NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Ocrelizumab for treating relapsing multiple sclerosis (ID937)

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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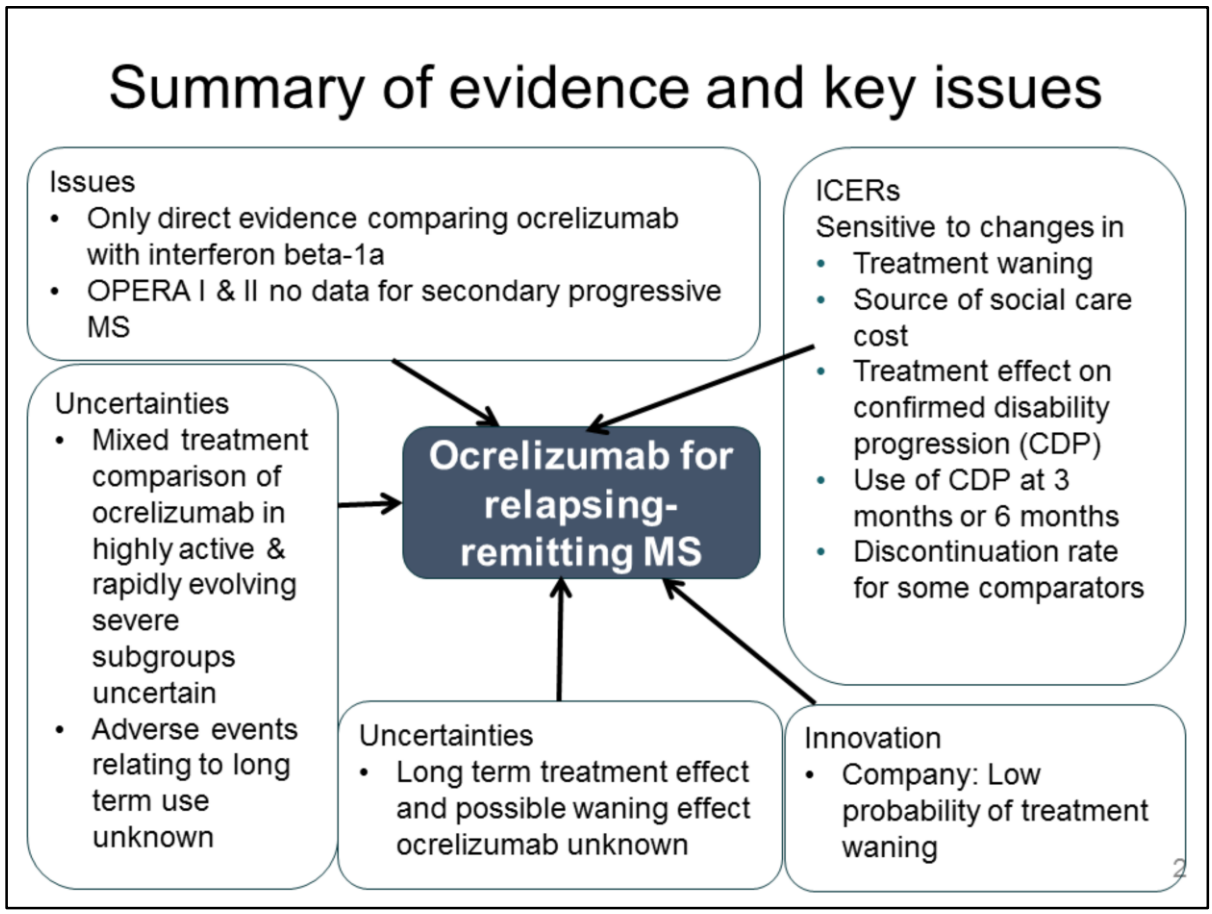
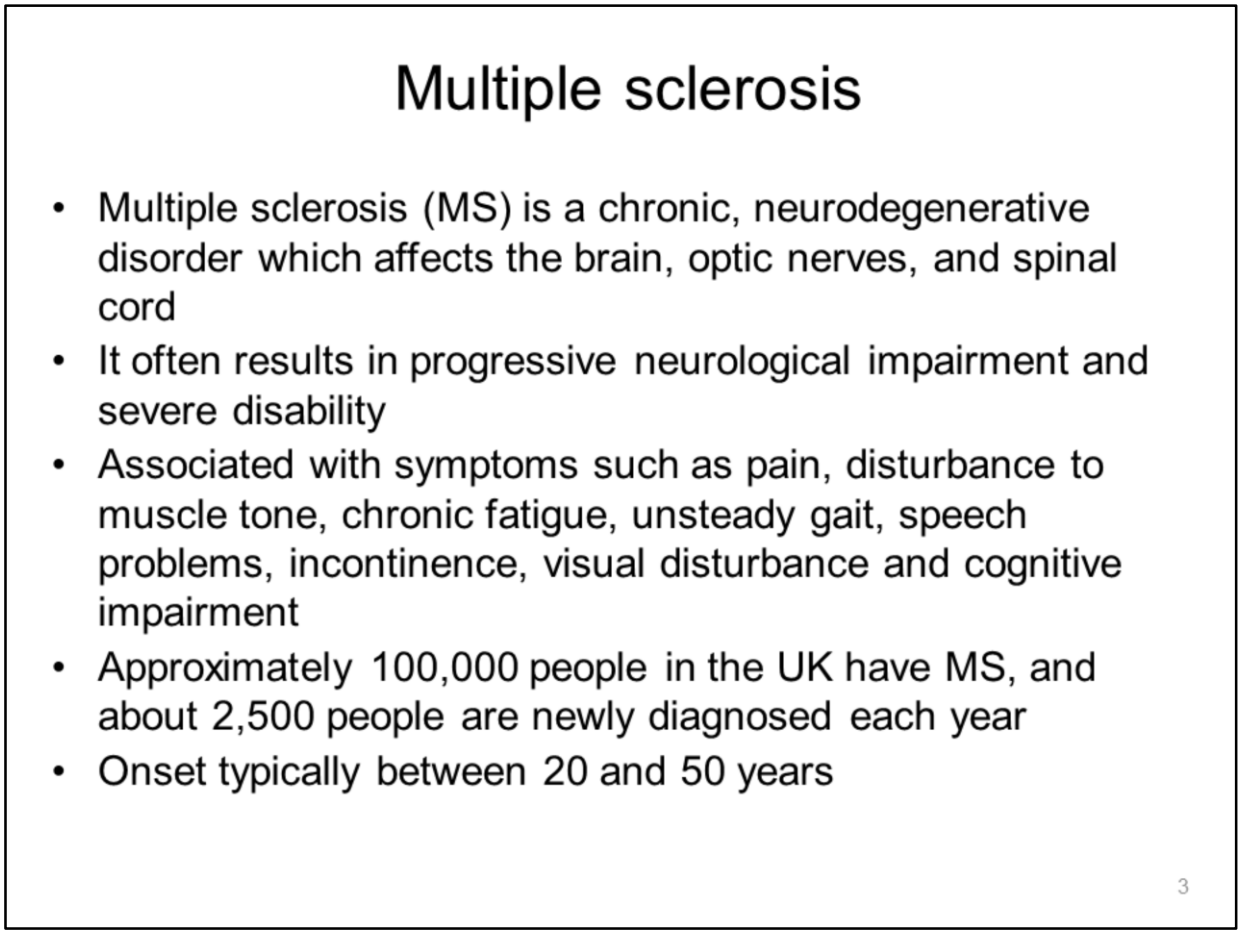
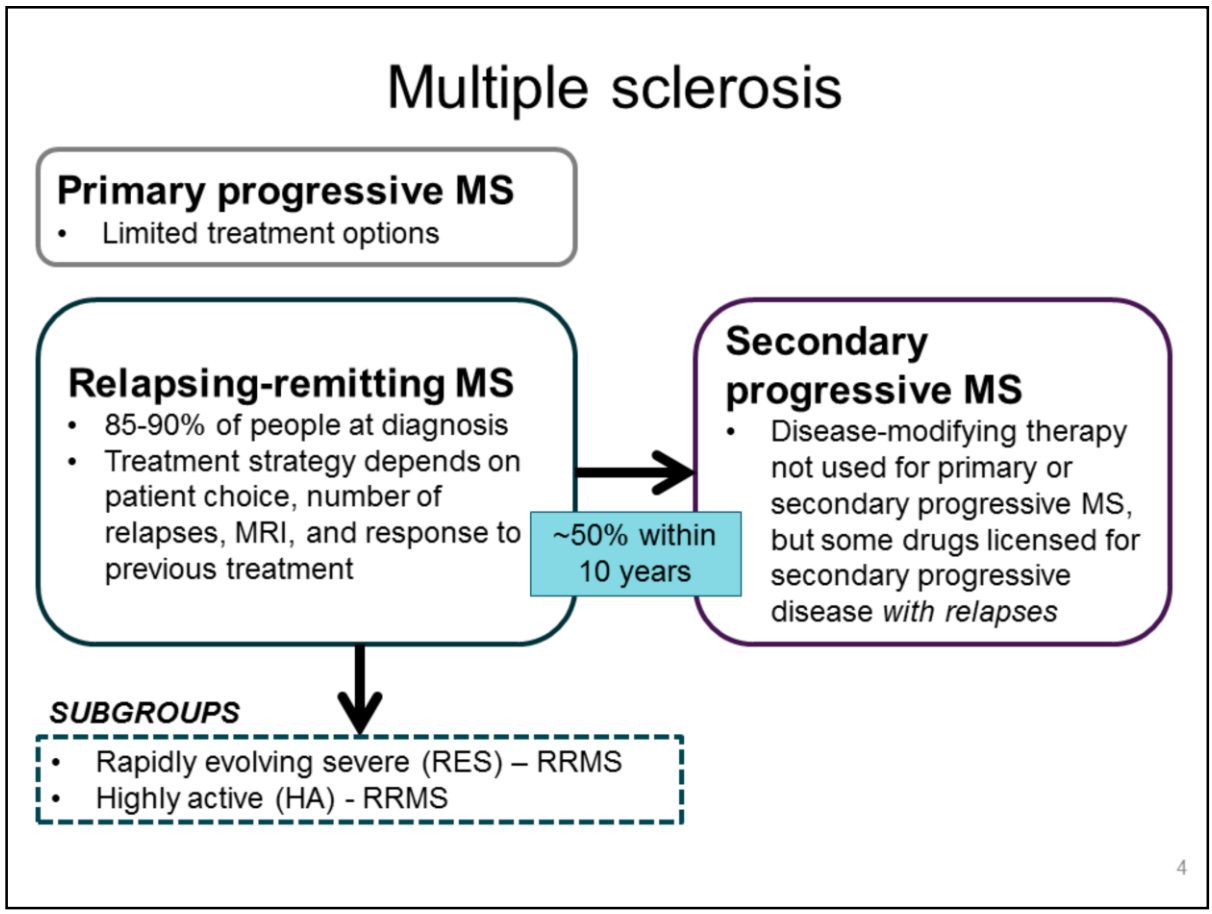
Summary of evidence and key issues





Currently no accurate data on incidence, approx. 100,000 people have MS in the UK based on study by McKenzie et al (2010) at the University of Dundee, growing by about 2.4% each year.


Multiple sclerosis
Primary progressive MS
• Limited treatment options
Relapsing-remitting MS
• 85-90% of people at diagnosis
• Treatment strategy depends on patient choice, number of relapses, MRI, and response to previous treatment
~50% within 10 years
Secondary progressive MS
• Disease-modifying therapy not used for primary or secondary progressive MS, but some drugs licensed for secondary progressive disease with relapses
SUBGROUPS
• Rapidly evolving severe (RES) – RRMS
• Highly active (HA) - RRMS
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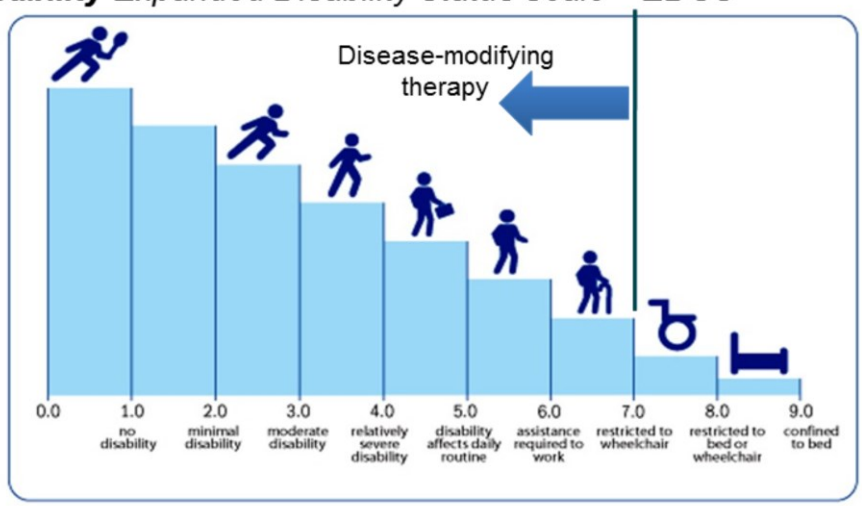
Relapsing-remitting multiple sclerosis

Treatment aims to reduce frequency of **relapse** and slow **disability**

1. ***Relapses –*** symptoms lasting ≥24 hours without fever or infection
2. ***Disability*** *Expanded Disability Status Scale = EDSS*



