise ICERs for ocrelizumab vs. comparators calculated by ERG from company model.

One can draw some conclusions from the remaining comparisons with alemtuzumab and the blended ABCRs (for which discounted PAS prices are not available). These indicate that under

the company's base case for the ITT population: alemtuzumab dominates ocrelizumab; but if alemtuzumab is not an option for some patients, ocrelizumab has an ICER of £26,435 compared with blended ABCR (CS Table 59). The ICER for ocrelizumab varies between individual ABCR comparators, with a range from £22,841 compared with IFNβ-1a (Avonex) to £35,028 compared with Pegβ-1a (CS Appendix J.1.2 Table 63).

The company argues that the analysis excluding alemtuzumab is relevant for three reasons:

- The QALY difference between ocrelizumab and alemtuzumab is small ([redacted] over 50 years) and relies on the CARE-MS I and II trials for alemtuzumab, which the company argue are of lower quality than the OPERA I and II trials that underpin the effectiveness of ocrelizumab. Particularly because the CARE-MS trials were open label.
- There is uncertainty over the extent to which retreatment is required to maintain effectiveness for alemtuzumab. We note that the company base case includes costs for alemtuzumab retreatment for 19%, 16%, 14% and 13% of patients in years 3, 4, 5 and form year 6 onwards.
- The safety profile and monitoring requirements for alemtuzumab mean that it will not be suitable for every patient, so it is important to maintain a choice of treatments in RRMS.

They further argue that when alemtuzumab is not an option, the appropriate comparator is blended ABCR because, although the costs and QALYs differ between the individual β-interferons and glatiramer acetate, clinicians consider them to be 'broadly equivalent'.

The ERG accepts both points. There will be patients for whom alemtuzumab is not clinically appropriate and there is considerable uncertainty over the relative effectiveness and cost-effectiveness of the different β-interferon drugs and glatiramer acetate. However, we conclude that according to the company's base case assumptions, when alemtuzumab is an option it is estimated to be less expensive and more effective than ocrelizumab. And when alemtuzumab is not an option, there is variation in the ICER for ocrelizumab according to the ABCR comparator.

4.4.2 Sensitivity analyses

Probabilistic sensitivity analysis

The PSA results for the company's ITT base case analysis are reported in CS section B.3.8.1, Table 61 (PAS for ocrelizumab and list prices for comparators). The results are very similar to the corresponding deterministic analysis. The CS includes cost-effectiveness acceptability curves (CEAC) and cost-effectiveness scatterplots: CS Appendix J.1.3 Figure 47 and 48 for the ITT base case with PAS for ocrelizumab and list prices for comparators. The CEAC shows that alemtuzumab has the highest probability of being cost-effective above a threshold of around £15,000 per QALY gained. Excluding alemtuzumab (CS B.3.8.1 Figure 29), PEGβ -1a has the highest estimated probability of being cost-effective up to a threshold of about £42,000 per QALY gained, with ocrelizumab having the highest probability after that point.

One-way deterministic sensitivity analyses

The company conducted one-way sensitivity analysis, varying parameters between 95% confidence/credible interval limits or by 20% of the mean. The CS includes tornado diagrams illustrating how the net monetary benefit for ocrelizumab (at a threshold of £30,000 per QALY gained) varies: CS Figure 31 (B.3.8.2) for the comparison with IFNβ-1a (Rebif) and CS Appendix J.1.3 Figures 49 to 56 for other comparators. The results are consistently most sensitive to the treatment effects on disability progression (CDP). Results are also sensitive to discontinuation rates for dimethyl fumerate and teriflunomide.

Scenario Analyses

The CS also presents a series of scenario analyses testing the sensitivity of results to changes in data sources or assumptions (CS B.3.8.3.). Results for the company ITT base case with ocrelizumab PAS and list prices for comparators are shown in Table 65 of the CS. The cost-effectiveness of ocrelizumb in comparison with alemtuzumab, dimethyl fumerate, fingolimod, natalizumab and teriflunomide is not sensitive to any of the scenarios tested. However, some of the ICERs in comparison with the ABCR drugs do vary between scenarios: we summarise these findings in Table 53.

Ocrelizumab appears relatively less cost-effective in comparison with the ABCR drugs for four efficacy scenarios: CDP-24 instead of CDP-12 MTC effects (scenario 9); assumptions about waning of the effectiveness of treatment over time (scenarios 12 and 13); and a reduction in the

discontinuation rates for all drugs by 50% from year 3 onwards (scenario 14). Conversely, results were relatively more favourable for ocrelizumab in two scenarios: use of MTC results for the HA subgroup (scenario 10); and using social care cost estimates form the BOUNDS-MS study, CS Appendix M (scenario 16).

Table 53 Company scenario analyses (ocrelizumab PAS, list prices for comparators)

	ICER ocrelizumab vs. ABCR comparators				
	IFNβ-1a (Avonex)	**GA**	**IFNβ-1b**	**pegβ-1a**	**IFNβ-1 (Rebif)**
Company ITT base case	**22,841**	**27,304**	**23,711**	**35,028**	**25,911**
NATURAL HISTORY					
1) Baseline demographics: Pickin et al 2009	21,773	26,079	22,691	33,717	24,670
2) EDSS transitions: London Ontario	22,781	27,822	23,885	36,150	25,803
3) ARR: HA subgroup (natalizumab submission)	22,843	27,304	23,712	35,030	25,913
4) ARR: RES subgroup (natalizumab submission)	20,695	25,869	22,254	32,772	23,913
5) ARR: Held et al 2005 and UK MS Survey 2005	21,309	25,985	22,408	33,419	24,423
6) Relapse duration:1 month	22,910	27,358	23,759	35,134	25,983
7) Relapse duration: 2 months	22,775	27,252	23,665	34,927	25,843
8) Mortality risk: Kingwell et al 2012	21,987	26,690	22,941	34,830	25,198
EFFICACY					
9) Disability progression (CDP-24)	37,805	37,113	25,663	94,196	24,329
10) MTC HA subgroup	16,657	19,920	17,297	NR	18,006
11) MTC RES subgroup	25,071	29,036	25,613	NR	28,792
12) Treatment waning: 75% after 2 years and 50% after 5 years for all DMTs	34,704	40,986	35,193	56,070	40,523
13) Treatment waning: 75% after 2 years and 50% after 5 years for comparators; 75% after 4 years and 50% after 7 years for ocrelizumab	28,487	33,524	28,836	43,869	31,167
14) All-cause discontinuation: 50% after year 2	24,546	29,322	25,987	37,064	27,406
COSTS					
15) Health state costs (medical): BOUNDS-MS	21,732	26,203	22,633	33,854	24,756
16) Health state costs (social): BOUNDS-MS	13,296	17,698	14,221	25,469	16,423
17) Relapse cost: Hawton et al 2016	23,644	27,828	24,252	35,832	26,649
UTILITIES					
18) Health state utilities: Orme et al 2007	23,905	28,582	24,807	36,605	27,070
19) Relapse disutility: OPERA I and II regression	22,757	27,238	23,652	34,898	25,823

4.4.3 Subgroup Analyses

Finally, the company presents results for the HA and RES subgroup analyses in section B.3.9 of the CS. These analyses do not include alemtuzumab, because results are not available from the subgroup MTC analyses for the outcome of CDP12. As in the ITT analysis, daclizumab is excluded because of the EMA safety warning. We reproduce tables of deterministic results for the two subgroups below, using the ocrelizumab PAS and list price for comparators. These results are not informative because of the omission of alemtuzumab and the PAS price for fingolimod.

Table 54 Base case HA subgroup, deterministic: adapted from CS Table 67 (ocrelizumab PAS; list prices for comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]	-	-
Fingolimod	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Table 55 Base case RES subgroup, deterministic: adapted from CS Table 71 (ocrelizumab PAS; list prices for comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]	-	-
Natalizumab	[redacted]	[redacted]	[redacted]	1,065,854	1,065,854

4.5 ERG additional analysis

We made one very small correction to the company model, adding 3 decimal places for the ARR natural history data, as reported in CS Table 35. Results under the company base case are therefore slightly different to those reported in the CS.

The analyses presented below only include comparators in the scope for the population of interest: patients without HA or RES disease, HA and RES subgroups. Results below use the PAS price for ocrelizumab and list prices for comparators. We replicate the analyses including PAS prices for daclizumab, dimethyl fumerate, fingolimod and teriflunomide in Addendum 1 to this report.

For simplicity, we present results with a 'blended ABCR' comparator, based on the market share weights reported by the company (CS Table 55). We use scenario analysis to show how results differ for the separate β-interferon and GA comparators, reporting the range of results for the most and least cost-effective ABCR drug.

4.5.1 Additional scenario analysis on company base case

Results for the company ITT base case with relevant comparators for patients without HA or RES disease are shown in Table 56. The QALY results are the same as those reported in CS Table 57 and there are very small differences in the estimated costs and ICERs due to our use of more precise baseline ARR rates.

Table 56 Company base case ITT (PAS ocrelizumab; list prices for comparators)

Technologies	Total costs (£)	Total QALYs	ICER (£/QALY)	
			Ocrelizumab vs. comparator	Incremental
Blended ABCRs	[redacted]	[redacted]	£26,436	
Alemtuzumab	[redacted]	[redacted]	OCR dominated	£8,299
Teriflunomide [a]	[redacted]	[redacted]	£9,833	Dominated
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab [a]	[redacted]	[redacted]	OCR dominant	Dominated
Dimethyl fumarate [a]	[redacted]	[redacted]	OCR dominant	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a PAS available but not included in this analysis

Results of the company's one-way sensitivity analyses with our minor corrections are illustrated in Figure 7 and Figure 8 below. In addition to a comparison of ocrelizumab versus IFNβ-1a

(Rebif), we also present a comparison of ocrelizumab versus alemtuzumab. Neither of these comparators has a discounted PAS price available, so the results reflect prices paid in the NHS. The two figures show that efficacy at prevening disability progression is the major source of uncertainty over the model results.