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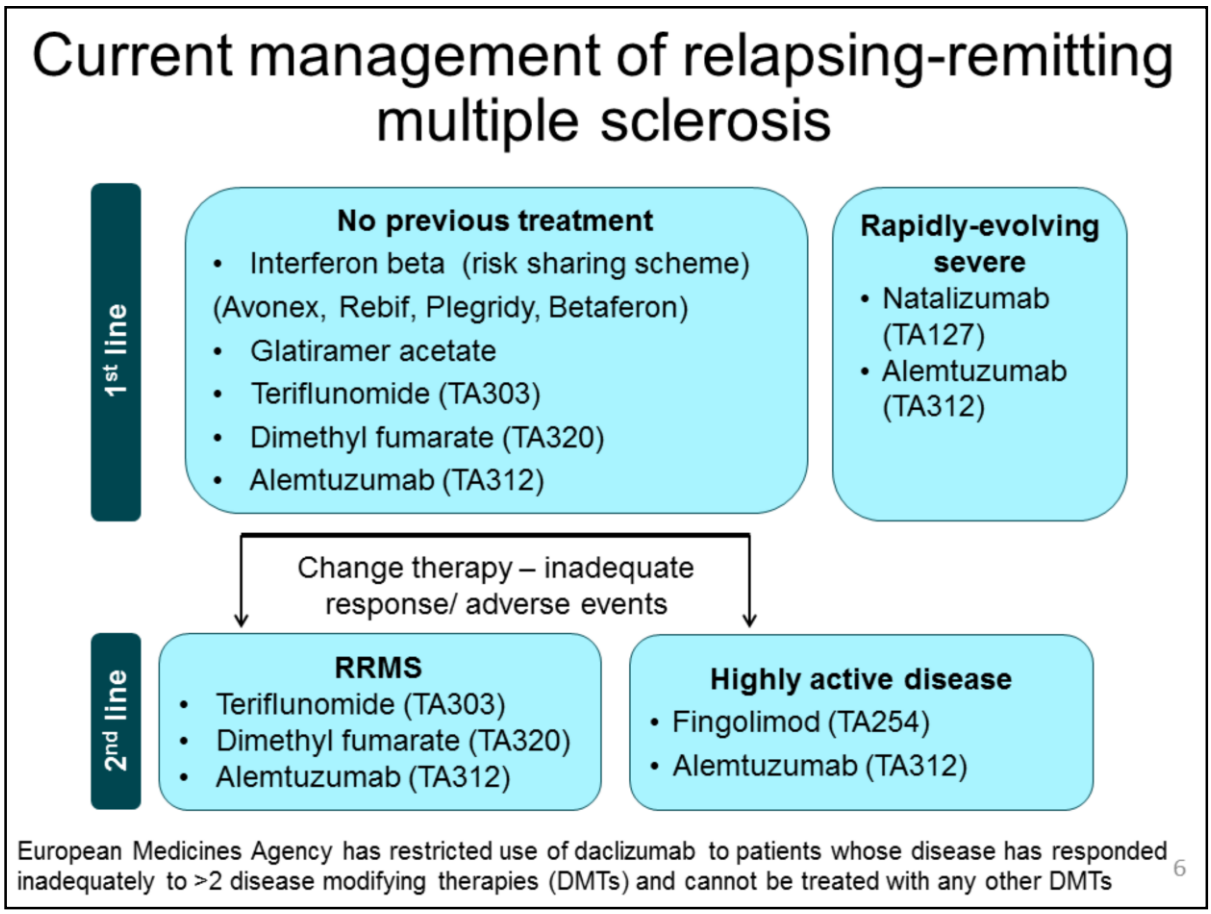
http://caregivinglyyours.blogspot.co.uk/2011/04/whats-your-edss-score.html



- This pathway is based on the NICE scope.
- Guidelines from the Association of British Neurologists define treatments as:
  - Moderate efficacy (category 1):
    - Beta interferon, glatiramer, teriflunomide
    - Dimethyl fumarate and fingolimod (both assumed to be slightly more effective than other category 1 drugs)
  - High efficacy (category 2): alemtuzumab and natalizumab
- NICE appraised beta interferons and glatiramer acetate in 2002 and did not recommend these treatments for MS. The Department of Health, in combination with patient groups and companies, set up a risk sharing scheme. The scheme allowed NHS patients to access beta interferons and glatiramer acetate while long-term data on outcomes were collected. The scheme ended in 2016, but beta interferons and glatiramer acetate continue to be commissioned by NHS England (policy here). NICE is appraising the beta interferons and glatiramer acetate in a multiple technology appraisal, scheduled for discussion by Committee B in November 2016. For the purposes of the current appraisal of daclizumab, the key point is that beta interferons and glatiramer acetate are currently used in the NHS and thus should be included as comparators.
- There are several beta interferons which differ in injection site and frequency:
  -Interferon beta 1a (Avonex, Biogen), intramuscular injection once a week.
  -Interferon beta 1a (Rebif, Merck), subcutaneous injection 3 times a week.
  -Peginterferon beta 1a (Plegridy, Biogen), subcutaneous injection every 2 weeks.
  -Interferon beta 1b (2 drugs from the same production line: Betaferon by Bayer and Extavia by Novartis), subcutaneous injection every other day.

Ocrelizumab (Ocrevus)

Marketing authorisation	Ocrelizumab is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features
Mechanism	Humanised monoclonal antibody that selectively depletes CD20+ B cells
Administration and dose	Intravenous (IV) infusion. First 600 mg dose administered as two 300 mg infusions 2 weeks apart. Subsequent doses are administered as a single 600 mg infusion every 6 months. A minimum interval of 5 months should be maintained between each dose
Cost	List price £4,790 per 300 mg vial. A simple discount PAS for ocrelizumab has been approved
Cost of a course of treatment	Per patient per year £19,160 based on twice yearly 600 mg infusions (list price)

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Source: company submission p9

Patient and professional feedback

- Relapses unpredictable in onset, severity, symptoms and duration. Recovery often incomplete, leading to accumulation of disability with each successive relapse.
- People with MS want a life free from impact of disease. Goal in taking disease-modifying therapies is to reduce risk of disease progression and disability.
- Potential benefits of infusion every 6 months:
  - lower frequency of administration than most therapies
  - less disruption of daily routines
  - increased adherence
  - reduction in side-effects
- Longer term studies needed to understand safety profile of ocrelizumab
  - Weakening immune system increases risk of infection and of cancer
  - One person contracted progressive multifocal leukoencephalopathy (PML) after switching from natalizumab to ocrelizumab. Unclear whether PML was linked to use of ocrelizumab, Roche are investigating further
- An effective treatment taken infrequently which carries minimal side effects would be welcomed by many people with relapsing MS

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Comments from consultees

This section summarises comments from:

- MS society
- MS trust

Company's decision problem and deviations from final scope

	Final NICE scope	Company submission	Company rationale	ERG comments
Population	People with relapsing forms of multiple sclerosis	Adults with relapsing remitting multiple sclerosis (RRMS)	OPERA I and II mostly included patients with RRMS	• Narrower than scope • Only patients ≤55 years included in trials • Clinical experts: infrequent use in people over 55 years
Outcomes	• Relapse rate • Severity of relapse • Disability • Symptoms • No disease activity • Mortality • Adverse effects • Health-related quality of life	Not assessed: • Severity of relapse • Symptoms	No comparative data to use in mixed treatment comparison	• Limited information on statistical analyses in company submission • Obtained and critiqued missing outcomes through clarification

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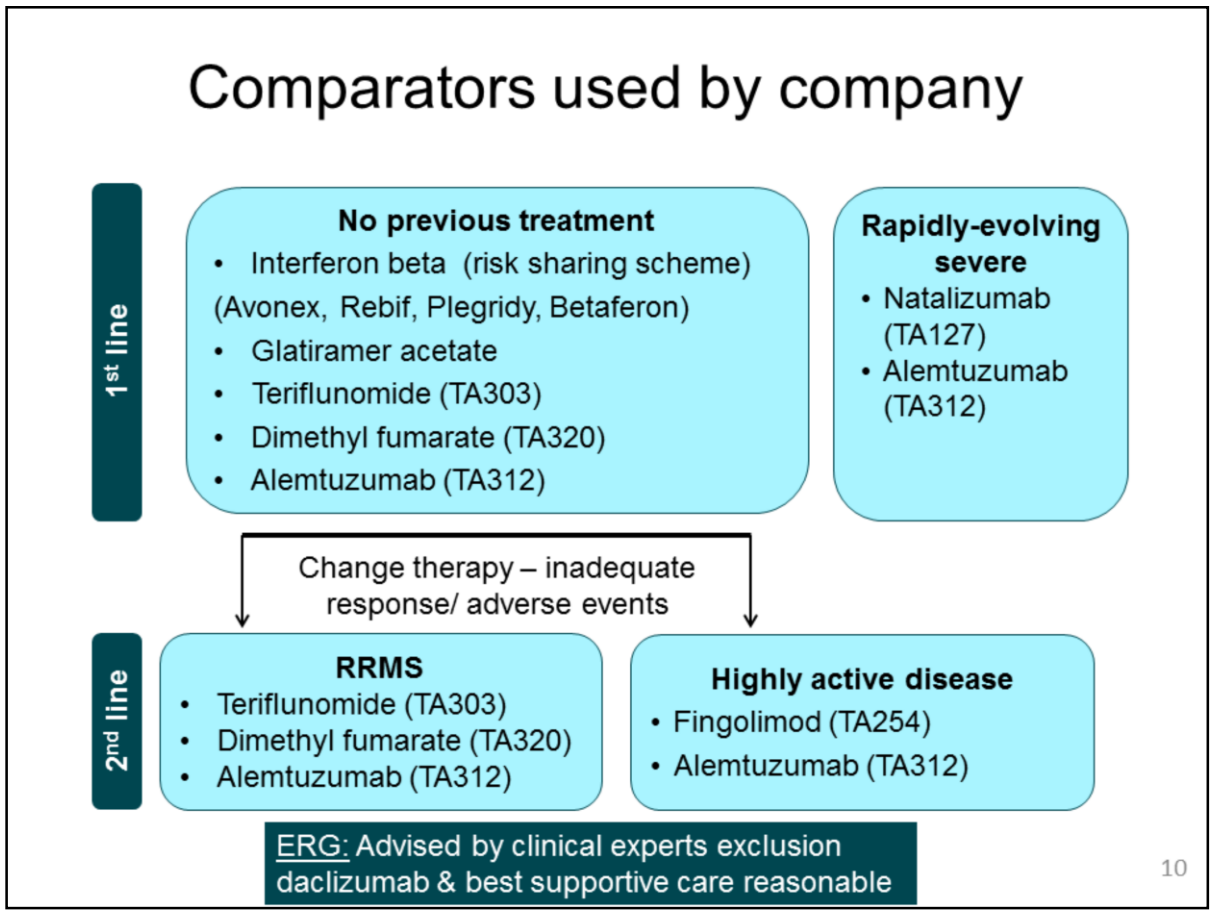

- Company included natalizumab and fingolimod in whole RRMS population analysis, which is outside of MA
- Company excluded daclizumab EMA restriction: inadequate response to ≥2 DMTs and treated with other DMTs is contraindicated or otherwise unsuitable
- Company excluded BSC and included natalizumab & fingolimod in whole RRMS population because, no subgroup data from OPERA studies in patients with relapsing SPMS
- ERG - Advised by clinical experts exclusion daclizumab & BSC reasonable
- Beta interferon and glatiramer acetate blended comparator

Key issues – clinical effectiveness

- Direct evidence only for ocrelizumab compared with interferon beta-1a
- Main trials OPERA I & II excluded patients over 55 (average age in trials 37) may impact on generalisability to NHS
- Mixed treatment comparisons results for highly active and RES subgroups very uncertain, low number of studies
- Company have included natalizumab and fingolimod as comparators in the whole RRMS population analysis, this is outside of their marketing authorisations
- Company excluded daclizumab from submission because EMA safety concerns restricted use to 3rd line
- Professional and patient group safety concerns about immune related reactions particularly progressive multifocal leukoencephalopathy (PML), impact of long-term use of ocrelizumab unknown

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EMA restriction on daclizumab: inadequate response to ≥2 DMTs and treated with other DMTs is contraindicated or otherwise unsuitable

Clinical evidence: OPERA trials

	WA21092 (OPERA I) n=821	WA21093 (OPERA II) n=835
Design	Phase III, randomised-controlled, active comparator, double-blind, double-dummy	
Population	18–55 years with a diagnosis of RMS ≥2 documented relapses within the previous two years or one relapse within the year before screening.	
Intervention	Ocrelizumab 600 mg n=410 Licensed dose	Ocrelizumab 600 mg n=417 Licensed dose
Comparator	IFNB-1α 44 µg n=411	IFNB-1α 44 µg n=418
Outcomes	• Annualised relapse rate (primary outcome) • Confirmed disability progression at 3 months • Confirmed disability progression at 6 months • No evidence of disease activity • Number of gadolinium-enhancing T1 leisons • Number of T2 hyperintense lesions • Number of T1 hypointense lesions • Brain volume change • Multiple sclerosis functional composite score • SF-36 physical component summary score	

Source: company submission document B p24, ERG report p45-46

WA21493 Phase II study with primary endpoint gd-enhancing lesions. No disease progression endpoint. Not included in MTC or economic model