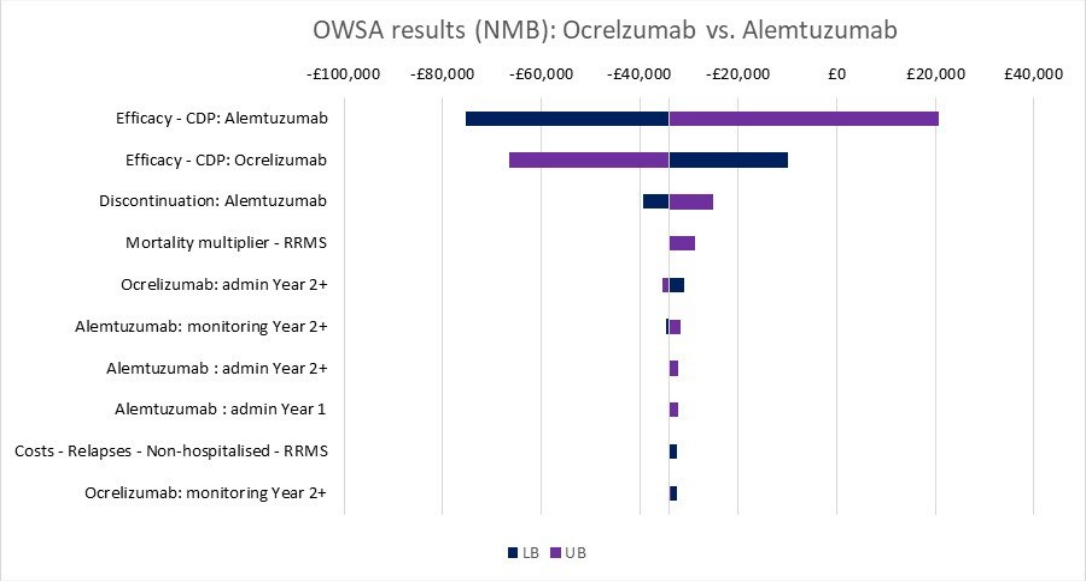


Figure 7 Tornado diagram: company ITT base case ocrelziumab vs alemtuzumab (PAS price for ocrelizumab)

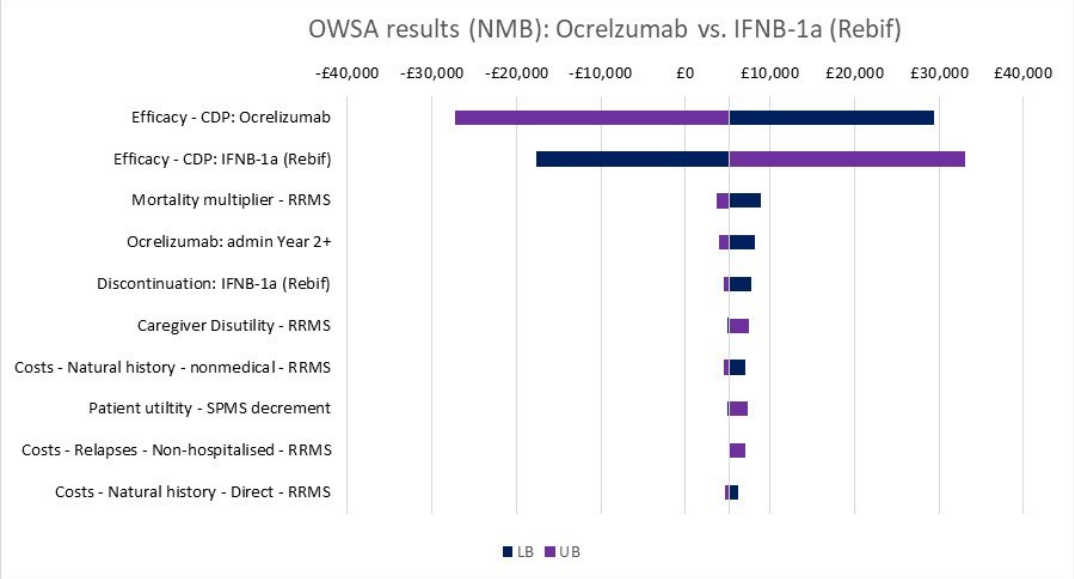


Figure 8 Tornado diagram: company ITT base case ocrelizumab vs IFNβ-1a (Rebif) (PAS price for ocrelizumab)

We reran a series of scenario analyses on the company's base case for the non HA/RES population, including those presented in CS Table 65 that were relevant for this group. In addition, we ran some analyses to address further uncertainties. Our rerun of the company's base case and scenarios was preceeded by a correction of model inputs for ARR by states, which were rounded off in the company's model. In our presentation of results, we exclude out of scope comparisons and present results as pairwise ICERs (ocrelizumab versus comparators).

For a complete list of scenarios and results using list prices (PAS for ocrelizumab) and PAS prices for all treatments where available, see Table 57 below and Table 3 of Addendum 1 to this ERG report respectively. A clear difference between these two results is that while daclizumab and DMF appear dominated in ERG Table 57, the ICERs for most scenarios are close to the threshold of £30,000 in the PAS analysis. Results are identical for ABCR and ALEM as PAS prices are not available. Key conclusions from Table 57 are discussed below:

- Treatment waning was a major driver, with the ICER for ocrelizumab exceeding £30,000 (versus ABCR) when the same assumption of equal waning was applied to all DMTs. An assumption of delayed waning for ocrelizumab improved cost-effectiveness.
- In our pairwise comparison of ocrelizumab versus the most cost-effective ABCR (pegIFNβ-1a), the ICER exceeds £30,000.
- In our pairwise comparison of ocrelizumab versus the least cost-effective ABCR (avonex), the ICER was under £30,000.

In Table 58 and Table 59 below, we present a rerun of the company's scenario analyses for the HA and RES subgroups for relevant comparators. In the HA subgroup, ocrelizumab is dominated by alemtuzumab in all scenarios but always dominates daclizumab and fingolimod. Similarly, in the RES subgroup, ocrelizumab is dominated in all scenarios by alemtuzumab but dominates daclizumab and natalizumab where applicable.

Table 57 ERG scenario analysis, company ITT base case (OCR PAS, list prices for comparators)

		ICER ocrelizumab vs. ABCR comparators				
		ABCR	**ALEM**	**DAC**	**DMF**	**TERI**
	Company ITT base case	26,436	OCR dominated	OCR dominant		9,833
Company scenarios						
1	Demographics: Pickin et al 2009	25,245	OCR dominated	OCR dominant		9,226
2	EDSS transitions: London Ontario	26,714	OCR dominated	OCR dominant		8,057
5	ARR: Held & UK MS Survey 2005	25,001	OCR dominated	OCR dominant		8,473
6	Relapse duration:1 month	26,502	OCR dominated	OCR dominant		9,858
7	Relapse duration: 2 months	26,373	OCR dominated	OCR dominant		9,810
8	Mortality risk: Kingwell et al 2012	25,768	OCR dominated	OCR dominant		8,274
9	Disability progression (CDP-24)	32,860	OCR dominated	OCR dominant		9,199
12	Waning: equal across DMTs	40,332	OCR dominated	OCR dominant		15,236
13	Waning: delayed waning for OCR	32,581	240,947	OCR dominant		11,763
14	Discontinuation: 50% fall year 3+	28,273	OCR dominated	OCR dominant		11,735
15	Medical costs: BOUNDS-MS	25,316	OCR dominated	OCR dominant		8,688
16	Social care costs: BOUNDS-MS	16,881	OCR dominated	OCR dominant		130
17	Relapse cost: Hawton et al 2016	27,101	OCR dominated	OCR dominant		10,509
18	HS utilities: Orme et al 2007	27,655	OCR dominated	OCR dominant		10,289
19	Relapse disutility: OPERA I and II	26,355	OCR dominated	OCR dominant		9,803
ERG scenarios						
1	No EDSS reductions in SPMS	18,839	OCR dominated	OCR dominant		5,175
2	No effect on SPMS conversions	26,868	OCR dominated	OCR dominant		9,796
3	No EDSS increase on conversion	28,273	OCR dominated	OCR dominant		11,300
4	Mortality multiplier Jick et al 2014	24,269	OCR dominated	OCR dominant		7,513
5	HCC adjustment ALEM: 0%	26,436	OCR dominated	OCR dominant		9,833
6	HCC adjustment OCR: 2.5%	27,996	OCR dominated	OCR dominant		11,566
7	HS costs: UK MS Survey	17,900	OCR dominated	OCR dominant		1,158
8	HS costs: Biogen BoI	26,809	OCR dominated	OCR dominant		10,207
9	ALEM retreatment maximum: 4	26,436	OCR dominated	OCR dominant		9,833
10	Carer disutility: maximum -0.05	28,015	OCR dominated	OCR dominant		10,432
11	Comparison with best ABCR	35,030	pegIFNβ-1a			
12	Comparison with worst ABCR	22,843	IFNβ-1a (Avonex)			

Table 58 ERG scenario analysis, company HA subgroup analysis (OCR PAS; list prices for comparators)