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Source: CS document B p24, ERG report p45-56
Inclusion criteria of the trial include EDSS score from 0 to 5.5, excluded any concomitant disease required chronic treatment with systemic corticosteroids or immunosuppressant during the course of the study

OPERA I, 32 countries including UK. OPERA II 24 countries including UK. Recruitment started September 2011
I & II identical in terms of inclusion/exclusion criteria, comparator, statistical analysis plan
Secondary analysis of endpoints were pooled from OPERA I & II for:

- Expanded Disability Status Scale (EDSS),
- specifically Confirmed Disability Progression (CDP) and
- Confirmed Disability Improvement (CDI)

OLE study ongoing assessing long-term safety tolerability and efficacy of ocrelizumab

Exclusion criteria

- Diagnosis of PPMS
- Inability to complete an MRI
- Disease duration ≥ 10 years if EDSS ≤2.0 at screening
- Previous treatment with alemtuzumab, anti-CD4, cladribine, daclizumab, teriflunomide, rituximab, ocrelizumab

Baseline characteristics (1)

characteristics similar in OPERA I & II and across study arms

Characteristic	OPERA I		OPERA II	
	Ocrelizumab n=410	IFNB-1a (Rebif) n=411	Ocrelizumab n=418	IFNB-1a (Rebif) n=418
Mean age, years (SD)	37.1 (9.3)	36.9 (9.3)	37.2 (9.1)	37.4 (9.0)
Female, n (%)	270 (65.9)	272 (66.2)	271 (65.0)	280 (67.0)
Region, n (%)				
United States	105 (25.6)	105 (25.5)	112 (26.9)	114 (27.3)
Rest of the world	305 (74.4)	306 (74.5)	305 (73.1)	304 (72.7)
Mean time since symptom onset, years (SD)	6.74 (6.37)	6.25 (5.98)	6.72 (6.10)	6.68 (6.13)
Mean time since diagnosis, years (SD)	3.82 (4.80)	3.71 (4.63)	4.15 (4.95)	4.13 (5.07)

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Source: company submission document b p28-29 table 8

Baseline characteristics (2)

Characteristic	OPERA I		OPERA II	
	Ocrelizumab n=410	IFNB-1a (Rebif) n=411	Ocrelizumab n=418	IFNB-1a (Rebif) n=418
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)
Mean expanded disability status scale (EDSS) score	2.86±1.24	2.75±1.29	2.78±1.30	2.84±1.38
No DMT	301 (73.8)	292 (71.4)	304 (72.9)	314 (75.3)
Previous DMT, n (%)*	107 (26.2)	117 (28.6)	113 (27.1)	103 (24.7)
No. of Gd-enhancing lesions on T1-weighted MRI, n (%)				
0	233 (57.5)	252 (61.9)	252 (61.0)	243 (58.6)
1	64 (15.8)	52 (12.8)	58 (14.0)	62 (14.9)
2	30 (7.4)	30 (7.4)	33 (8.0)	38 (9.2)
3	20 (4.9)	16 (3.9)	15 (3.6)	14 (3.4)
≥4	58 (14.3)	57 (14.0)	55 (13.3)	58 (14.0)

ERG: Previous DMT use slightly higher for ocrelizumab than IFNB-1a in OPERA II

*Previous disease modifying therapies (DMTs) included: interferon (most common ~20%), glatiramer acetate (~10%), natalizumab, fingolimod, dimethyl fumarate, other

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Source: company submission document b p28-29 table 8
Scores on the EDSS range from 0 to 10.0, with higher scores indicating worse disability

Clinical effectiveness results: OPERA I & II

Annualised relapse rate (primary endpoint)

	OPERA I n=821		OPERA II n=835	
	Ocrelizumab 600 mg	IFNB-1a 44 µg	Ocrelizumab 600 mg	IFNB-1a 44 µg
Week 96 (95% CI)	0.156 (0.122, 0.200)	0.292 (0.235, 0.361)	0.155 (0.121, 0.198)	0.290 (0.234, 0.361)
Rate ratio (95% CI)	0.536 (0.400, 0.719)		0.532 (0.397, 0.714)	

Disability progression (secondary endpoint, pre-specified pooled analysis)

	Ocrelizumab 600 mg	IFNB-1a 44 µg
Confirmed disability progression at 3 months (95% CI)*	9.75 (7.63, 11.87)	15.18 (12.55, 17.81)
Hazard ratio (95% CI)	0.60 (0.45, 0.81)	
Confirmed disability progression at 6 months (95% CI)*	7.58 (5.68, 9.48)	12.03 (9.63, 14.44)
Hazard ratio (95% CI)	0.60 (0.43, 0.84)	
Confirmed disability improvement at 3 months (95% CI)*	20.70 (17.60, 24.08)	15.64 (12.85, 18.75)
Relative risk (95% CI)	1.33 (1.05, 1.68)	

*Kaplan-Meier estimate for proportion of patients with outcome specified in table, 96 weeks from start of trial

Source: company submission document b p35-37
Primary analysis for OPERA I cut-off date 2nd April 2015 & OPERA II cut-off date 12th May 2015
Assessed in pooled data set OPERA I & II: CDP-12 , CDP-24 and CDI-12

Primary endpoint
OPERA I: ARR reduced by 46% 96 weeks
OPERA II: ARR reduced by 47% 96 weeks

Secondary endpoint
Pooled CDP-12, CDP-24 and CDI-12 to increase power

Disability progression defined in line with other studies:
≥1.0 point from the baseline EDSS score when the baseline score was ≤5.5
≥0.5 point from the baseline EDSS score when the baseline score was >5.5

Secondary endpoints for MRI outcomes were also included: Gd-enhancing T1 lesions, new and/or enlarged T2 hyperintense lesions, new T1 hypointense lesions, brain volume.

Non-confirmatory endpoints (not reported on slide)
Statistically non-significant endpoints trials were
- In opera I Brain volume
- In opera I & II no evidence of disease activity (NEDA) and SF-36

Clinical effectiveness: OPERA I & II trial MRI outcomes (secondary endpoints)

Endpoint	OPERA I n=821		OPERA II n=835	
	Ocrelizumab 600 mg	IFNB-1a 44 µg	Ocrelizumab 600 mg	IFNB-1a 44 µg
Gd-enhancing T1 lesions* (95% CI)	0.016 (0.009, 0.030)	0.286 (0.200, 0.409)	0.021 (0.012, 0.036)	0.416 (0.309, 0.561)
Rate ratio (95% CI)	0.058 (0.032, 0.104)		0.051 (0.029–0.089)	
New and/or enlarged T2 hyperintense lesions* (95% CI)	0.323 (0.256, 0.407)	1.413 (1.123, 1.777)	0.325 (0.259, 0.409)	1.904 (1.536, 2.359)
Rate ratio (95% CI)	0.229 (0.174, 0.300)		0.171 (0.130–0.225)	
New T1 hypointense lesions* (95% CI)	0.420 (0.337, 0.524)	0.982 (0.780, 1.237)	0.449 (0.359, 0.560)	1.255 (1.003, 1.571)
Rate ratio (95% CI)	0.428 (0.328, 0.557)		0.357 (0.272–0.470)	
Brain volume (95% CI)	0.572 (0.660, 0.485)	0.741 (0.830, 0.651)	–0.638 (–0.734, 0.543)	–0.750 (–0.851, 0.649)
Mean difference (95% CI)	0.168 (0.053, 0.283)		0.112 (–0.018, 0.241)	

* mean number per MRI scan
** mean percentage decrease from week 24 to week 96 of trial

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Source: company submission document b p35-37
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- In opera I & II no evidence of disease activity (NEDA) and SF-36

Clinical effectiveness: OPERA I & II trial other outcomes (secondary endpoints)

Endpoint	OPERA I n=821		OPERA II n=835	
	Ocrelizumab 600 mg	IFNB-1a 44 µg	Ocrelizumab 600 mg	IFNB-1a 44 µg
No evidence of disease activity*	47.4 (41.5, 53.3)	27.1 (22.1, 32.6)	43.9 (38.1, 49.9)	24.1 (19.1, 29.6)
Relative risk	1.74 (1.39, 2.17)		1.81 (1.41, 2.32)	
Disability: Multiple Sclerosis Functional Composite score**	0.213 (0.153, 0.273)	0.174 (0.113, 0.235)	0.276 (0.222, 0.331)	0.169 (0.112, 0.226)
Mean difference	0.039 (–0.039–0.116)		0.107 (0.034, 0.180)	
Short Form 36 Physical Component Summary**	0.036 (–0.860, 0.931)	–0.657 (–1.590, 0.275)	0.326 (–0.545, 1.198)	–0.833 (–1.760, 0.094)
Mean difference	0.693 (–0.414, 1.800)		1.159 (0.051, 2.268)	

*Proportion of patients with no evidence of disease activity, in patients with baseline EDSS score ≥ 2.0
** Mean change from baseline to week 96 of trial

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Source: company submission document b p35-37
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<u>Non-confirmatory endpoints (not reported on slide)</u>
Statistically non-significant endpoints trials were
- In opera I Brain volume
- In opera I & II no evidence of disease activity (NEDA) and SF-36

Subgroups

- Subgroups (included in economic analysis)
  - Previously treated highly active (pre-specified)
  - Rapidly evolving severe (post-hoc)

- Compared with INFB-1a, ocrelizumab reduced:
  - annual relapse rate
  - confirmed disability progression at 3 months
  - confirmed disability progression at 6 months

    across all baseline patient demographic and disease characteristic subgroups in OPERA I & II

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Highly active inadequate responders (HA) (pre-specified):
Patients treated with interferons or glatiramer acetate for at least 1 year, and
•Had at least one relapse in the previous year, and
•Had at least one T1 Gd-enhancing lesion on brain MRI at baseline, or
•Had at least nine T2 hyperintense lesions on brain MRI at baseline

Rapidly evolving severe (RES) (post hoc):
•Patients had at least two relapses in the previous year, and
•Had at least one T1 Gd-enhancing lesion on brain MRI at baseline, or
•Had an increase in T2 hyperintense lesion count on brain MRI at baseline (changing from 0-5 to 6-9, >9 lesions or 6-9 lesions to >9 lesions), compared to previous MRI

Mixed treatment comparisons

- Direct evidence comparing ocrelizumab with INFB-1a only
- Method
  - Annualised relapse rate: random effects model with vague prior distribution for between-study variance.
  - Disability progression: random effects model with informative prior distribution for the between-study variance.
- 33 studies included in mixed treatment comparison identified through systematic review, includes comparators not in scope (cladribine, teriflunomide)
  - Company & ERG: inclusion of comparators outside scope has negligible impact on MTC results
- 16 studies included in subgroup (HA/RES) MTC, networks disconnected
  - Connected using whole RRMS population data from ABCR treatments, assumes treatment effect is same as subgroups

ERG: MTCs are appropriate and unlikely to have omitted any evidence

Abbreviations: RE, random effects model; FE, fixed effects model

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13 studies excluded from SR
- 2 used unlicensed doses or regimes
- 11 short trial duration

INCOMIN (IFNB-1b compared with IFNB-1a) excluded from base case for cdp-24 – Company: study considered an outlier by clinical experts. <ERG is this appropriate?>

Evidence informing mixed treatment comparison

Company: confirmed disability progression 3 months network provides better estimates than the confirmed disability progression 6 months network

ERG: confirmed disability progression 6 months more robust measure of lasting disability progression, less likely to be confused with longer relapses

Analysis network		Outcome			
		Annualised relapse rate	Confirmed disability progression 3 months	Confirmed disability progression 6 months	All-cause discontinuation
Whole RRMS population and meta-regression on trial duration	Trials, n	30	22	21	26
	DMTs, n	17	17	15	17
Highly active 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
Rapidly evolving severe 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

NA: Not applicable (subgroups were not analysed for this outcome); DMT disease modifying therapy.
a Numbers in brackets are the total number in the network, including the linking trials that provided whole RRMS population ABCR data.