		ICER ocrelizumab vs. comparators		
		ALEM	**DAC**	**FINGO**
Company HA subgroup analysis		NA	NA	OCR dominant
Disability progression: CDP-24				
1	HA MTC CDP-24	OCR dominated	OCR dominant	OCR dominant
2	ITT MTC CDP-24	OCR dominated	OCR dominant	OCR dominant
3	British Columbia EDSS transitions	OCR dominated	OCR dominant	OCR dominant
4	ARR from Pazold/UK-MS Survey	OCR dominated	OCR dominant	OCR dominant
5	No effect on SPMS conversion	OCR dominated	OCR dominant	OCR dominant
6	No EDSS rise on conversion	OCR dominated	OCR dominant	OCR dominant
7	Effect 75% year 3-4; 50% year 6+	OCR dominated	OCR dominant	OCR dominant
8	Delayed waning of effect OCR	OCR dominated	OCR dominant	OCR dominant
9	HS costs: BOUNDS	OCR dominated	OCR dominant	OCR dominant
10	HS costs: UK MS Survey	OCR dominated	OCR dominant	OCR dominant
11	HS costs: Biogen BoI	OCR dominated	OCR dominant	OCR dominant

NA: MTC results not available for scenario

Table 59 ERG scenario analysis, company RES subgroup analysis (OCR PAS; list prices for comparators)

		ICER ocrelizumab vs. comparators		
		ALEM	**DAC**	**NAT**
Company RES subgroup analysis		NA	£10,636	£1,065,854 SW
Disability progression: CDP-24				
1	RES MTC CDP-24	OCR dominated	NA	£91,265 SW
2	ITT MTC CDP-24	OCR dominated	OCR dominant	£203,440 SW
3	British Columbia EDSS transitions	OCR dominated	NA	£68,025 SW
4	ARR from Pazold/UK-MS Survey	OCR dominated	NA	£95,653 SW
5	No effect on SPMS conversion	OCR dominated	NA	£75,992 SW
6	No EDSS rise on SPMS conversion	OCR dominated	NA	£77,466 SW
7	Effect 75% year 3-4; 50% year 6+	OCR dominated	NA	£161,079 SW
8	Delayed waning of effect OCR	OCR dominated	NA	£252,936 SW
9	HS costs: BOUNDS	OCR dominated	NA	£80,591 SW
10	HS costs: UK MS Survey	OCR dominated	NA	£90,162 SW
11	HS costs: Biogen BoI	OCR dominated	NA	£92,806 SW

SW: south west quadrant – less effective and less expensive, so higher ICER indicates ocrelizumab is relatively more cost-effective. NA: MTC results not available for scenario.

4.5.2 ERG base case

Table 60: Assumptions and parameter changes in ERG base case analysis

Parameter	CS base case	ERG base case	Justification
Treatment effects			
Measure of disability progression	CDP-12	CDP-24	CDP-24 provides a more robust measure of disability progression, which is less likely to include long episodes of relapse.
Effect on SPMS conversion	50% of CDP treatment effect assumed	No additional effect on SPMS conversion	Assumption not evidence based. Indirect effect is accounted for via effect on EDSS progression
HA and RES subgroups	Subgroup MTCs	ITT MTC	Sparsity of data and post-hoc nature of MTC subgroups
Transition probabilities- conversion from RRMS to SPMS			
Increase in EDSS on conversion to SPMS	EDSS state always increases by 1	No increase	EDSS transitions for SPMS already captured in the transition matrix (TA441, paragraph 4.20).
Treatment effect waning			
Waning of treatment effects	None	Decline by 25% after 2 years and by 50% after 5 years for all treatments	This is a conservative assumption, consistent with previous appraisals. Tested in scenario analyses.
Health-related quality of life			
Caregiver disutilities	Sourced from TA127 (maximum disutility 0.14 at EDSS 9)	Assume maximum, disutility of 0.05 at EDSS 9	Daclizumab appraisal (TA441, paragraph 4.21) and expert opinion.
Resource use cost			
Source of health state costs	Tyas et al (2007), with direct medical costs and 25% of non-medical costs	UK MS Survey 2007 uprated to 2014/15 costs in ERG report for TA320 (DMF). With Biogen Burden of Illness estimates in sensitivity analysis	NICE committee on daclizumab concluded that uprated UK MS Survey or Biogen Burden of Illness (BOI) estimates could be used (TA441, paragraph 4.18). We prefer UK MS Survey results as they are in public domain.
Alemtuzumab retreatment rates	CS assumes 13% continuing retreatment from year 6 onwards	No retreatment from year 5 (maximum of 4 courses of treatment)	CS assumption not backed by evidence. NICE committee on daclizumab favoured a maximum of 4 treatment courses (TA441 paragraph 4.15)
Half-cycle correction (HCC)	HCC applied with 5% adjustment for alemtuzumab	Addition of 5% uplift in half the cost of ocrelizumab	To offset HCC for cost of drugs at beginning of model cycle

4.5.2.1 ERG analysis: people without HA or RES

The rationale for our base case assumptions are stated and compared with the company's base case assumptions in Table 60 above. In Table 61 below, we present our base case results for the non-HA or RES population, based on the PAS price for ocrelizumab and list prices for comparators. A version of our base case results using PAS prices for all treatments where available is presented in Table 8 of Addendum 1 to this ERG report. Our findings show that ocrelizumab is dominated by alemtuzumab under our preferred assumptions. While ocrelizumab dominates daclizumab and DMF in Table 61, it is less cost-effective in the PAS analysis with an ICER exceeding £30,000 for these comparisons. The ICER for ocrelizumab compared with ABCR is £43,772 per QALY gained.

Table 61 ERG base case, non-HA/RES (PAS ocrelizumab; list prices for comparators)

Technologies	Total costs (£)	Total QALYs	ICER (£/QALY)	
			Ocrelizumab vs. comparator	Incremental
Blended ABCRs	[redacted]	[redacted]	£43,772	
Alemtuzumab	[redacted]	[redacted]	OCR dominated	£1,992
Teriflunomide	[redacted]	[redacted]	£10,302	Dominated
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab	[redacted]	[redacted]	OCR dominant	Dominated
Dimethyl fumarate	[redacted]	[redacted]	OCR dominant	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a PAS available but not included in this analysis

We carried out scenario analyses to test the sensitivity of our base case model to key uncertainties (see Table 62). While the results for ocrelizumab versus alemtuzumab, daclizumab, DMF and teriflunimide are very similar for the company and ERG base cases, they differ for ocrelizumab versus ABCR: in all scenarios around the ERG base case (Table 62), the ICER for ocrelizumab versus ABCR exceeds £30,000, whereas for most of the scenarios around the company's base case (Table 57), the ICER for ocrelizumab versus ABCR is below £30,000. In the all-PAS version of ERG base case scenario analyses (Table 9 in Addendum 1 to this report), the ICER of ocrelizumab is above £30,000 for almost all scenarios in comparisons of ocrelizumab versus ABCR, daclizumab, DMF and teriflunomide.

Table 62 Scenario analyses, ERG base case non-HA/RES (ocrelizumab PAS, list prices for comparators)

	ICER ocrelizumab vs. ABCR comparators				
	ABCR	**ALEM**	**DAC**	**DMF**	**TERI**
ERG base case	43,772	OCR dominated	OCR dominant		10,302
NATURAL HISTORY					
Demographics Pickin 2009	44,442	OCR dominated	OCR dominant		8,508
RRMS EDSS transitions LO	55,995	OCR dominated	OCR dominant		11,106
No EDSS regression in SPMS	42,211	OCR dominated	OCR dominant		7,159
Effect on SPMS conversion 50%	41,810	OCR dominated	OCR dominant		13,214
EDSS increase on conversion	46,501	OCR dominated	OCR dominant		10,969
Relapse duration 1 month	43,872	OCR dominated	OCR dominant		10,345
Relapse duration 2 months	43,676	OCR dominated	OCR dominant		10,261
Mortality multiplier Kingwell	44,386	OCR dominated	OCR dominant		8,086
Mortality multiplier Jick	43,342	OCR dominated	OCR dominant		7,078
EFFICACY					
CDP 12-week confirmation	39,524	OCR dominated	OCR dominant		12,033
No waning of treatment effect	33,082	OCR dominated	OCR dominant		6,090
Delayed waning for OCR	39,077	OCR dominated	OCR dominant		10,357
Discontinuation falls 50% year 3	47,629	OCR dominated	OCR dominant		12,379
ALEM retreatment ongoing	43,772	OCR dominated	OCR dominant		10,302
COSTS					
No HCC adjustment ALEM	43,772	OCR dominated	OCR dominant		10,302
No HCC adjustment OCR	41,917	OCR dominated	OCR dominant		7,724
Health state costs: Biogen BoI	47,237	OCR dominated	OCR dominant		20,720
Medical costs: BOUNDS-MS	40,129	OCR dominated	OCR dominant		OCR dominant
Social costs: BOUNDS-MS	40,129	OCR dominated	OCR dominant		OCR dominant
Relapse cost: User input	44,382	OCR dominated	OCR dominant		11,414
UTILITIES					
Health state utilities: Orme 2007	47,292	OCR dominated	OCR dominant		10,956
Relapse disutility: Regression analysis of trial EQ-5D data	43,649	OCR dominated	OCR dominant		10,249
Carer disutility: max -0.14	43,000	OCR dominated	OCR dominant		9,671

4.5.2.2 ERG analysis: HA subgroup

The results for the ERG base case analysis in the HA subgroup are shown in Table 63, with scenario analysis in Table 64 for the ocrelizumab PAS and list prices for comparators. Corresponding analyses based on all available PAS prices are shown in Tables 10 and 11 in Addendum 1 to this report. These show that ocrelizumab is dominated by alemtuzumab under ERG preferred assumptions. The ICERs for ocrelizumab versus fingolimod are subject to uncertainty in the all-PAS analyses.