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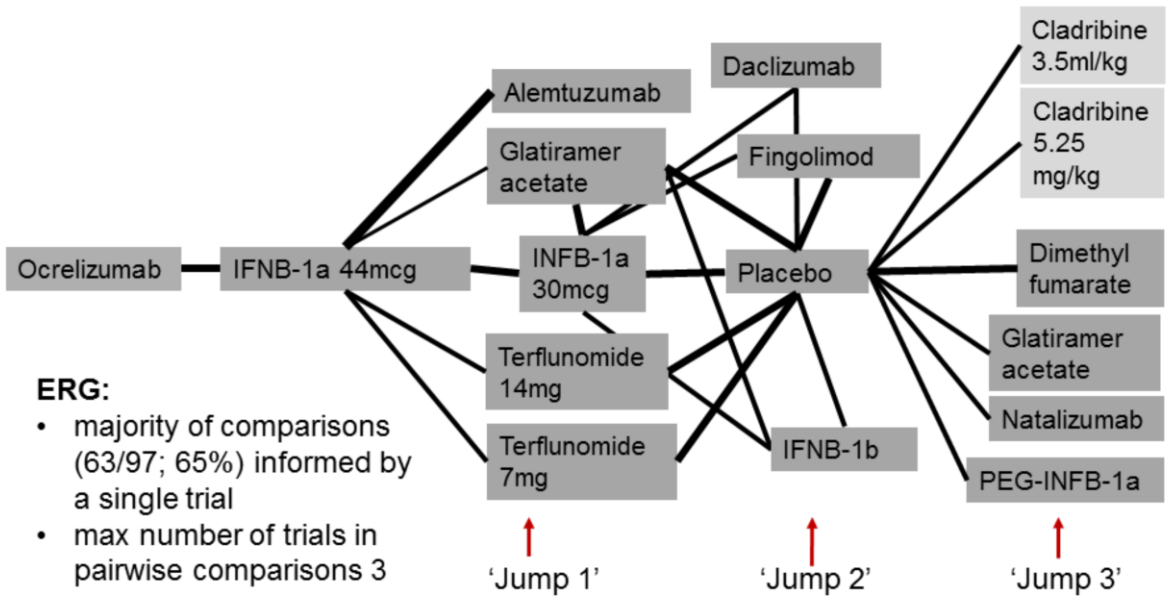
Annual relapse rate, whole RRMS population, network of studies (example)



ERG:

- majority of comparisons (63/97; 65%) informed by a single trial
- max number of trials in pairwise comparisons 3

Number of 'Jumps' relates to the number of intermediate comparisons

Key Not in scope developed by NICE In scope developed by NICE

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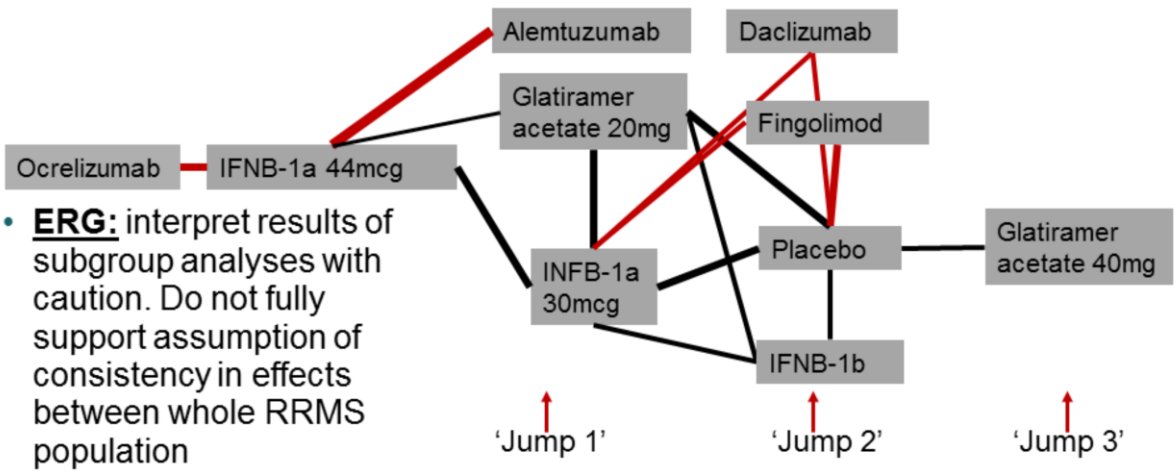
Annual relapse rate, highly active, network of studies (example)

- 8 studies included in subgroup (HA/RES) MTC, networks disconnected
  - Connected using ITT data from ABCR treatments, assumes treatment effect in ITT is the same as subgroups



- **ERG:** interpret results of subgroup analyses with caution. Do not fully support assumption of consistency in effects between whole RRMS population

Note: Black lines represent 'linking' studies using whole RRMS population data
Number of 'Jumps' relates to the number of intermediate comparisons

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Mixed treatment comparison: annual relapse rate whole RRMS population

Whole RRMS population
Second line highly active
Rapidly evolving severe

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- Whole RRMS population 30 studies
  - Ocrelizumab more effective than 9 comparators (in the scope)
  - Credible intervals cross 1.0 when ocrelizumab is compared with natalizumab or alemtuzumab
- Highly active subgroup 8 studies (21 including 'linking' studies) – supports whole RRMS population results
- Rapidly evolving severe subgroup 9 studies (22 including 'linking' studies) – no evidence of difference between ocrelizumab and daclizumab

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Mixed treatment comparison: confirmed disability progression 3 months

company preferred measure of disability progression

Whole RRMS population
Second line highly active
Rapidly evolving severe

24

- Whole RRMS population 22 studies:
  - Ocrelizumab more effective than placebo and 7 comparators (in the scope)
  - Credible intervals cross 1.0 when ocrelizumab compared with pegIFNB-1a, natalizumab, daclizumab and alemtuzumab
- Rapidly evolving severe subgroup: suggests ocrelizumab less effective than daclizumab but all results credible intervals span 1.0.
- Highly active subgroup: similar to whole RRMS population, ocrelizumab no longer more effective than fingolimod

CONFIDENTIAL

Mixed treatment comparison: confirmed disability progression 6 months

ERG preferred measure of disability progression

Whole RRMS population
Second line highly active
Rapidly evolving severe

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ERG: confirmed disability progression 6 months more robust measure of lasting disability progression, less likely to be confused with longer relapses

- Whole RRMS population 21 studies
  - Ocrelizumab more effective than placebo and IFNB-1a
  - Credible intervals cross when ocrelizumab compared with other comparators
- Rapidly evolving severe & highly active subgroup
  - all credible intervals span 1.0, suggests no difference

CONFIDENTIAL

Mixed treatment comparison: all-cause discontinuation

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- Whole RRMS population 26 studies
  - greater odds of all-cause discontinuation for ocrelizumab compared with alemtuzumab and natalizumab
  - lower odds of all-cause discontinuation in patients who receive ocrelizumab compared to pegIFNB-1a and IFNB-1a (Rebif)
- Rapidly evolving severe & highly active subgroup
  - Analyses not done, usually not reported by subgroup, assume that all-cause discontinuation rates are no different in the subgroups from whole RRMS population

Mixed treatment comparison: limitations

- Company
  - Using data from different time points assumes:
    - ARR relapse rate is constant over time
    - confirmed disability progression proportional hazards assumption holds
    - Binomial outcomes odds ratios are constant over time
  - Sensitivity analyses using network meta-regression to adjust for time point suggests assumptions are valid
  - Ratio of number of treatments to number of studies is low for some MTCs
  - Subgroups highly uncertain
    - high chance of publication bias because subgroups not pre-specified (do not have to publish if not pre-specified)
    - Post-hoc analysis definition of subgroups varied

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Adverse reactions

Infusion-related reactions, upper respiratory tract infections, and nasopharyngitis were more common in the ocrelizumab group

Variable, n (%)	OPERA I Trial		OPERA II Trial	
	Ocrelizumab n=408	IFNB-1a n=409	Ocrelizumab n=417	IFNB-1a n=417
Any adverse event	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection*	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)
Neoplasm	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse event	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)

*infection as defined in the Medical Dictionary for Regulatory Activities or with evidence of pathogen

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Safety

company: no long term treatment waning effect, ocrelizumab generates low neutralising antibodies

- No unexpected safety findings
- Number of adverse events similar in ocrelizumab and IFNB-1a arms
- Most common was infusion related reaction with first infusion, most grade 1 or 2
- Low anti-drug anti-bodies (ADAs) <1%

	Ocrelizumab n=825	IFNB-1a (Rebif®) n=826
Anti-ocrelizumab neutralising antibodies		
Baseline prevalence of ADAs, n Positive sample at baseline, n (%)	5 (0.6)	4 (0.5)
Post-baseline incidence of ADAs, n Positive for ADA, n (%)	3 (0.4)	7 (0.9)
Anti-IFNB-1a neutralising antibodies		
Baseline prevalence of ADAs, n Positive sample at baseline, n (%)	42 (5.3)	35 (4.4)
Post-baseline incidence of ADAs, n Positive for ADA, n (%)	67 (8.4)	170 (21.3)

Higher proportion ADAs for IFNB-1a than ocrelizumab

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Open label extension trial OPERA I & II

Company assume no treatment waning effect for ocrelizumab, economic model sensitive to changes in this assumption

OPERA I & II patients entered in to open label extension trial (n=835)

- To evaluate long term safety tolerability and efficacy

Annualised relapse rate in open label extension

ERG: prefer conservative approach to assumptions in line with previous appraisal, sustained effect in long term not yet proven.

- Base case: decline 25% after 2 years and 50% after 5 years for all treatments

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Company

- negligible neutralising antibodies, unlike other therapies
- 4 year open label extension data shows sustained treatment effect across different time points for annualised relapse rate, confirmed disability progression and MRI outcomes
- decreases inflammation of immune system, may reduce probability of treatment waning effect

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Open label extension trial OPERA I & II

Company assume no treatment waning effect for ocrelizumab, economic model sensitive to changes in this assumption

Confirmed disability progression at 6 months in open label extension trial

interferon beta-1a
ocrelizumab

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Company

- negligible neutralising antibodies, unlike other therapies
- 4 year open label extension data shows sustained treatment effect across different time points for annualised relapse rate, confirmed disability progression and MRI outcomes
- decreases inflammation of immune system, may reduce probability of treatment waning effect

Key issues: cost effectiveness

- Is it appropriate to
  - not include a treatment waning effect for ocrelizumab?
  - use confirmed disability progression at 3 months rather than at 6 months?
  - use EDSS health state costs from Tyas et al 2007?
  - take natural history transitions (EDSS, relapse rate) from variety of data sets?
  - assume that adverse event rate and health state utilities are the same for whole RRMS population and rapidly evolving severe / highly active subgroups?
  - exclude PML for ocrelizumab in adverse events (included for natalizumab)?
  - include beta-interferons and glatiramer acetate as blended comparator?

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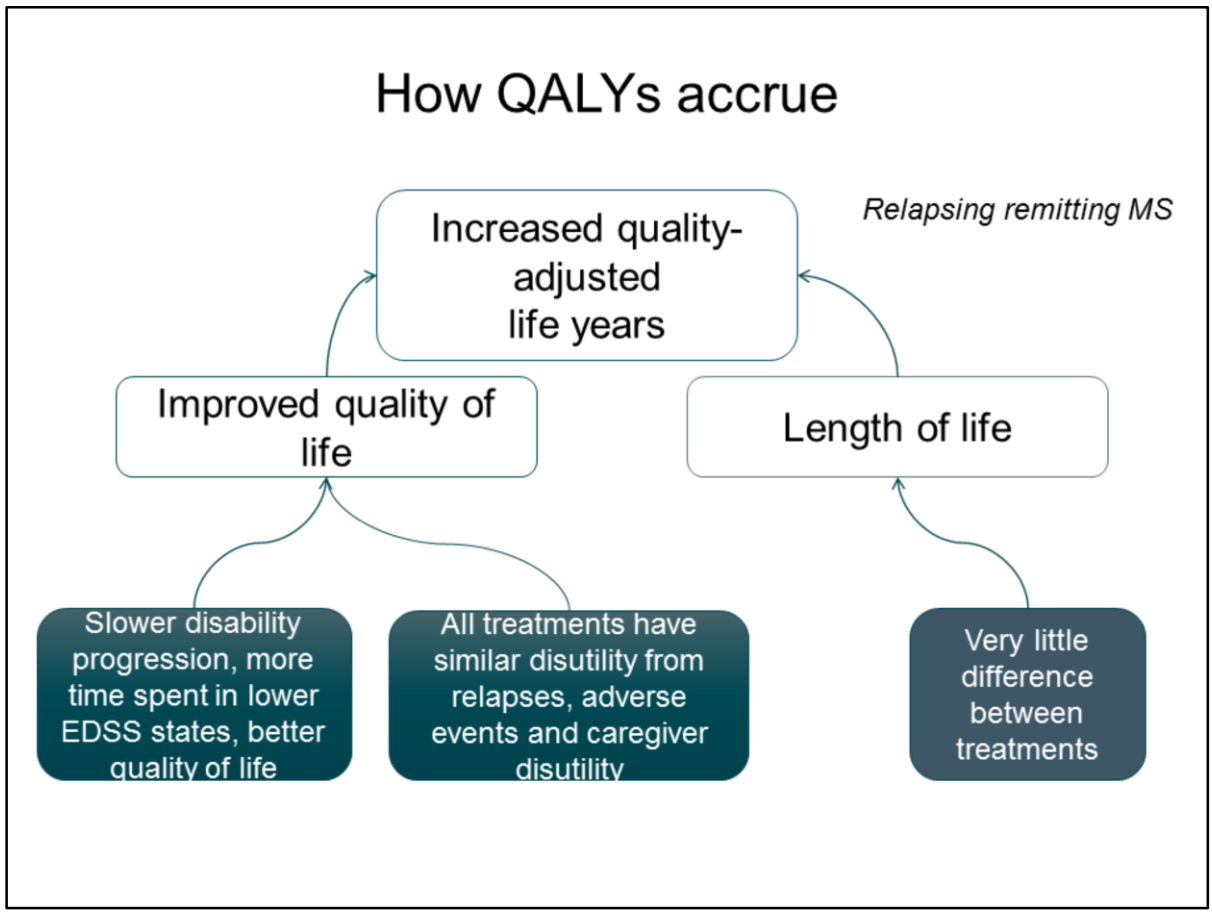
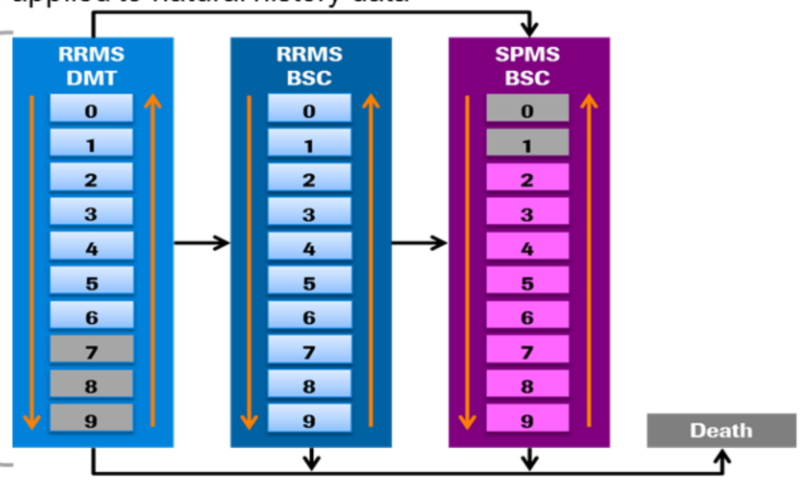