Table 63 ERG HA subgroup (OCR PAS, list prices for comparators)

Technologies	Total costs (£)	Total QALYs	OCR vs comparator (£/QALY)	Incremental ICER (£/QALY)
Alemtuzumab	[redacted]	[redacted]	OCR dominated	
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab	[redacted]	[redacted]	OCR dominant	Dominated
Fingolimod	[redacted]	[redacted]	OCR dominant	Dominated

Table 64 Scenario analyses, ERG HA subgroup (OCR PAS, list prices for comparators)

	ICER ocrelizumab vs. comparators		
	ALEM	**DAC**	**FINGO**
ERG HA subgroup analysis	OCR dominated	OCR dominant	OCR dominant
1 HA MTC CDP-24	OCR dominated	OCR dominant	OCR dominant
2 HA MTC CDP-12	NA	NA	OCR dominant
3 British Columbia EDSS transitions	OCR dominated	OCR dominant	OCR dominant
4 ARR from Pazold/UK-MS Survey	OCR dominated	OCR dominant	OCR dominant
5 50% effect on SPMS conversion	OCR dominated	OCR dominant	OCR dominant
6 EDSS rise on SPMS conversion	OCR dominated	OCR dominant	OCR dominant
7 No waning of treatment effects	OCR dominated	OCR dominant	OCR dominant
8 Delayed waning of effect OCR	OCR dominated	OCR dominant	OCR dominant
9 HS costs: BOUNDS	OCR dominated	OCR dominant	OCR dominant
11 HS costs: Biogen BoI	OCR dominated	OCR dominant	OCR dominant

4.5.2.3 ERG analysis: RES subgroup

Finally, Table 65 and Table 66 below show the ERG preferred analysis and scenarios for the RES subgroup with the ocrelizumab PAS and list prices for comparators. It can be seen that alemtuzumab dominates ocrelizumab under all scenarios tested. Compared with natalizumab, ocrelizumab has favourable ICERs (note that ocrelizumab is estimated to be less effective but also less costly than ocrelizumab). Results with the PAS for daclizumab as well are shown in Tables 12 and 13 of Addendum 1 to this ERG report.

Table 65 ERG RES subgroup (OCR PAS, list prices for comparators)

Technologies	Total costs (£)	Total QALYs	OCR vs comparator (£/QALY)	Incremental ICER (£/QALY)
Alemtuzumab	[redacted]	[redacted]	OCR dominated	
Ocrelizumab	[redacted]	[redacted]	-	Dominated
Daclizumab	[redacted]	[redacted]	OCR dominant	Dominated
Natalizumab	[redacted]	[redacted]	£183,633 SW	Dominated

SW: south west quadrant – less effective and less expensive, so higher ICER indicates ocrelizumab is relatively more cost-effective.

Table 66 Scenario analyses, ERG RES subgroup (OCR PAS, list prices for comparators)

	ICER ocrelizumab vs. comparators		
	ALEM	**DAC**	**NAT**
ERG RES subgroup analysis	OCR dominated	OCR dominant	£183,633 SW
1 RES MTC CDP-24	OCR dominated	NA	£110,264 SW
2 RES MTC CDP-12	NA	£14,013	£217,721 SW
3 British Columbia EDSS transitions	OCR dominated	OCR dominant	£202,010 SW
4 ARR from Pazold/UK-MS Survey	OCR dominated	OCR dominant	£192,069 SW
5 50% effect on SPMS conversion	OCR dominated	OCR dominant	£230,696 SW
6 EDSS rise on SPMS conversion	OCR dominated	OCR dominant	£248,566 SW
7 No waning of treatment effects	OCR dominated	OCR dominant	£107,477 SW
8 Delayed waning of effect OCR	OCR dominated	OCR dominant	£354,302 SW
9 HS costs: BOUNDS	OCR dominated	OCR dominant	£188,358 SW
11 HS costs: Biogen BoI	OCR dominated	OCR dominant	£195,656 SW

SW: south west quadrant – less effective and less expensive, so higher ICER indicates ocrelizumab is relatively more cost-effective. NA: MTC results not available for scenario.

5 Innovation

The company makes a case for ocrelizumab being an innovative therapy (CS section B.1.2), arguing that ocrelizumab has a mechanism of action distinct from that of other DMTs, establishing a new standard of care in RRMS because of:

- Less frequent administration than other DMTs, possibly mitigating the risk of non-adherence;
- A favourable safety profile, requiring no additional monitoring tests or MRI screening;
- A low probability of long-term treatment waning based on biologically plausible contributory factors, associated evidence following literature review and consultation with clinical experts;
- A durable treatment effect based on the supporting data from the OLE phase;
- Decreasing inflammation of the innate immune system based on pre-clinical investigations using an animal model of human MS disease;
- Reversibility of the pharmacodynamic effect based on the half-life of ocrelizumab (26 days), with the Phase II trial indicating a median time to B cell repletion of 72 weeks (range 27–175 weeks).[44]

The CS further states that the MTC indicates that ocrelizumab is a highly efficacious DMT linked with lower healthcare utilisation (two infusions per year) and less frequent monitoring compared to other high efficacy DMTs, leading to a step-change in treatment for all RRMS patients and potential earlier treatment with a high efficacy DMT.

The ERG agrees that the above considerations are plausible benefits of ocrelizumab, but the assertions regarding safety, patient adherence and treatment waning are as yet unproven in the long-term.

6 DISCUSSION

The company's searches for evidence of clinical effectiveness evidence and the overall approach to the company's evidence synthesis, including the assessment of direct and indirect effects, is generally well-structured, logical, and based on established methods. The company's economic model also follows a logical approach based on established methods. However, there are a number of weaknesses and uncertainties which we have summarised below.

6.1 Summary of clinical effectiveness issues

- The MTC analyses of CDP-12 and CDP-24 assume proportional hazards. The company provided evidence to suggest that this assumption is supported for the comparison of ocrelizumab against interferon β-1a, but it is unclear whether the assumption would be supported for comparisons among other DMTs.
- To enable MTC networks to be formed for HA and RES disease severity subgroups, the company utilised ITT data from trials of 'ABCR' comparators (types of interferon β and glatiramer acetate). The underlying assumption is that, for these treatments, the treatment effect observed in the ITT population would be the same as the treatment effects in the subgroup populations. However, the company has not clearly justified that this assumption is supported. Overall, given the limitations of the subgroup analyses, including that they were post-hoc and potentially at risk of selection bias, both the company and ERG consider the MTC results for these subgroups to be unreliable.
- There are marked differences between trials included in the MTCs in the proportions of patients who were treatment-naïve and treatment-experienced, and also in the time since onset of symptoms. The the ERG is therefore uncertain whether the consistency assumption of MTC analysis is supported.
- There is uncertainty around some individual input data for the MTCs. (i) An independent MTC which the company used to provide ITT CDP-12 outcomes for some comparisons against alemtuzumab, obtained by the company from the 'HAS Reimbursement dossier' has not been critiqued by the company and the ERG is unable to locate the dossier to check it. (ii) It is unclear whether the placebo arm in the Calbrese 2012 trial was included in MTC analysis. (iii) The company does not adequately justify why the Etemadefir 2006 trial was excluded from MTC analyses of ARR.

- The company did not conduct any sensitivity analyses to investigate whether MTC outcomes were sensitive to the inclusion of trials that were judged to be at high risk of bias.
- In the OPERA trials there are unbalanced missing data for some secondary outcomes (though these outcomes do not inform the economic analysis).

6.2 Summary of cost effectiveness issues

Decision problem addressed

The company's economic analysis generally addresses the decision problem set in the NICE scope. However, the CS presents results including comparators that are outside of the scope (fingolimod and natalizumab in the company's ITT base case analysis) and excluding comparators that are in scope (alemtuzumab). This is not a serious problem because the model is easily adapted to present only relevant incremental comparisons.

The appropriateness of excluding daclizumab is less clear-cut, given the EMA safety warning issued after finalisation of the scope for this appraisal. For completeness, we report cost-effectiveness results for daclizumab alongside other comparators as information for the Committee.

We do have concern about bias relating to the use of ITT effectiveness evidence to drive cost-effectiveness estimates for patients without HA or RES disease. DMTs indicated for this group differ from those for people with HA and RES MS, thus incremental cost-effectiveness should be considered separately for the three subgroups. In response to a clarification question, the company shows that effectiveness estimates from the OPERA trials are rather less favourable for the non-HA/RES subgroup than for the whole ITT population. However, conducting a revised MTC for people without HA or RES MS is not possible for this appraisal, and might not be possible at all unless sufficient other trials report results excluding HA and RES subgroups.

Model structure and assumptions

The model follows the NICE reference case.

The model reflects many features of models used to inform previous NICE appraisals of DMTs for MS, including the choice of model structure and health states and sources for many of the input parameters. It also adopts a number of assumptions employed in previous appraisals, which we consider reasonable. These include:

- Stopping rules for DMTs: EDSS>=7 or conversion to SPMS
- No impact of treatment on severity or duration of relapses
- Treatment reduces disability progression but not regression
- Rates of withdrawal from treatment and adverse effects are constant over time
- DMT does not directly affect mortality. An indirect effect is modelled because treatment reduces EDSS progression and mortality rates are modelled to rise with EDSS

However, we identified a number of assumptions in the company model not supported by evidence that the experts who we consulted thought were unlikely or unrealistic:

- Confirmation of disability progression at 12 weeks. We believe that CDP-24 weeks is a more robust measure, less likely to be confounded by longer-lasting temporary relapses
- Effect on rate of conversion from RRMS to SPMS (assumed 50% of relative effect on CDP)
- Conversion from RRMS to SPMS is accompanied by a one-point increase in EDSS
- Probability of EDSS improvement in SPMS disease
- No waning of treatment effects over time
- Rates of retreatment for alemtuzumab assumed 13% from year 6 onwards

Data sources

Generally, we agreed with the company's choice of data sources to inform model parameters. The model uses estimates of EDSS transition probabilities from the British Columbia dataset, which we consider appropriate in the absence of a placebo arm in the OPERA trials. The resulting transition matrix allows for improvements in EDSS as well as deterioration. As mentioned above, we believe that CDP-24 is a better measure of treatment effectiveness in preventing disability progression than CDP-12.

The company used estimates of health state costs from Tyas et al. 2007 (uprated for inflation) in their base case model and estimates from the BOUNDS-MS burden of disease study in scenario analysis. Recent NICE appraisals have used other sources of health state cost estimates, including UK MS Survey (at 2011/12 prices) and a burden of disease study presented in the submission for the NICE daclizumab appraisal. We consider that the latter sources give more realistic estimates of current UK prices from an NHS and PSS perspective.

Company base case results

The company's base case analysis for the ITT population suggests that: alemtuzumab dominates ocrelizumab; but if alemtuzumab is not an option for some patients, ocrelizumab has an ICER of £26,435 compared with blended ABCR (CS Table 59). The ICER for ocrelizumab varies between individual ABCR comparators, with a range from £22,841 compared with IFNβ-1a (Avonex) to £35,028 compared with Pegβ-1a (CS Appendix J.1.2 Table 63).

The company results for the HA and RES subgroups suggest that ocrelizumab is cost-effective compared with fingolimod and natalizumab respectively. However, these results exclude alemtuzumab, because results are not available from the subgroup MTC analysis for the outcome of CDP-12 that the company used. As in the ITT analysis, daclizumab is excluded because of the EMA safety warning.

The CS also reports one-way sensitivity analysis, scenario analyses and probabilistic analysis, which are reproduced and discussed in this ERG report.

Summary of additional work undertaken by the ERG

The ERG analysis consists of three parts:

- A rerun of the company's model after minor corrections, but essentially maintaining the company's base case assumptions. Out of scope comparators are excluded from results of this analysis.
- A base case analysis based on alternative assumptions that the ERG found more plausible following consultations with experts and after consideration of available evidence. The ERG also explores additional scenarios for individual parameters.
- A PAS analysis reported in Addendum 1 to this ERG report. As previously stated, cost-effectiveness results reported by the company do not reflect prices paid in the NHS, since the PAS price for ocrelizumab is compared to the list prices of comparators.

Our findings show that ocrelizumab is dominated by alemtuzumab under our preferred assumptions. While ocrelizumab dominates daclizumab and DMF based on the PAS price for ocrelizumab and list prices for comparators, it is less cost-effective in the all-PAS analysis. The ICER for ocrelizumab compared with ABCR is £43,772 per QALY gained.

The ERG base case analysis in the HA subgroup shows that ocrelizumab is dominated by alemtuzumab under ERG preferred assumptions. The ICERs for ocrelizumab versus fingolimod are subject to uncertainty in the all-PAS analyses.

For the RES subgroup, we found that alemtuzumab dominates ocrelizumab under all scenarios tested. Compared with natalizumab, ocrelizumab has favourable ICERs (note that ocrelizumab is estimated to be less effective but also less costly than natalizumab). Results with the PAS for daclizumab are shown in Tables 12 and 13 of Addendum 1 to this ERG report.

7 REFERENCES

1. Lunde H, Assmus J, Myhr K, Bø L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. Journal of neurology, neurosurgery, and psychiatry. 2017;88:621-5.
2. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. Journal of neurology, neurosurgery, and psychiatry. 2014;85(1):76-84.
3. Marrie R, Elliott L, Marriott J, Cossoy M, Blanchard J, Leung S, et al. Effect of comorbidity on mortality in multiple sclerosis. Neurology. 2015;85:240-7.
4. Lorscheider J, Buzzard K, Jokubaitis V, Spelman T, Havrdova E, Horakova D, et al. Defining secondary progressive multiple sclerosis. Brain. 2016;139 (Pt 9):2395-405.
5. MS-EPIC Team. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol. 2016;80:499-510.
6. Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Practical neurology. 2015;15(4):273-9.
7. National Institute for Health and Care Excellence (NICE). Multiple sclerosis in adults: management. Clinical guideline (CG186). 2014.
8. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292-302.

9. Comi G, Radaelli M, Sørenson P. Evolving concepts in the treatment of relapsing multiple sclerosis. Lancet. 2017;389:1347-56.
10. Pardo G, Jones D. The sequence of disease‐modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. J Neurol. 2017;264:2351-74.
11. Wiendl H, Bourdette D, Ciccarelli O. Can immune reprogramming with alemtuzumab induce permanent remission in multiple sclerosis? Neurology. 2017;89(11):1098-100.
12. ICER (Institute for Clinical and Economic Review). A look at disease-modifying therapies for multiple sclerosis. Do these new drugs meet an important need? Boston, MA, USA: ICER; 2017.
13. National Institute for Health and Care Excellence. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (TA254). 2012.
14. National Institute for Health and Care Excellence. Alemtuzumab for treating relapsing‐remitting multiple sclerosis (TA312). 2014.
15. National Institute for Health and Care Excellence. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (TA127). 2007.
16. EMA (European Medicines Agency). EMA restricts use of multiple sclerosis medicine Zinbryta. London: EMA; 2017. Report No.: EMA/424159/2017.
17. National Institute for Health and Care Excellence. Multiple sclerosis - interferon beta, glatiramer acetate (review TA32) [ID809]. 2018.
18. F. Hoffman-La Roche Ltd. Sumary of product characteristics - Ocrevus [draft version] [confidential document]. 2017.
19. National Institute for Health and Care Excellence. Daclizumab for treating relapsing–remitting multiple sclerosis (TA441). 2017.
20. EMA (European Medicines Agency). Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis 2015.
21. Tolley K, Hutchinson M, You X, Wang P, Sperling B, Taneja A, et al. A network meta-analysis of efficacy and evaluation of safety of subcutaneous pegylated interferon beta-1a versus other injectable therapies for the treatment of relapsing-remitting multiple sclerosis. PLoS One. 2015;10(6):e0127960:1-21.
22. Huisman E, Papadimitropoulou K, Jarrett J, Bending M, Firth Z, Allen F, et al. Systematic literature review and network meta-analysis in highly active relapsing–remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. BMJ Open. 2017;7:e013430:1-10.

23. Li R, Sun X, Shu Y, Mao Z, Xiao L, Qiu W, et al. Sex differences in outcomes of disease-modifying treatments for multiple sclerosis: A systematic review. Multiple Sclerosis and Related Disorders. 2017;12:23-8.
24. ICER (Institute for Clinical and Economic Review). Disease-modifying therapies for relapsing-remitting and primary-progressive multiple sclerosis: effectiveness and value Boston, MA, USA: ICER; 2017.
25. CADTH (Canadian Agency for Drugs and Technologies in Health). Clinical review report. Ocrelizumab (Ocrevus). CADTH Common drug review. 2017.
26. Chan A, Cutter G, Fox R, Xiao J, Lewin J, Edwards M. Comparative effectiveness of delayed-release dimethyl fumarate versus glatiramer acetate in multiple sclerosis patients: results of a matching-adjusted indirect comparison. J Comp Eff Res. 2017;6:313-23.
27. Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. Mult Scler Relat Disord. 2016;9:23-30.
28. La Mantia L, Di Pietrantonj C, Rovaris M, Rigon G, Frau S, Berardo F, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2016;Issue 11. Art.No.: CD009333.
29. La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2016;Issue 4. Art. No.: CD009371.
30. Melendez-Torres G, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation. Health Technol Assess. 2017;21(52):1-396.
31. Merkel B, Butzkueven H, Traboulsee A, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: a systematic review. Autoimmun Rev. 2017;16:658-65.
32. Riera R, GJM P, Torloni M. Alemtuzumab for multiple sclerosis. Cochrane Database Syst Rev. 2016;Issue 4. Art. No.: CD011203.
33. Siddiqui M, Khurana I, Budhia S, Hettle R, Harty G, Wong S. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing-remitting multiple sclerosis. Curr Med Res Opin. 2017;epub ahead of print.

34. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2015;Issue 9. Art. No.: CD011381
35. Tsivgoulis G, Katsanos A, Mavridis D, Grigoriadis N, Dardiotis E, Heliopoulos I, et al. The efficacy of natalizumab versus fingolimod for patients with relapsing-remitting multiple sclerosis: a systematic review, indirect evidence from randomized placebo-controlled trials and meta-analysis of observational head-to-head trials. PLoS One. 2016;11(9): e0163296:1-14.
36. Vitaliti G, Matin N, Tabatabaei O, Di Traglia M, Pavone P, Lubrano R, et al. Natalizumab in multiple sclerosis: discontinuation, progressive multifocal leukoencephalopathy and possible use in children. Expert Rev Neurother. 2015;15:1321-41.
37. Weideman A, Tapia-Maltos M, Johnson K, Greenwood M, Bielekova B. Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. Front Neurol. 2017;8:577:1-12.
38. Xie Q, Li X, Sun J, Yuan B, Li Y, Wang L, et al. A meta-analysis to determine the efficacy and tolerability of anti-B-cell monoclonal antibodies in multiple sclerosis. Experimental and Therapeutic Medicine. 2017;13(6):3061-6.
39. Zagmutt F, Carroll C. Meta-analysis of adverse events in recent randomized clinical trials for dimethyl fumarate, glatiramer acetate and teriflunomide for the treatment of relapsing forms of multiple sclerosis. Int J Neurosci. 2015;125:798-807.
40. Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2017;2017 (11) (no pagination)(CD010968).
41. Lucchetta R, Riveros B, Wiens A, Bonetti A, Mendes A, Tonin F, et al. Systematic review and network meta-analysis of disease-modifying therapies in relapsing-remitting multiple sclerosis [protocol]. PROSPERO record number CRD420170591202017.
42. Tramacere I, Benedetti M, Capobussi M, Castellini G, Citterio A, Del Giovani C, et al. Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2016;Issue 5. Art. No.: CD012186.
43. Wilson K, McCool R, Glanville J, Edwards M, Fleetwood K. Systematic review and network meta-analysis of treatment for relapsing-remitting multiple sclerosis. York, UK: York Health Economics Consortium; 2017.