How QALYs accrue
Relapsing remitting MS
Increased quality-adjusted life years
Improved quality of life
Length of life
Slower disability progression, more time spent in lower EDSS states, better quality of life
All treatments have similar disutility from relapses, adverse events and caregiver disutility
Very little difference between treatments

Company's model

- Cohort multi-state Markov model with 1 year cycle length, time horizon 50 years
- Discount rate costs and outcomes 3.5%
- Population - people with RRMS, age 37
- Subgroups: Analyses done for RRMS, rapidly evolving severe RRMS and highly active RRMS
- Treatment effect – hazard ratios from MTC using confirmed disability progression 3 months base case applied to natural history data

Probability of changing EDSS state - natural history data

assumed treatment slows progression & reduce relapses



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Model assumptions (1)

Factor	Company base case	Company justification	ERG preferred
Measure of disability progression	confirmed disability progression3 months	quality and amount of data in MTC for confirmed disability progression 6 months low	confirmed disability progression 6 months • more robust measure • long episodes of relapse less likely
Source of EDSS cost	Tyas et al. (2007) direct medical costs and 25% of non-medical costs	In line with previous appraisals TA303 (teriflunomide), TA312 (alemtuzumab)	UK MS Survey 2007 updated to 2011/12 costs from ERG report TA320. • Daclizumab committee considerations.
Effect on converting to secondary progressive MS	50% of confirmed disability progression treatment effect assumed	Consistent with natalizumab appraisal	No additional effect on converting to secondary progressive: • not evidence based • accounted for via EDSS progression
Highly active and rapidly evolving severe subgroups	Subgroup mixed treatment comparison	-	Mixed treatment comparison of whole population - Sparse data and post-hoc nature of MTC subgroup

ERG: One small correction to model, added 3 decimal points to ARR natural history data to increase precision

Source: company submission document b p87, 122-123; ERGR p158

Model assumptions (2)

Factor	Chosen values	Company justification	ERG preferred
Treatment waning effect	None	Low probability of treatment waning sustained treatment effect demonstrated	Decline 25% after 2 years and 50% after 5 years for all treatments Conservative in line with previous appraisals
Increase in EDSS on conversion to SPMS	EDSS state always increases by 1	Similar to previous appraisals	No increase • EDSS transitions captured in the transition matrix
Source of caregiver disutility	Maximum disutility 0.14 at EDSS 9	TA127 (natalizumab)	Assume maximum disutility of 0.05 • Daclizumab appraisal and expert opinion
Alemtuzumab retreatment rates	13% continuing retreatment from year 6 onwards	Estimated from Touhy et al	Max 4 courses of treatment • CS not supported by evidence • Daclizumab appraisal
Half-cycle correction	applied with 5% adjustment for alemtuzumab	-	Addition of 5% uplift in half the cost of ocrelizumab • To offset for cost of drugs at beginning of model cycle

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Natural history data disability progression RRMS & SPMS

- British Columbia dataset from Canada used for long-term natural history
  - does not differentiate between RRMS and SPMS patients
  - scenario analysis with London Ontario dataset - different transitions for RRMS and SPMS
  - Some NICE appraisals combined British Columbia or London Ontario with trial placebo arm data; no placebo arm in OPERA I & II

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

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Health related quality of life

- Compared with literature, OPERA trial utility values are higher (younger age at baseline; 37 years)
- Assumed same utility for whole RRMS population, highly active and rapidly evolving severe
- Disutility for relapse of -0.071
- Utility decrement of -0.045 was applied to all SPMS utilities
- Disutility for caregiver's included, derived from studies in Alzheimer's (TA127)
- Disutility for adverse events taken from daclizumab and alemtuzumab company submisssions

EQ-5D-3L from OPERA I and II pooled for both treatment arms & trials

Utility decrements for EDSS state 7-9 were taken from MS trust survey (Orme et al, 2007)

	OPERA studies (pooled analysis), adjusted using Orme et al 2007		Caregiver disutility
EDSS	RRMS	SPMS	
0	0.881	0.836	0.000
1	0.843	0.798	-0.001
2	0.770	0.725	-0.003
3	0.705	0.660	-0.009
4	0.644	0.599	-0.009
5	0.601	0.556	-0.020
6	0.493	0.448	-0.027
7	0.308	0.263	-0.053
8	-0.038	-0.083	-0.107
9	-0.184	-0.229	-0.140

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Disutility for relapse (-0.071) from ScHARR model appraisal of beta interferons and glatiramer acetate

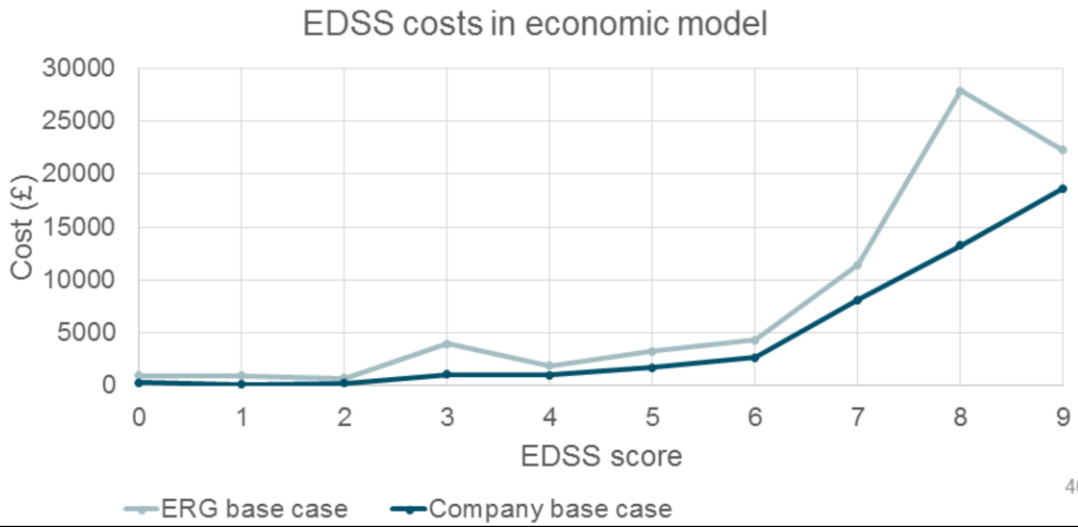
Adverse events in economic model

- AEs included in model if occurrence of ≥5% in either arm in pooled analysis of OPERA I and II
- AEs assumed constant over time
- AEs assumed the same in whole RRMS population and rapidly evolving severe highly active subgroups because of lack of data
- PML not included for ocrelizumab because low rates, included for natalizumab

	Ocrelizumab		IFNB-1a	
AE, %	2-year probability	Yearly probability	2-year probability	Yearly probability
Arthralgia	5.6	2.8	6.2	3.1
Back pain	6.4	3.3	4.5	2.3
Bronchitis	5.1	2.6	3.5	1.8
Depression	7.8	4.0	6.5	3.3
Fatigue	7.8	4.0	7.7	4.0
Headache	11.3	5.8	15.0	7.8
Influenza-like illness	4.6	2.3	21.4	11.4
Infusion related reaction	34.3	18.9	9.7	5.0
Injection site pain	0.1	0.2	5.4	11.0
Insomnia	5.6	2.8	4.6	2.3
Nasopharyngitis	14.80	7.7	10.2	5.2
Upper respiratory tract infection	15.20	7.9	10.5	5.4
Urinary tract infection	11.60	6.0	12.1	6.2
Sinusitis	5.6	2.8	5.4	2.8

Health-state costs

- Company uses health-state costs from Tyas et al. 2007 based on the MS Trust survey
  - Company: robust and used in previous appraisals
  - Adjusted to include direct medical costs and 25% direct non-medical costs
  - Inflated to 2016 prices using PSSRU 2016 inflation index
- ERG uses costs preferred by committee for interferon beta and glatiramer acetate MTA ID809 UK MS survey costs inflated to 2015/16



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Cost-effectiveness results

- Company presented interferons as blended comparator in base case

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators

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Sensitivity and scenario analyses

- Model sensitive to changes in:
  - Treatment waning assumptions
    - Lower ICERs for ocrelizumab when no treatment waning effect assumed for ocrelizumab
  - Treatment effect on confirmed disability progression
    - Higher ICERs for some lower for others
  - Source of EDSS costs
- Probabilistic results similar to deterministic

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Source: company submission document b page 138 – 139

Scenarios:

- Natural history for EDSS transitions in RRMS and SPMS and off treatment: London Ontario
- Efficacy: disability progression set to 24-week confirmation (CDP-24)
- ARR natural history: highly active subgroup (natalizumab NICE submission)
- ARR natural history: Rapidly evolving severe subgroup (natalizumab NICE submission)
- ARR natural history: Held et al 2005 and UK MS Survey 2005 (alemtuzumab NICE submission)
- Relapse duration:1 month
- Relapse duration: 2 months
- Direct medical costs RRMS and SPMS: BOUNDS-MS study
- Direct nonmedical costs RRMS and SPMS: BOUNDS-MS study
- Relapse cost: average of Hawton et al 2016 (see B.3.5.2)
- Efficacy: MTC population highly active subgroup
- Efficacy: MTC population Rapidly evolving severe subgroup
- Baseline demographics: UK Risk Sharing Scheme (Pickin et al 2009)
- Patient utilities: Orme et al 2007
- Treatment waning: 75% after 2 years and 50% after 5 years for all DMTs
- Treatment waning: 75% after 2 years and 50% after 5 years for comparators; 75% after 4 years and 50% after 7 years for ocrelizumab
- Mortality risk: Kingwell et al 2012
- All-cause discontinuation: 50% after year 2
- Relapse disutility from OPERA I and II regression analysis

Innovation

Company:

- Only disease modifying therapy to consistently demonstrate efficacy across all disease outcomes in RRMS and delays in progression in PPMS
  - glycoengineered humanised monoclonal antibody
  - selectively targets circulating B cells expressing CD20
  - immune responses to antigen challenge remain despite depletion of B cells
- Single infusion every 6 months, less than most DMTs
- Safety profile – monitoring less frequent
- Treatment waning chance low
- Half life 26 days, reversibility allows patient to receive other therapies in future

Equality and diversity

- No potential issues relating to equality and diversity identified

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Authors

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  Technical Lead
- **Frances Nixon**
  Technical Adviser
- with input from the Lead Team Mark Chapman, Richard Hoddes and Nigel Westwood and Chair, Amanda Adler

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ocrelizumab in relapsing forms of multiple sclerosis, ID937

Document B

Company evidence submission

November 2017

File name	Version	Contains confidential information	Date
ID937 Ocrelizumab in relapsing forms of multiple sclerosis	V1	Yes	27th November 2017

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables

Figures

Abbreviations

ABCR	Avonex, Betaferon, Copaxone, Rebif
ABN	Association of British Neurologists
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ARR	Annualised relapse rate
BID	Twice daily
BSC	Best supportive care
BVL	Brain volume loss
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CEAC	Cost-effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
DIC	Deviance information criterion
DMF	Dimethyl fumarate
DMT	Disease modifying treatment
EAE	Experimental autoimmune encephalomyelitis
ECG	Electrocardiogram
EDSS	Expanded disability status scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol five dimensions
ERG	Evidence Review Group
FAD	Final appraisal determination
FDA	Food and Drug Administration
GA	Glatiramer acetate
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
HRQL	Health-related quality of life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFNB	Interferon-beta
IRR	Infusion-related reaction
ISR	Injection site reaction
ITT	Intent-to-treat
IV	Intravenous
JC	John Cunningham (virus)
LLN	Lower limit of normal
LYG	Life years gained

MHCII	Major histocompatibility complex II
MIMS	Mitoxantrone in multiple sclerosis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
MSFC	Multiple sclerosis function composite
MTA	Multiple Technology Appraisal
MTC	Mixed treatment comparison
NBR	Negative binomial regression
NEDA	No evidence of disease activity
NHS	National Health Service
NMA	Network meta-analysis
NR	Not reported
OCR	Ocrelizumab
OLE	Open-label extension
OTC	Over the counter
PASLU	Patient Access Scheme Liaison Unit
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PSSRU	Personal Social Services Research Unit
PRISMS	Prevention of relapses and disability by interferon beta-1a subcutaneously in multiple sclerosis
QAD	Every other day
QALY	Quality adjusted life years gained
QD	Once daily
QM	Once monthly
QW	Once weekly
RES	Rapidly evolving severe
RMS	Relapsing multiple sclerosis
ROW	Rest of the world
RRMS	Relapsing remitting multiple sclerosis
RSS	Risk sharing scheme
SAE	Serious adverse events
SD	Standard deviation
SF-36 PCS	36-item Short-Form Health Survey Physical Component Summary
SPMS	Secondary progressive multiple sclerosis
SR	Systematic review
TB	Tuberculosis
TIW	Three times a week
UTI	Urinary tract infection

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation in adults with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

The full marketing authorisation of ocrelizumab is for adults with relapsing forms of multiple sclerosis (MS) with active disease defined by clinical or imaging features, which covers both RRMS and relapsing forms of secondary progressive multiple sclerosis (SPMS). In clinical practice the transition to SPMS is commonly characterised in retrospect due to the unpredictable nature of the MS disease course on an individual patient level. The OPERA studies did not capture at baseline or track post-baseline the classification of patients by RRMS or SPMS disease type. As such there is no trial data available specifically for the sub-population of adults with relapsing forms of SPMS.