44. Kappos L, Li D, Calabresi P, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011;378:1779-87.
45. Hauser S, Bar-Or A, Comi G, Giovannoni G, Hartung H, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376:221-34.
46. Lavery A, Verhey L, Waldman A. Outcome measures in relapsing-remitting multiple sclerosis: capturing disability and disease progression in clinical trials. Mult Scler Int. 2014;Article ID 262350:1-13.
47. van Munster C, Uitdehaag B. Outcome measures in clinical trials for multiple sclerosis. CNS Drugs. 2017;31:217-36.
48. CPMP (Committee for Proprietary Medicinal Products). Points to consider on multiplicity issues in clinical trials. London: EMEA; 2002.
49. EMA (European Medicines Agency). Guideline on adjustment for baseline covariates in clinical trials. London: EMA; 2015. Report No.: EMA/CHMP/295050/2013.
50. Healy B, Engler D, Glanz B, Musallam A, Chitnis T. Assessment of definitions of sustained disease progression in relapsing-remitting multiple sclerosis. Mult Scler Int. 2013;Article ID 189624:1-9.
51. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002;359:1453-60.
52. Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. Clin Ther. 2003;25:105-18.
53. Dias S, Welton N, Sutton AJ, Ades A. NICE DSU Technical Support Document 2: A Genearlised Linear Modelling Framework for Pairwise and Network Meta-analysis of Randomised Controlled Trials (last update September 2016). 2011.
54. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in medicine. 2015;34(6):984-98.
55. MRC Biostatistics Unit. DIC: Deviance Information Criteria 2017 [Available from: https://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-dic/.

56. Dias S, Sutton AJ, Welton N, Ades A. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment (last updated April 2012). 2011.
57. Jansen J, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011;14:417-28.
58. Dias S, Welton N, Sutton AJ, Caldwell DM, Lu G, Ades A. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials (last updated April 2014). 2011.
59. Maruish M, Kosinski M, Bjorner J, Gandek B, Turner-Bowker D, Ware J. User's manual for the SF-36v2 health survey. 3 ed. Lincoln, RI, USA: Quality Metric Inc; 2011.
60. Kurtzke J. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-52.
61. Larson R. Psychometric properties of the Modified Fatigue Impact Scale. International journal of MS care. 2013;15:15-20.
62. Amtmann D, Kim J, Chung H, Bamer A, Askew R, Wu S, et al. Comparing CESD-10, PHQ-9, and PROMIS depression instruments in individuals with multiple sclerosis. Rehabil Psychol. 2014;59:220-9.
63. Yang H, Duchesneau E, Foster R, Guerin A, Ma E, Thomas NP. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. Journal of Medical Economics. 2017;20(10):1056-65.
64. Frasco MA, Shih T, Incerti D, Diaz Espinosa O, Vania DK, Thomas N. Incremental net monetary benefit of ocrelizumab relative to subcutaneous interferon β-1a. Journal of Medical Economics. 2017;20(10):1074-82.
65. NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis. 2014. Report No.: Reference: NHS ENGLAND/ D04/P/b.
66. Biogen. Daclizumab for relapsing multiple sclerosis: Company evidence submission. 2016.
67. Pickin M, Cooper CL, Chater T, O'Hagan A, Abrams KR, Cooper NJ, et al. The Multiple Sclerosis Risk Sharing Scheme Monitoring Study–early results and lessons for the future. BMC neurology. 2009;9(1):1.

68. Chilcott J, Miller DH, McCabe C, Tappenden P, O'Hagan A, Cooper NJ, et al. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosisCommentary: Evaluating disease modifying treatments in multiple sclerosis. BMJ. 2003;326(7388):522.
69. National Institute for Health and Care Excellence. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology appraisal guidance [TA32]. 2002.
70. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ open. 2014;4(1):e004073.
71. Patzold U, Pocklington PR. Course of multiple sclerosis. Acta Neurologica Scandinavica. 1982;65(4):248-66.
72. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value in health. 2007;10(1):54-60.
73. Office for National Statistics (ONS). National life tables, UK: 2013–2015. 2016.
74. National Institute for Health and Care Excellence. Dimethyl fumarate for treating relapsing‐remitting multiple sclerosis (TA320). 2014.
75. Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: results from a UK General Population survey. University of York: Centre for Health Economics; 1995. Contract No.: Report.
76. Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. Journal of neurology, neurosurgery, and psychiatry. 2014:jnnp-2014-307721.
77. Willis M, Harding K, Pickersgill T, Wardle M, Pearson O, Scolding N, et al. Alemtuzumab for multiple sclerosis: long term follow-up in a multi-centre cohort. Multiple Sclerosis Journal. 2016;22(9):1215-23.
78. Coles AJ, Cohen JA, Fox EJ, Giovannoni G, Hartung H-P, Havrdova E, et al. Alemtuzumab CARE-MS II 5-year follow-up Efficacy and safety findings. Neurology. 2017;89(11):1117-26.
79. Havrdova E, Arnold DL, Cohen JA, Hartung H-P, Fox EJ, Giovannoni G, et al. Alemtuzumab CARE-MS I 5-year follow-up Durable efficacy in the absence of continuous MS therapy. Neurology. 2017;89(11):1107-16.
80. Hawton A, Green C. Multiple sclerosis: relapses, resource use, and costs. The European Journal of Health Economics. 2016;17(7):875-84.

81. Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Multiple Sclerosis Journal. 2012;18(2_suppl):7-15.
82. Kobelt G, Berg J, Lindgren P, Kerrigan J, Russell N, Nixon R. Costs and quality of life of multiple sclerosis in the United Kingdom. The European Journal of Health Economics. 2006;7(2):96-104.
83. Tyas D, Kerrigan J, Russell N, Nixon R. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? Value Health. 2007;10:386-9.
84. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J, Group MS, et al. New insights into the burden and costs of multiple sclerosis in Europe. Multiple Sclerosis Journal. 2017;23(8):1123-36.
85. Thompson A, Kobelt G, Berg J, Capsa D, Eriksson J, Miller D, et al. New insights into the burden and costs of multiple sclerosis in Europe: Results for the United Kingdom. Multiple Sclerosis Journal. 2017;23(2_suppl):204-16.

8 APPENDICES

Appendix 1 Dosing regimens of the intervention and comparators

DMT	Abbreviation	Brand name	Dosing (for RRMS in the NHS)
Alemtuzumab	ALEM	Lemtrada	IV, 2 per 12 months
Daclizumab	DAC	Zinbryta	SC, 1 per month
Dimethyl fumarate	DMF	Tecfidera	Oral, 2 per day
Glatiramer acetate	GA	Copaxone	SC, every other day or 3 per week [a]
Fingolimod	FINGO	Gilenya	Oral, 1 per day
Interferon β-1a	IFNβ-1a	Avonex	IM, 1 per week
		Rebif	SC, 3 per week
Peginterferon β-1a	PEGβ-1a	Plegridy	IM, 1 per 2 weeks
Interferon β-1b	IFNβ-1b	Betaferon	SC, every other day
		Extavia	SC, every other day
Natalizumab	NAT	Tysabri	IV, 1 per 4 weeks
Ocrelizumab	OCR	Ocrevus	IV, 1 per 6 months [b]
Teriflunomide	TERI	Aubagio	Oral, 1 per day

IM, intramuscular injection; IV, intravenous infusion; SC, subcutaneous injection.
[a] Dosing depends upon which of 2 preparations is used.
[b] First dose is split into two half-doses 2 weeks apart.

Appendix 2 Company and ERG risk of bias assessments for the ocrelizumab trials

NICE quality assessment criteria for RCT	Judgements	OPERA I	OPERA II	Phase II trial Kappos 2011
1. Was the method used to generate random allocations adequate?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
ERG comments: OPERA I & II: Randomisation was performed centrally with the use of an independent interactive web-response system. Randomisation was stratified by region (United States versus rest of the world) and baseline EDSS (<4.0 versus ≥4.0). The [redacted]. **Phase II trial:** A randomisation list was generated by an independent group within Roche. This list was provided to an interactive voice response system, which then randomised patients (1:1:1:1) to one of the four treatment groups stratified by geographical region.				
2. Was the concealment of treatment allocation adequate?	CS:	Yes	Yes	Unclear
	ERG:	Yes	Yes	Yes
ERG comments: OPERA I & II: [redacted] **Phase II trial:** The randomisation list was not disclosed to the study centres, monitors, project statisticians, or to the project team at Roche and Genentech.				
3. Were the groups similar at the outset of the study in terms of prognostic factors?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
ERG comments: There were only minor differences in all measured baseline variables between the arms within each trial. An exception is the proportion of patients without previous DMT which varied 23% across the arms within the phase II trial (proportions were 47% in the OCR 600mg arm; 69-70% in the placebo and IFNβ-1a arms), as well as slight differences for the duration of MS and the numbers of gadolinium-enhancingT1 lesions (clarification A7b).				
4. Were the care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes	No
	ERG:	Yes	Yes	No
ERG comments: OPERA I & II: Double-blind, double-dummy design wherein all patients received both infusion and injection in order to maintain blinding. Each trial centre had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial. MRI scans were analysed centrally by personnel who were unaware of the treatment assignments. **Phase II trial:** All individuals directly involved in the study remained blinded to the dose of ocrelizumab. Project statisticians remained blinded until data lock and statistical analysis at week 24. Treatment assignment was masked for patients in the placebo and both ocrelizumab groups throughout the study. In the interferon β-1a group, only the raters were masked to allocation; therefore comparisons of the other groups with this group on the primary and secondary outcomes were exploratory.				