The proposed population for this technology appraisal is narrower than the marketing authorisation because the evidence base on ocrelizumab is largely limited to this population.

Post-hoc analysis was conducted to approximate the proportion of SPMS patients in the OPERA studies. As a proxy for SPMS, patients who had experienced disease progression unrelated to relapses were examined. This analysis indicated that between 2% to 10% of the ITT population could be considered to have SPMS. This is consistent with the OPERA studies being in predominantly [~90% or greater] RRMS patients.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsing forms of MS.	The submission focuses on adults with RRMS.	The pivotal studies (OPERA I and II) predominantly included patients with RRMS.
Intervention	Ocrelizumab	As per scope	N/A
Comparator(s)	For people with 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) For people with rapidly evolving severe (RES) RRMS: • alemtuzumab • natalizumab • daclizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with highly active RRMS despite previous treatment: • alemtuzumab • fingolimod • daclizumab (only if alemtuzumab is contraindicated or otherwise	For people with RRMS: • alemtuzumab* • dimethyl fumarate • teriflunomide • beta-interferon • glatiramer acetate • daclizumab • natalizumab† • fingolimod† For people with rapidly evolving severe (RES) RRMS: • alemtuzumab* • natalizumab • daclizumab‡ For people with highly active RRMS despite previous treatment: • alemtuzumab* • fingolimod • daclizumab‡	* In order to allow for consideration of patient preference and treatment choice (see Section B.1.3), results including and excluding alemtuzumab are presented † Comparators natalizumab and fingolimod are only licensed and/or approved by NICE in sup-populations of RRMS. However due to limitations of the subgroup mixed treatment comparison (MTC) (see Section B.2.9.1), these comparators are also included in the ITT MTC and economic analysis for consideration in decision making. Sensitivity analyses excluding these comparators can be found in Appendix D.1.4. ‡ The EMA has applied a restriction to daclizumab due to safety concerns and is indicated for 'patients who have had an inadequate response to at least two DMTs and cannot be treated with other DMTs' (1). We therefore do not consider daclizumab a relevant comparator for evaluating cost-effectiveness of ocrelizumab. Daclizumab is included in the ITT and subgroup MTCs but not included in the economic analysis. There is no subgroup data available from

	unsuitable) For people with SPMS with active disease, evidenced by relapses: • best supportive care		the OPERA studies in patients with relapsing SPMS (see text in Section B.1.1).
Outcomes	• relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance • freedom from disease activity • mortality • adverse effects of treatment	As per scope for ocrelizumab.	Some outcomes (severity of relapse, symptoms, and freedom from disease activity) could not be assessed in a MTC due to lack of comparative data or use of different scales and definitions in trials.
Subgroups to be considered	If the evidence allows the following subgroups will be considered (in addition to those specified above for comparators): • 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	Subgroup analysis for ocrelizumab in people whose disease has responded inadequately to previous treatment is reported in appendix E ('treatment experience'). No additional subgroups are included in the submission due to lack of evidence.	There is a lack of comparative data available in the public domain for a MTC in these specific sub-populations.
Special considerations including issues related to equity or equality	Not applicable		

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 2. See Appendix C for details of the summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Description of the technology

UK approved name and brand name	UK approved name: ocrelizumab Brand name: Ocrevus®
Mechanism of action	Ocrelizumab is a humanised monoclonal antibody that selectively depletes CD20+ B cells (2, 3) B cells have been independently implicated in the pathophysiology of MS through their role in antigen presentation, cytokine production, autoantibody production and ectopic lymphoid follicle-like structures in the central nervous system (4).
Marketing authorisation/CE mark status	A positive CHMP opinion was received in November 2017; the expected date of marketing authorisation is January 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication of Ocrevus is for the treatment of adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features (5).
Method of administration and dosage	Ocrelizumab is administered as an intravenous (IV) infusion. The first 600 mg dose is administered as two 300 mg infusions two weeks apart. Subsequent doses are administered as a single 600 mg infusion every six months. A minimum interval of five months should be maintained between each dose The following two premedications 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. In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes prior to each ocrelizumab infusion.
Additional tests or investigations	The draft SmPC recommends hepatitis B virus (HBV) screening in all patients before initiation of treatment with ocrelizumab as per local guidelines (5). As per routine practice, if progressive multifocal leukoencephalopathy (PML) is suspected dosing with ocrelizumab must be withheld and evaluation including MRI scan preferably with contrast (compared

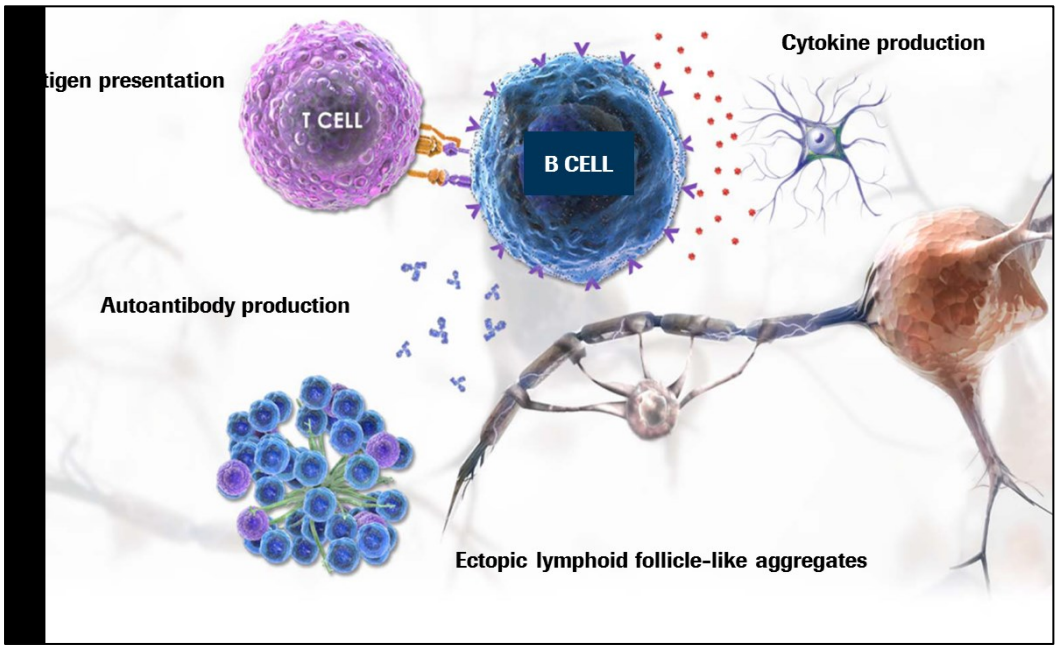
	with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.
List price and average cost of a course of treatment	List price is £4,790 per 300 mg vial. The average cost per patient per year is £19,160 based on twice yearly 600mg infusions. Net price incorporating the patient access scheme (PAS) is [redacted].
Patient access scheme (if applicable)	The PAS is a simple discount and is approved by the Department of Health and PASLU.

B.1.3 Health condition and position of the technology in the treatment pathway

Multiple sclerosis (MS) is a chronic autoimmune disease, characterised by inflammation of the central nervous system (CNS) that leads to demyelination, axonal loss and progressive neuronal degeneration (6, 7). Despite the availability of treatments, the disease remains incurable; it progressively worsens, and can result in irreversible disability and cognitive impairment (6). It predominantly affects women, with an approximate ratio of 3:1 (8-11). Life expectancy for patients with MS is 5–10 years shorter than for the general population (12, 13), with approximately 50% of patients dying from complications in the advanced stage of MS (14).

B cells have been independently implicated in the pathophysiology of MS through their role in antigen presentation, cytokine production, autoantibody production and ectopic lymphoid follicle-like structures in the central nervous system (4).

Figure 1: Functional roles of B cells in MS



Source: (15-17)

Studies have suggested that the innate immune system may play an important role in the progression of MS by influencing the effector function of T and B cells (18). For instance, persistent activation of microglial cells, the most common immune cells in the central nervous system, has been observed in the chronic phase of relapsing-remitting experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, and a correlation has been observed between activated microglial cells and loss of neuronal synapses (19). Studies are

ongoing to further elucidate the role of activated microglia in the pathogenesis of MS progression.

In addition to immune-mediated inflammatory mechanisms, magnetic resonance imaging (MRI) studies reveal a much more widespread and global damage of the brain and spinal cord, which may initially be clinically silent (20, 21). This subclinical activity can be a precursor of clinical events. For example, a T1-weighted gadolinium (Gd)-enhanced brain scan highlights areas of active inflammation, where the blood-brain barrier has become permeable to Gd, indicating active lesions that are new or enlarging (7). A change in the T1 lesion volume correlates strongly with disability progression (22). In T2-weighted scans, lesions appear as hyperintense white areas, providing information on lesion load and provide a good association with conversion to definite MS when detected as a clinically isolated syndrome (23, 24).

Types of MS

MS is a disease continuum with three main presenting phenotypes based on the relative presence and clinical dominance of either episodic active neuroinflammation with associated disability or disability progression independent of inflammation (25, 26):

- Relapsing-remitting (RRMS);
- Secondary progressive (SPMS);
- Primary progressive (PPMS).

RRMS is the most common phenotype of MS, with an incidence of approximately 85% at diagnosis (27). Patients with RRMS experience unpredictable and recurring clinical episodes of acute neurological dysfunction (relapses) that are driven by acute neuroinflammation. This is followed by a recovery of function (remission) in some patients although studies have shown that over 25% of patients will have residual disability following a relapse (28). A relapse is a clinically evident ‘attack’ of neuroinflammation and demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, either completely or partially (29). Current pharmacological management in RRMS includes the use of DMTs, aimed at reducing the frequency and/or severity of relapses and/or slowing disability progression. MS disease should be controlled as early as possible and experience with DMTs indicates that there is a window of opportunity where early use may control the disease in some patients (30, 31).

In RRMS, disability worsening occurs as a result of incomplete recovery from relapses (32); a higher number of relapses in the first 2 years after disease onset is significantly associated with worse outcomes (higher probability and shorter time for attaining disability levels) (33).

Most patients with RRMS will eventually transition to **SPMS**, in which there is a period of steady disease progression with less discernible clinical signs of acute neuroinflammation after an initial period of neuroinflammatory-driven relapsing-remitting disease. Prior to the widespread use of highly efficacious DMTs, most patients with RRMS were thought to eventually develop SPMS (6, 34). A study by Ahrweiller et al. demonstrated that 35% of patients with SPMS would experience at least one relapse (35).

Approximately 15% of MS patients are diagnosed with **PPMS** which is characterised by a gradual disability progression from onset with minimal discernible clinical signs of neuroinflammation characterised by relapses and remissions (36). Delayed diagnosis and an unrelenting progressive disease course together with the current lack of licensed DMTs for PPMS would necessitate the focus of any new treatment to be the preservation of patient independence (upper limb function) rather than just patient mobility (lower limb function) (37).

Epidemiology

There are currently no accurate data on the exact number of people with MS in the UK, but estimates have been made by taking data from Mackenzie *et al.* and adapting it to overall prevalence from the MS Society (38, 39). The Mackenzie study estimated that the number of people with MS in the UK was growing by around 2.4% per year, due to people with MS living longer (38).Through extrapolation, the prevalence of MS in England in 2017 is estimated as 89,030 patients, with an incidence of 5,110 newly diagnosed patients each year.

Patients are typically between 20 and 45 years of age when they are initially diagnosed with RRMS (6). Given the fact that most patients will transition to SPMS, and using the prevalence data from Mackenzie et al. and the MS Society, as well as RRMS prevalence data from Fox et al. and Jick et al., the estimated prevalence of patients with RRMS in 2017 is 57,870 (approximately 65% of the England MS patient population) (38-41).

Clinical pathway of care

DMTs recommended by NICE in the UK for the treatment of RRMS include interferon beta (IFNB) therapies - IFNB-1a, IFNB-1b, and pegylated IFNB-1a (pegIFNB-1a) - glatiramer

acetate, teriflunomide, dimethyl fumarate (DMF), daclizumab, natalizumab, fingolimod, and alemtuzumab (42). However, due to variations in current management of MS, there is no typical first-line therapy used (43). Instead the recommended treatment paradigm is defined by extent of disease activity. Natalizumab, fingolimod, daclizumab and alemtuzumab can substantially reduce relapses and disability progression (44-48), but early use of these DMTs in the disease course is limited by safety concerns and specific patient eligibility criteria as defined by EMA and NICE (49).