Continued on next page

5. Were there any unexpected imbalances in drop-outs between groups?	CS:	Yes	Yes	No
	ERG:	No	No	No
ERG comments: OPERA I & II: There were higher dropout rates in the IFNβ-1a than the OCR arms (11-14% in the OCR arms; 17-23% in the IFNβ-1a arms). However, the specific reasons for dropout do not appear to be unexpected and imbalances are relatively minor. The most frequent reasons for dropout were adverse events (3-4% in OCR arms; 6% in IFNβ-1a arms), lack of efficacy (1-2% in OCR arms; 3-4% in IFNβ-1a arms), withdrawal of consent (2-3% in OCR arms; 3-6% in IFNβ-1a arms), and unspecified "other" reasons (2% in OCR arms; 3-4% in IFNβ-1a arms). **Phase II trial:** At the end of the 24-week randomised phase of the trial, there was a higher dropout rate in the OCR (7.3%) than the IFNβ-1a arm (5.6%) and none in the placebo arm (0%). After 48 weeks, when all patients had received OCR, the sequence remained the same (OCR 10.9%, IFNβ-1a 9.3%, placebo 3.7%. The proportions and reasons for dropout were similar between the OCR and IFN arms. The main difference is that no adverse events and no withdrawal of consent occurred in the placebo arm. No patients were withdrawn due to lack of efficacy.				
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	CS:	No	No	No
	ERG:	No	No	No
ERG comments: There is no suggestion that the OPERA trials measured more outcomes than reported. However, several exploratory patient-reported/disability outcomes which are relevant to the NICE scope and were measured in both trials are not reported in the CS. These include EDSS scores and fatigue scores (for further details see section 3.1.5). There is no suggestion that the Phase II trial measured more outcomes than reported.				
7. Did the analysis (1) include an intention-to-treat (ITT) analysis? (2) If so, was this appropriate and (3) were appropriate methods used to account for missing data?	CS:	Yes	Yes	Yes
	ERG: (primary outcome only)	1. Yes 2. Yes 3. Yes	1. Yes 2. Yes 3. Yes	1. Yes 2. Yes 3. Yes
ERG comments: OPERA I & II: The primary outcome was analysed appropriately according to ITT. However, although the CS implies that secondary analyses (apart from NEDA) were performed in the ITT population, Table 11 in the CS shows sample sizes for all secondary outcomes were smaller than the ITT population (see section 3.1.6.1 above). The ERG judgements for secondary outcomes in OPERA I & II would be: 1. No; 2. Not applicable; 3: Unclear. **Phase II trial:** The primary outcome was analysed appropriately according to ITT.				

Appendix 3 Expanded Disability Status Scale (EDSS)

The EDSS[60] reflects disability of MS patients based on neurological examination by describing symptoms and signs in eight functional systems as well as ambulatory function and the ability to carry out activities of daily living. The functional systems are: “pyramidal” (weakness or difficulty moving limbs); “cerebellar” (ataxia, loss of coordination or tremor); “brainstem” (problems with speech, swallowing and nystagmus); “sensory” (numbness or loss of sensations); “bowel and bladder function”; “visual function”; “cerebral” (or mental) functions; and “other”.

Each functional system is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability) and the overall (ordinal) scale is calculated such that it ranges from 0 (normal neurological examination) to 10 (death due to MS). The scale is divided into 0.5-point increments, each of which is associated with a textual description of the disability state that the score reflects. Scores from 0 to 4.0 are determined by functional systems scores, meaning that in this range the EDSS primarily assesses impairment whilst EDSS steps 5.0 to 9.5 are defined by walking-related disability.[47]

Although widely used, the EDSS faces several criticisms,[20, 47] including that: the scale relies on walking as the main measure of disability; it has high intra- and inter-rater variability; it is non-linear, with the rate of disability progression varying depending upon the baseline score; and several domains are not captured (e.g. cognitive function, mood, energy level and quality of life). A pragmatic means of dealing with the non-linearity of the scale is that a clinically meaningful change is often defined as 1.0 or more for baseline scores of 0 to 5.5, or 0.5 or more for baseline scores >5.5.[47] According to clinical experts advising the ERG, an EDSS score around 7.0, when MS patients effectively become confined to a wheelchair, is an appropriate stopping rule for DMT therapies that aim to prevent relapses, since this approximates the transition point from RRMS to SPMS. The minimum clinically important difference has been determined to be a 1.0 point change when EDSS is below 5.5 and a 0.5 point change when EDSS is between 5.5 and 8.5.

Expanded Disability Status Scale (EDSS)

Score	Description
1.0	No disability, minimal signs in one functional system
1.5	No disability, minimal signs in more than one functional system
2.0	Minimal disability in one functional system
2.5	Mild disability in one functional system or minimal disability in two functional systems
3.0	Moderate disability in one functional system, or mild disability in three or four functional systems. No impairment to walking
3.5	Moderate disability in one functional system and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Appendix 4 ERG quality assessment of the company's MTC analyses

Criterion	ERG assessment
NMA purpose	
1. Are the MTC results used to support the evidence for the clinical effectiveness of the intervention?	Yes, for the comparison of ocrelizumab with treatments in the scope which have not been compared to ocrelizumab directly.
2. Are the MTC results used to support the evidence for the cost-effectiveness of the intervention?	Yes. The MTC is the source for economic model estimates of disease progression, relapse rates, and all-cause discontinuation of treatment. The CS also states that MTCs were done for other outcomes but are not reported as they were not considered relevant for the economic evaluation for NICE (these were relapse free proportion, proportion of patients with serious adverse events, and discontinuation due to adverse events).
Evidence selection	
3. Are inclusion/exclusion criteria adequately reported?	Yes, CS Appendix Table 3 describes the inclusion and exclusion criteria for the company's systematic review of clinical effectiveness, which incorporates the MTC. The CS also mentions a feasibility assessment in which additional criteria for the MTC were applied, CS Appendix Table 9. These related to doses or regimens which are not approved/licensed (presumably by the EMA), and studies with controlled treatment durations less than 48 weeks (11 trials were excluded on this criterion).
4. Is quality of the included studies assessed?	Yes. Risk of bias criteria are applied to all studies included in the MTC and judgements are briefly summarised in CS section B.2.9.1 and also presented in a colour coded table (CS Appendix D.1.3, Table 13).
Methods – statistical model	
5. Is the statistical model described?	Yes. CS Appendix D.1.1 describes the statistical analysis methods used. A Bayesian MTC model was used for all outcomes, as described by NICE DSU TSD 2.[53] The base case MTC for each outcome is based on a random effects model with a vague prior distribution for the between-study variance. Sensitivity analyses were conducted to explore variations to base case assumptions, using alternative priors, fixed effect models and meta-regression on follow-up time.
6. Has the choice of outcome measure used in the analysis been justified?	Yes. The CS reports MTC results for outcomes that are used in the economic model. The outcomes are: ARR, CDP-12, CDP-24 and al- cause discontinuation.
7. Has a structure of the network been provided?	Yes, network diagrams are provided in CS section B.2.9 for the ITT and subgroup population MTC networks, and also in CS Appendix D for the restricted networks, the sensitivity analyses and the meta-regression MTCs.

Appendix 4 continued

8. Is homogeneity considered?	Yes. CS Appendix D Table 27 provides statistical heterogeneity assessment results (as I^2 values) for head to head pairwise comparisons, colour coded according to categorisations of low (I^2 = 0% to 25%), low to moderate (I^2 = 25% to 50%), moderate to high (I^2 = 50% to 75%) and high heterogeneity (I^2 = 75% to 100%) (the ERG assumes this is for the ITT base case MTCs rather than for the subgroup MTCs). The majority of comparisons produced low heterogeneity estimates, with seven (21%) of the 34 comparisons classified as moderate to high, and none classified as high. For the seven moderate to high comparisons the CS provides forest plots (with tau-squared and p values for statistical heterogeneity) and a discussion, in varying in detail across comparisons, of potential sources of heterogeneity. The company provided forest plots for all pairwise comparisons following an ERG request. A random effects model was used in the base case MTC analysis, which is recommended where heterogeneity is identified or suspected.
9. Are the studies homogenous in terms of patient characteristics and study design?	Unclear. The trials appear to be reasonably well balanced on a range of baseline characteristics (e.g. age, sex, EDSS score, previous relapses), but there are notable imbalances across trials in the proportions of patients who were treatment-naïve/experienced and in the time since the onset of symptoms.
10. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	Separate MTC analyses are conducted for the RES and HA subgroups (though not necessarily to investigate heterogeneity, rather, to adhere to the NICE scope), and meta-regression was conducted to assess the impact of trial follow-up.
11. Is the assumption of similarity stated?	No. An explicit statement of the similarity assumption across the trials is not given.
12. Is any of the programming code used in the statistical programme provided (for potential verification)?	Yes, following request (clarification A13).