The choice of DMT prescribing in RRMS is largely driven by an informed discussion and consensus between the prescribing clinician and the patient based on the level of disease activity, patient risk tolerance, patient preference and patient lifestyle considerations such as family planning (50-52).

In the daclizumab NICE final appraisal determination (FAD), it states that "the clinical experts explained that the choice of treatment varies between patients and between hospitals because there is no single treatment pathway" (53). Furthermore, a concordant relationship between healthcare professionals and patients is required so that the personal preferences of the patient are considered when evaluating the benefit-risk profiles of the various treatment options (54). For instance, the daclizumab FAD recorded feedback from patient experts which stated that some patients may refuse alemtuzumab due to the irreversible immunosuppressive effects and adverse events associated with this treatment (53). Furthermore, it was recorded in the alemtuzumab FAD that a clinical specialist had stated during a committee meeting that alemtuzumab is "*not for everybody*" and that treatment would be offered to those patients, among other characteristics, who would likely comply with the required monitoring for adverse events (55). This was corroborated by external advice obtained from clinical experts at a Roche UK advisory board, who highlighted the importance of considering patient preference when choosing treatment[1].

Treatment decisions in MS are also confounded by the uncertainty regarding the sustained efficacy of DMTs. For instance, although alemtuzumab is an induction therapy of two years, 5-year follow up data of the pivotal phase 3 studies have shown that a considerable proportion of patients need additional courses of alemtuzumab or switch to other DMTs in subsequent years due to recurring disease activity (Table 46).

[1] As a result, this submission presents scenarios that include and exclude alemtuzumab treatment as a comparator for ocrelizumab

Despite this lack of a single treatment pathway, the Association of British Neurologists (ABN) has provided guidance on the treatment of RRMS (56). The ABN guidelines divide the treatments into two broad classes, mostly based on relapse rate reductions:

- Category 1 - Moderate efficacy drugs (average relapse reduction 30–50%): IFNB, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod;
- Category 2 - High efficacy drugs (average relapse reduction substantially more than 50%): alemtuzumab and natalizumab.

There are no strict guidelines on stopping DMT use, however, clinicians should consider stopping DMT in the following situations (56):

1. Significant side effects;
2. Development of non-relapsing secondary progressive MS;
3. Pregnancy;
4. Loss of mobility (EDSS 6.5 is the upper limit governing patient eligibility for a DMT).

According to NICE recommendations, patients with RRMS who have had two or more clinical relapses within two years are considered to have 'active' disease that requires DMT use. 'Highly active' is defined by NICE as patients who have an unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year despite treatment with IFNB. The ABN classifies patients with highly active RRMS as ≥1 relapse in the previous year and either ≥1 Gd-enhancing MRI lesions or at least nine T2 hyperintense lesions, despite treatment with IFNB or glatiramer acetate.

NICE guidelines recommend natalizumab as treatments for rapidly evolving severe (RES) RRMS only; RES is defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI (57). Fingolimod is recommended as an alternative to natalizumab for those patients at risk of developing progressive multifocal leukoencephalopathy (PML) (58).

Table 3: NICE recommendations on DMTs for RRMS

Active RRMS	Highly active RRMS despite previous treatment	Rapidly-evolving severe RRMS
Dimethyl fumarate	Fingolimod	Natalizumab
Alemtuzumab	Alemtuzumab	Alemtuzumab
Teriflunomide	Daclizumab	Daclizumab
Interferon beta (current appraisal paused)		

Glatiramer acetate (current appraisal paused)		

With the introduction of progressively more efficacious DMTs in RRMS, there has been a parallel stepwise increase in the associated safety concerns with these treatments and has led to very complex and burdensome patient safety monitoring algorithms. These constrain both the patient and the NHS providing the DMT service (54). For instance, in October 2017, the EMA's Pharmacovigilance Risk Assessment Committee issued a final opinion to recommend further restrictions on the use of daclizumab following a review on the effect of this medicine on the liver; daclizumab is now recommended only for those patients who have had an inadequate response to at least two DMTs and cannot be treated with other DMTs (1)[2]. Furthermore, natalizumab has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML), therefore patients should be monitored at regular intervals throughout the course of treatment (59).

Table 4: DMT safety concerns and monitoring requirements

DMT	Common AEs	Safety issues	Monitoring requirements
IFNB-1a/b (e.g. PegIFNB-1a) (60)	ISRs, lymphopenia flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, asthenia, depression, haematologic abnormalities, arthralgia	Hepatic injury. anaphylaxis, depression, injection site necrosis, congestive heart failure, leukopenia thrombotic microangiopathy, seizures, autoimmune disorders, decreased peripheral blood counts	Blood counts, liver function tests, renal function tests
Glatiramer acetate (61)	ISRs, post-injection reaction (vasodilation, rash, dyspnoea, chest pain within minutes)	Cutaneous necrosis	Renal function (in patients with renal impairment)
Dimethyl fumarate (62)	Flushing, abdominal pain, diarrhoea, nausea	Anaphylaxis and angioedema, PML, lymphopenia	Blood counts, liver function tests, renal function tests, MRI before treatment and if PML suspected during treatment
Teriflunomide (63)	Headache, diarrhoea, nausea, alopecia, increased alanine aminotransferase	Hepatic injury, teratogenicity, bone marrow effects, potential immunosuppression, infection, peripheral neuropathy, skin AEs, increased blood pressure, respiratory effects, pancreatitis, thrombocytopenia	Blood counts, tuberculin skin test (before treatment), liver function tests, blood pressure tests

[2] As a result, daclizumab is not considered to be a relevant comparator and has been excluded from the economic analysis

Fingolimod (64)	Headache, liver transaminase elevation, diarrhoea, cough, influenza, sinusitis, infection, back pain, abdominal pain, pain in extremity	Asystole and sudden death, infections, PML, macular oedema, posterior reversible encephalopathy syndrome, respiratory effects, hepatic injury, teratogenicity, increased blood pressure, basal cell carcinoma	Blood counts, liver function tests, blood pressure tests, ECG monitoring after first dose, pre-treatment ophthalmology assessment, MRI before treatment, varicella zoster virus test before treatment
Daclizumab (65)	Nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, depression, pharyngitis, increased alanine aminotransferase	Hepatic injury, immune-mediated disorders, infections, depression	Blood counts, liver function tests, at risk patients monitored for tuberculosis
Natalizumab (59)	Headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis vaginitis, depression, pain in extremity, abdominal discomfort, diarrhoea, rash	PML, hypersensitivity reactions, immunosuppression/infections, hepatic injury	Liver function tests, MRI scan (before treatment and annually), anti JCV tests
Alemtuzumab (66)	Rash, headache, pyrexia, nasopharyngitis, nausea, vomiting, infection (UTI, upper respiratory tract, viral including herpes, fungal), fatigue, insomnia, urticaria, pruritus, thyroid gland disorders, arthralgia, pain in extremity, back pain, oropharyngeal pain, abdominal pain, diarrhoea, sinusitis, paraesthesia, dizziness, flushing	Infusion-associated reactions and anaphylaxis (including bradycardia), thyroid disorders and other autoimmune cytopenias, glomerulonephritis, malignancy (thyroid cancer, melanoma, lymphoproliferative disorders), infections	Monthly blood counts, monthly urinalysis, thyroid function tests, HPV test, monthly renal function tests, tuberculin skin test before treatment, varicella zoster virus test before treatment
Ocrelizumab (5)	Infusion-related reactions, upper respiratory tract infections	Infusion-related reactions, infections, neoplasms	HBV screening before treatment; no post-treatment monitoring required

AE, adverse events; ECG electrocardiogram; HBV, hepatitis B virus; HPV, human papillomavirus; IRR, infusion-related reactions; ISR injection site reactions; JCV, John Cunningham virus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; UTI, urinary tract infection

Unmet need in RRMS

There is unmet need in the field of MS for a DMT with a benefit–risk profile that supports initiation at any time during the disease course of MS, and which preserves neurological function, inhibits the accumulation of irreversible disability and improves HRQoL. An ideal

DMT for MS would be efficacious, well-tolerated and reduce the burden of treatment administration and safety monitoring to improve adherence and relieve capacity in the healthcare system (67).

Current DMTs approved by NICE do not consistently demonstrate efficacy across all outcomes for RRMS, particularly regarding disability progression. The limitations of the efficacy of DMTs highlighted in the scope for this appraisal are summarised below.

Table 5: Efficacy limitations of DMTs for RRMS

DMT type	Description
Oral treatments	Dimethyl fumarate and teriflunomide: low efficacy regarding CDP in placebo-controlled trials (68-70)
Escalation treatments	Fingolimod: inconsistent and low efficacy in placebo controlled studies (46, 57, 71) Daclizumab: inconsistent CDP data with no superiority over an active comparator therefore it is questionable if this can be considered a true escalation therapy (72)
Induction treatments	Alemtuzumab: no CDP-12 data in an open-label study; uncertainty on sustained efficacy without re-treatment (considerable re-treatment rates in follow up data therefore it is questionable if this can be considered a true induction therapy) (45, 73-75)

Ocrelizumab provides an alternative treatment option that addresses the unmet need in MS as it is the only DMT in RRMS to consistently demonstrate efficacy across confirmed disability progression outcomes and across studies compared with an active comparator. It is also the first DMT to demonstrate near-complete suppression of subclinical disease activity as measured by MRI.

Furthermore, the safety profile coupled with the need for just two infusions per year means that ocrelizumab will require a lower healthcare utilisation with less frequent monitoring than the other high efficacy DMTs; therefore, ocrelizumab may potentially change the treatment paradigm leading to earlier treatment with a high efficacy DMT.

B.1.4 Equality considerations

No equality issues relating to ocrelizumab have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Ocrelizumab was evaluated in two phase III studies and one phase II study (Table 6). The Phase II study is not included in the mixed treatment comparison (MTC) or used to populate the economic model because the primary endpoint was total number of Gd-enhancing lesions at weeks 12, 16, 20, and 24 (i.e. shorter than 48 weeks) and did not include a disease progression endpoint (76). Results of the Phase II study are not discussed further.

Table 6: Clinical effectiveness evidence

Study	WA21493	WA21092 (OPERA I)	WA21093 (OPERA II)
Study design	Phase II, placebo-controlled trial	Phase III, randomised-controlled, active comparator, double-blind, double-dummy designs	
Population	Patients aged 18–55 years with a diagnosis of RRMS and two or more documented relapsed within 3 years before screening	Patients aged 18–55 years with a diagnosis of RMS and two or more documented relapses within the previous two years or one relapses within the year before screening	
Countries (study centres)	20 countries (100 sites) Belgium (2), Bulgaria (7), Canada (3), Czech (5), Denmark (1), Finland (2), France (6), Germany (8), Italy (2), Mexico (4), Netherlands (1), Romania (2), Russia (6), Serbia (3), Slovakia (5), Spain (6), Switzerland (1), Ukraine (4), United Kingdom (4), USA (28)	32 countries (114 sites) Argentina (3), Australia (1), Austria (1), Belgium (3), Bulgaria (5), Brazil (3), Switzerland (2), Chile (1), Czech Republic (6), Estonia (2), Finland (1), France (5), Germany (10), Hungary (3), Israel (1), Italy (4), Lithuania (3), Latvia (2), Mexico (2), Netherlands (1), Peru (4), Poland (4), Portugal (1), Russian Federation (11), Serbia (3), Slovakia (4), South Africa (1), Spain (4), Tunisia (3), Ukraine (5), United Kingdom (2), USA (40)	24 countries (166 sites) Argentina (2),Belgium (1), Bulgaria (4), Bosnia and Herzegovina (2), Belarus (4), Brazil (3), Canada (8), Czech Republic (4), Croatia (4), Germany (10), France (7), Ireland (1), Italy (10), Mexico (6), Norway (1), Poland (9), Russian Federation (9), Slovakia (3), Spain (10), Sweden (4), Turkey (8), Ukraine (4), United Kingdom (4), USA (48)
Intervention(s)	Ocrelizumab 600 mg (n=55) and 2000 mg (n=56) The 600 mg OCR group received 300 mg on days 1 and 15 of the first treatment cycle and then 600 mg for subsequent cycles (weeks 24, 48 and 72). The 2000 mg group had an infusion of 1000 mg in the first treatment cycle on days 1 and 15 and then an infusion of 1000 mg for the subsequent treatment cycles	Ocrelizumab 600 mg (n=410) First dose consisted 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	Ocrelizumab 600 mg (n=417) First dose consisted of two 300 mg OCR/placebo IV infusions by 14 days apart; subsequent doses consisted of one 600 mg OCR/placebo IV infusion; maximum 4 doses
Comparator(s)	Placebo (n=54) IFNB-1a (Avonex®) 30 µg (n=54)	IFNB-1a (Rebif®) 44 µg (n=411); injections 3x weekly, during double-blind treatment period	IFNB-1a (Rebif®) 44 µg (n=418); injections 3x weekly, during double-blind treatment period
Indicate if trial supports application for marketing authorisation	No	Yes	Yes
Indicate if trial used in the economic model	No	Yes	Yes
Rationale for use/non-use in the model	Not used in the model: study duration < 48 weeks and did not have disease progression as an endpoint	Phase III, randomised-controlled trial	

Reported outcomes specified in the decision problem	N/A	• Relapse rate • Severity of relapse • Disability • Symptoms of MS such as fatigue, cognition and visual disturbance • Freedom from disease activity • Mortality • Adverse effects of treatment • Health-related quality of life • Discontinuation
All other reported outcomes	N/A	• Total no. of Gd-enhancing T1 lesions as detected by brain MRI at weeks 24, 48 and 96 • Total no. of new and/or enlarged T2 hyperintense lesions, detected by brain MRI at weeks 24, 48 and 96 • Proportion of patients who had CDI for ≥12 weeks • Total number of new T1 hypointense lesions at weeks 24, 48 and 96 • Change from baseline in MSFC score to week 96 • % change in brain volume as detected by brain MRI from week 24 to week 96 • Proportion of patients who had no evidence of disease activity (NEDA) by week 96*

CDI: Confirmed disability improvement; IFN: Interferon; IV: Intravenous; MSFC, multiple sclerosis functional composite; NEDA: No evidence of disease activity; OCR: Ocrelizumab; RMS: Relapsing multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis

*Patients who completed the 96-week treatment period were considered to have evidence of disease activity if at least one relapse, a CDP event or at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions or new or enlarged T2 lesions) was reported during the 96-week treatment period; otherwise the patient was considered to have NEDA.