Appendix 4 continued

Sensitivity analysis	
13. Does the study report sensitivity analyses?	Yes, sensitivity analyses are reported for the ITT population MTC (but not for the RES and HA subgroups) for the four outcomes on choice of prior distribution, fixed effects model, meta-regression on follow-up time (trial duration), and two restricted networks which excluded comparators not within the NICE scope.
Results	
14. Are the results of the MTC presented?	Yes. CS section B.2.9 provides a narrative description of the results with forest plots showing comparison between ocrelizumab and comparator DMTs. CS Appendix D.1.4 provides cross-tabulation of numerical results (i.e. illustrating pairwise comparisons between all included treatments) for the base case ITT MTCs (not for sensitivity analyses, patient subgroups or the restricted networks).
15. Does the study describe an assessment of the model fit?	Yes. The deviance information criterion (DIC) is used to assess model fit for the choice of prior distribution (DIC values are provided in CS Appendix D.1.4). The DIC is also used to judge the similarity in fit between the base case MTCs and the sensitivity analysis MTCs; the similarity in fit between the base case MTCs and the meta-regression on trial duration; and the MTC models assuming consistency and inconsistency. If DIC values for the sensitivity analyses are within 3 units of each other they are regarded as indicating a similar fit. For the assessment of consistency, if the DIC for the inconsistency model is lower than the consistency model by more than 3 points then potential inconsistency is suspected (as recommended by NICE DSU TSD number 4[58]).
16. Has there been any discussion around the model uncertainty?	Yes – CS section B.2.9.1 discusses the uncertainties in the results of the MTCs, in terms of inconsistency assessments, risk of bias, data limitations, and the subgroup analyses.
17. Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	Yes – credible intervals are provided for all point estimates.
Discussion - overall results	
18. Does the study discuss both conceptual and statistical heterogeneity?	No. Only a brief mention is made of heterogeneity across the studies included in the MTC (CS Appendix section D.1.1, page 105) in terms of the proportion of patients included in the trials with forms of MS other than RRMS.

Appendix 4 continued

Discussion - validity	
19. Are the results from the MTC compared, where possible, to those just using direct evidence?	Yes. Consistency is discussed in CS section B.2.9 (pages 68 to 69), based on the results of the consistency assessments conducted. Also, as stated above (see item 8) the CS provides results of pairwise comparisons from head to head trials for comparisons where there was moderate to high heterogeneity. Following an ERG request (clarification A20) the company provided results of all head to head pairwise comparisons, which permits comparison of the results of the head to head studies with the results of the MTC (i.e. direct and indirect evidence).

DSU = Decision Support Unit ; TSD = Technical Support Document

Appendix 5 Contribution of ocrelizumab and comparator trials to the company's MTC analyses

Trial (for references see Table 26[a])	ARR			CDP-12			CDP-24			All-cause discont. ITT (Table 33[a])
	ITT (Table 30[a])	HA (Table 34[a])	RES (Table 35[a])	ITT (Table 31[a])	HA (Table 36[a])	RES (Table 37[a])	ITT (Table 32[a])	HA (Table 38[a])	RES (Table 39[a])	
ADVANCE	ITT			ITT			ITT			ITT
AFFIRM	ITT		SG	ITT		SG	ITT		SG	ITT
BEYOND	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR				ITT
Bornstein 1987				ITT	ITT ABCR	ITT ABCR				
BRAVO	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR	
Calabrese 2012	ITT	ITT ABCR	ITT ABCR							
CAMMS 223	ITT			HAS MTC			ITT			ITT
CARE-MS I	ITT		SG				ITT			ITT
CARE-MS II	ITT	SG	SG				ITT	SG	SG	ITT
CLARITY	ITT			ITT			ITT			ITT
CombiRx	ITT	ITT ABCR	ITT ABCR				ITT	ITT ABCR	ITT ABCR	
CONFIRM	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR SG pooled with DEFINE	ITT ABCR SG pooled with DEFINE	ITT	ITT ABCR	ITT ABCR	ITT
Complymer 1 MS trial	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR				ITT
DECIDE	ITT	SG	SG	ITT			ITT	SG		ITT
DEFINE	ITT			ITT	SG pooled with CONFIRM	SG pooled with CONFIRM	ITT			ITT
Etemadifir 2006										
EVIDENCE	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR	ITT
FREEDOMS	ITT	SG	SG	ITT	SG	SG	ITT	SG		ITT
FREEDOMS II	ITT			ITT			ITT			ITT
GALA	ITT	ITT ABCR	ITT ABCR							
IFNB MS	ITT	ITT ABCR	ITT ABCR	ITT	ITT ABCR	ITT ABCR				ITT
INCOMIN	ITT	ITT ABCR	ITT ABCR							ITT
MSCRG	ITT	ITT ABCR	ITT ABCR				ITT	ITT ABCR	ITT ABCR	ITT
OPERA I	ITT	SG	SG	ITT	SG	SG	ITT	SG	SG	ITT
OPERA II	ITT			ITT			ITT			ITT
PRISMS				ITT	ITT ABCR	ITT ABCR				ITT

REGARD	ITT	ITT ABCR	ITT ABCR				ITT	ITT ABCR	ITT ABCR	ITT
SELECT	ITT	SG	SG	ITT		SG	ITT	SG		ITT
Stepien 2013	ITT	ITT ABCR	ITT ABCR							
TEMSO	ITT			ITT	SG pooled with TOWER	SG	ITT	SG pooled with TOWER		ITT
TENERE	ITT									ITT
TOWER	ITT			ITT	SG pooled with TEMSO		ITT	SG pooled with TEMSO		ITT
TRANSFORMS	ITT	SG	SG	ITT	SG	SG				ITT
Total no. of trials (no. after pooling)	30 (30)	21 (19)	22 (21)	22 (22)	16 (11)	16 (14)	21 (21)	15 (11)	10 (9)	26 (26)

[a] Table in the company's clarification response
HAS MTC: Data were obtained from a MTC that included CAMMS 223, CARE MS-I, and CARE MS-II CAMMS223 reported by HAS (Haute Autorité de Santé) (no references to this MTC, no details of it and no critique of it were provided by the company).
ITT: Trial contributed ITT data to the specified analysis.
ITT ABCR: Trial contributed ITT data for ABCR comparators to the specified analysis in lieu of subgroup data.
SG: Trial contributed subgroup data to the specified analysis.
Shaded cells indicate where pooled data were employed.

Appendix 6 ERG check of the company's risk of bias assessments for comparator RCTs

Introduction

It was not feasible within the timescale of this technology assessment for the ERG to check the company's risk of bias judgements for all the trials that they included in their SLR. The ERG noted that for up to 31 of the 46 trials included in the company's SLR, independent ERG reports are available from previous NICE DMT technology appraisals which already provide assessments of the risks of bias. We compared the risk of bias judgements in these reports against the company's judgements in CS Appendix Table 13 to provide an indication of whether the company's risk of bias judgements are likely to be generally appropriate.

Methods

One reviewer checked the risk of bias assessments that are provided in the ERG reports available from previous NICE appraisals of DMTs. Where these were reported in a similar format to that given in CS Appendix Table 13, the reviewer noted whether there was agreement between the independent ERG and company judgements on risk of bias. In cases where ERG reports provided judgements phrased as "high" or "low" risk of bias these were translated into "yes" or "no" answers to match the questions in CS Appendix Table 13. In cases where only a narrative statement was provided this was also translated into a "yes" or "no" answer if this could be clearly discerned.

Results

Risk of bias assesments in ERG reports from previous NICE DMT appraisals were available for up to 31 of the 46 trials included in the company's SLR. The number of available assessments varied with the risk of bias question, since not all ERGs answered the same risk of bias questions as those given in CS Appendix Table 13. For each trial a single ERG report was the source of the risk of bias data, since ERG reports generally focused only on the pivotal trials for the specific DMT under assessment in each NICE appraisal.

Question 1: Was randomisation carried out appropriately? The independent ERG judgements and company judgements for this question agreed for 30/31 trials (97%).

Question 2: Was the concealment of treatment allocation adequate? The independent ERG judgements and company judgements for this question agreed for 21/31 trials (68%). For 9 of the remaining 10 trials the company's answer for this question was 'unclear' whereas the ERG judgements were 'low' (i.e. for these further 9/31 trials (29%) where the

company and ERG judgements differed, the company's judgements were conservative relative to those of the ERGs).

Question 3: Were the groups similar at the outset of the study in terms of prognostic factors? There were only 11 trials where a comparison was available between ERG and company judgements for this question, but in most (9/11) of these (82%) the judgements were in agreement.

Question 4: Were the care providers, participants and outcome assessors blind to treatment allocation? ERG and company answers to this question could not be compared easily since the ERGs gave separate answers for each group specified in the question whereas the company gave an overall answer for the three groups.

Question 5: Were there any unexpected imbalances in dropouts between groups? The independent ERG judgements and company judgements for this question agreed for 14/30 trials (47%). For 5 of the remaining 10 trials the company's answer for this question was 'yes' whereas the ERG judgements were 'no', and for 1 trial the company's judgement was 'unclear' whereas the ERG judgement was 'low' (i.e. for these further 6/30 trials (20%) the company's judgements were conservative relative to those of the ERGs).

Question 6: Is there any evidence to suggest that the authors measured more outcomes than they reported? The independent ERG judgements and company judgements for this question agreed for 19/30 trials (63%). For 2 of the remaining 10 trials the company's answer for this question was 'unclear' whereas the ERG judgements were 'no', and for 1 trial the company's judgement was 'yes' whereas the ERG judgement was 'no' (i.e. for these further 3/30 trials (10%) the company's judgements were conservative relative to those of the ERGs).

Question 7: Included an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? There were only 11 trials where a comparison was available between ERG and company judgements for this question. In 4/11 trials (36%) the judgements were in agreement. For 2 of the remaining 7 trials the company's answer for this question was 'unclear' whereas the ERG judgements were 'no' (i.e. for these further 2/11 trials (18%) the company's judgements were conservative relative to those of the ERGs).