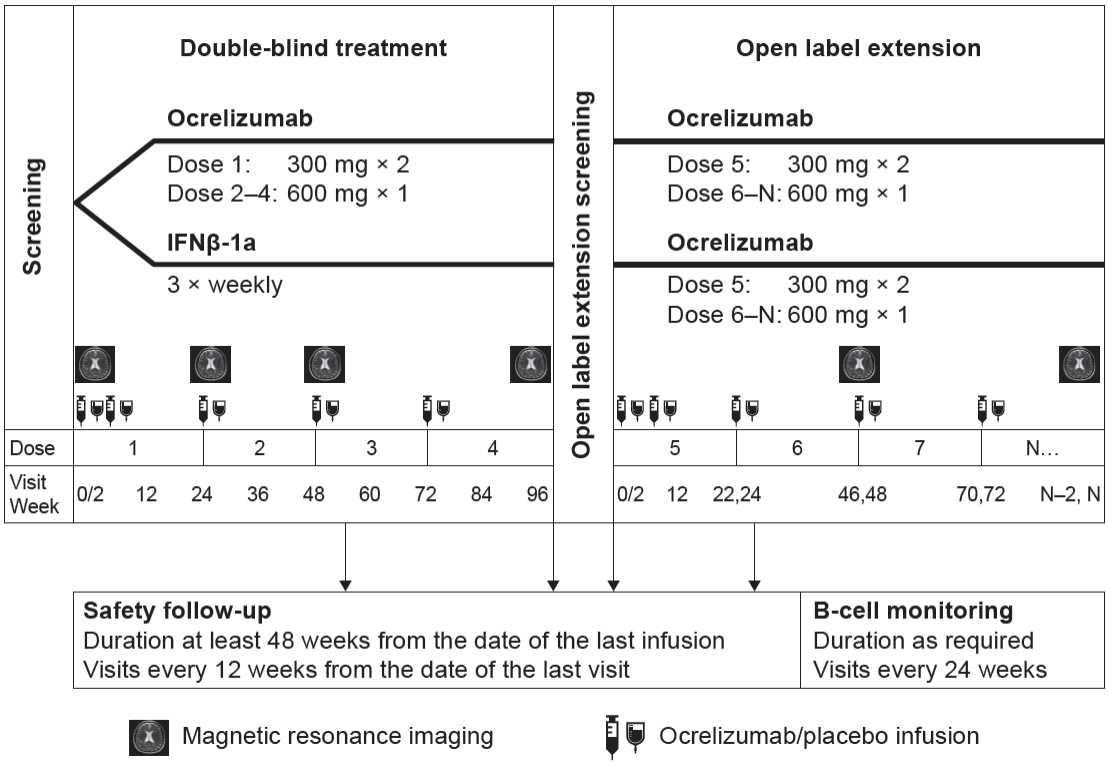
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

OPERA I and OPERA II were identically designed international, randomised, active-controlled trials that assessed the efficacy and safety of ocrelizumab compared with IFNB-1a (Rebif®) in patients with RMS. Data were collected by the site investigators, queries were responded to by site personnel, and the data were analysed by F. Hoffman-La Roche; the aggregated and individual results of the participants were reviewed by F. Hoffman-La Roche and the OPERA I and OPERA II steering committee. An independent data and safety monitoring committee reviewed ongoing safety data and provided guidance on trial continuation, modification, or termination (77). There were no overlapping trial centres between OPERA I and OPERA II.

Both studies were independent pivotal trials and sufficiently powered for their respective primary analysis. However, for secondary analysis of endpoints based on the Expanded Disability Status Scale (EDSS), specifically Confirmed Disability Progression (CDP) and Confirmed Disability Improvement (CDI), data from the two trials were pooled to maintain sufficient power to detect relevant treatment differences.

Patients were randomly assigned, in a 1:1 ratio, to receive ocrelizumab at a dose of 600 mg by means of intravenous infusion every 24 weeks, given as 300 mg infusions on days 1 and 15 of the first 24-week treatment period and subsequently as single 600 mg infusions or IFNB-1a at a dose of 44 µg (Rebif®, EMD Serono), administered subcutaneously three times weekly throughout the 96-week treatment period (Figure 2) (77).

Figure 2: Design of OPERA I and OPERA II



The key methodology of the OPERA I and OPERA II trials are summarised in Table 6 and the study design is shown in Figure 2. Both studies consisted of a screening period (approximately two weeks prior to randomisation), followed by 96 weeks of double-blind, double-dummy treatment. Patients who completed the 96-week treatment period had the option to enter the single-group open-label extension (OLE) with ocrelizumab, providing they fulfilled the eligibility criteria at OLE screening (78, 79). The safety follow-up included all participants who withdrew prematurely from study treatment during the 96-week treatment period or during the OLE, as well as those who did not enter the OLE. The OLE phase of OPERA I and II is ongoing; data is due to be presented at a scientific meeting in 2018, please refer to confidential Appendix L for further details.

OPERA I and OPERA II were identical in terms of endpoints, inclusion and exclusion criteria (Table 7) comparator, and statistical analysis plan. The primary endpoint was the efficacy of ocrelizumab in reducing relapses, as measured by protocol-defined annual relapse rate

(ARR), at 96 weeks, compared with IFNB-1a (Rebif®). Secondary endpoints included disability outcomes (12-and 24-week CDP and 12-week CDI), MRI measures (including Gd-enhancing T1 lesions, T2 lesions and brain volume loss [BVL]), no evidence of disease activity (NEDA) status and functional/health-related quality of life (HRQoL) measures. OPERA I and OPERA II also evaluated the safety and tolerability of ocrelizumab during the double-blind and open-label extension phases (78, 79).

Table 7: Key inclusion and exclusion criteria for OPERA I and OPERA II

Inclusion criteria	Key exclusion criteria
• Ages 18–55 years at screening, inclusive • Diagnosis of MS, in accordance with the revised McDonald criteria (80) • 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	• Diagnosis of PPMS • Disease duration of more than 10 years in patients with an EDSS ≤2.0 at screening • Inability to complete an MRI <u>Exclusions related to general health</u> • Pregnancy or lactation • Any concomitant disease required chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study • History of or active primary or secondary immunodeficiency • Congestive heart failure (New York Heart Association III or IV functional severity) • 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 prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit • History or known presence of recurrent or chronic infection (e.g. HIV, syphilis, TB) • History of PML <u>Exclusions related to medications</u> • Contraindication to IFNB-1a or incompatibility with IFNB-1a use • Previous treatment with B-cell targeted therapies (i.e. rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab) • 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. Patients previously treated with natalizumab were eligible for this study only if duration of treatment with natalizumab was <1 year • Treatment with fingolimod or other sphingosine-1-phosphate receptor modulator, within 24 weeks prior to screening (only

	patients with T lymphocyte count ≥LLN were eligible for the study)

EDSS, expanded disability status scale; HIV, human immunodeficiency virus; IFNβ, interferon beta; LLN, lower limit of normal; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; TB, tuberculosis

In total, 1,656 patients underwent randomisation (intent-to-treat population [ITT]); 821 patients in OPERA I and 835 patients in OPERA II (77). The demographic and disease characteristics at baseline were similar between OPERA I and OPERA II.

Table 8: Baseline demographics and disease characteristics in OPERA I and II

Characteristic	OPERA I Trial		OPERA II Trial	
	Ocrelizumab n=410	IFNB-1a (Rebif) n=411	Ocrelizumab n=417	IFNB-1a (Rebif) n=418
Mean age, years (SD)	37.1 (9.3)	36.9 (9.3)	37.2 (9.1)	37.4 (9.0)
Female, n (%)	270 (65.9)	272 (66.2)	271 (65.0)	280 (67.0)
Geographic region, n (%)				
United States	105 (25.6)	105 (25.5)	112 (26.9)	114 (27.3)
Rest of the world	305 (74.4)	306 (74.5)	305 (73.1)	304 (72.7)
Mean time since symptom onset, years (SD)	6.74 (6.37)	6.25 (5.98)	6.72 (6.10)	6.68 (6.13)
Mean time since diagnosis, years (SD)	3.82 (4.80)	3.71 (4.63)	4.15 (4.95)	4.13 (5.07)
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)
	n=408	n=409	n=417	n=417
No. previous DMT, n (%)	301 (73.8)	292 (71.4)	304 (72.9)	314 (75.3)
	n=408	n=409	n=417	n=417
Previous DMT, n (%)	107 (26.2)	117 (28.6)	113 (27.1)	103 (24.7)
Interferon	81 (19.9)	86 (21.0)	80 (19.2)	75 (18.0)
Glatiramer acetate	38 (9.3)	37 (9.0)	39 (9.4)	44 (10.6)
Natalizumab	0	1 (0.2)	1 (0.2)	0
Fingolimod	1 (0.2)	0	4 (1.0)	0
Dimethyl fumarate	1 (0.2)	0	0	0
Other	2 (0.5)	3 (0.7)	1 (0.2)	1 (0.2)
Mean EDSS score*	2.86±1.24	2.75±1.29	2.78±1.30	2.84±1.38
No. of Gd-enhancing lesions on T1-weighted MRI, n (%)	n=405	n=407	n=413	n=415
0	233 (57.5)	252 (61.9)	252 (61.0)	243 (58.6)
1	64 (15.8)	52 (12.8)	58 (14.0)	62 (14.9)
2	30 (7.4)	30 (7.4)	33 (8.0)	38 (9.2)
3	20 (4.9)	16 (3.9)	15 (3.6)	14 (3.4)
≥4	58 (14.3)	57 (14.0)	55 (13.3)	58 (14.0)
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)

Mean volume of lesions on T2-weighted MRI, cm^3 (SD)	10.84 (13.90)	9.74 (11.28)	10.73 (14.28)	10.61 (12.30)
Normalised brain volume, cm^3 (SD)	1500.93 (84.10)	1499.18 (87.68)	1503.90 (92.63)	1501.12 (90.98)

EDSS: Expanded disability status scale; MRI: Magnetic resonance imaging
*Scores on the EDSS range from 0 to 10.0, with higher scores indicating worse disability
Data were missing for some patients in the demographic and disease characteristics table; these are listed below (77)

1 Data on the number of relapses within the previous 12 months were missing for 1 patient in the IFNB-1a group in the OPERA I trial and for 1 patient in each group in the OPERA II trial
2 Data on the number and volume of lesions on T2-weighted MRI were missing for 2 patients in the ocrelizumab group and for 3 in the IFN β-1a group in the OPERA I trial and for 3 in the ocrelizumab group and 2 in the IFN β-1a group in the OPERA II trial
3 Data on the normalised brain volume were missing for 4 patients in the ocrelizumab group and for 7 in the IFN β-1a group in the OPERA I trial and for 3 in the ocrelizumab group and 4 in the IFN β-1a group in the OPERA II trial
4 Data on the mean EDSS score were missing for 1 patient in the IFN β-1a group in the OPERA I trial

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Efficacy analyses were performed in the ITT population (all the patients who underwent randomisation), however, for the end point of NEDA, the analysed population was restricted to patients with an EDSS score of ≥2 at baseline. The ARR was analysed with the use of a negative binomial model testing for treatment differences between ocrelizumab and IFNB-1a, with adjustment according to geographic region and baseline expanded disability status scale (EDSS) score (Table 9). A significant result at a two-sided alpha of 0.05 would show the superiority of ocrelizumab with regard to a lower ARR than that observed with IFNB-1a (Table 9) (77).

The sample size for each trial was based on an estimated ARR of 0.165 in the ocrelizumab group and 0.33 in the IFNB-1a group. Using a two-sided t-test, it was calculated that a sample of 400 patients per group 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 IFNB-1a (assuming a withdrawal rate of approximately 20%). According to the statistical analysis plans of the individual trials, 10 secondary efficacy end points were prespecified to be tested in a hierarchical order at a two-sided alpha of 0.05. Seven end points of this hierarchy were to be tested in each individual trial, and three endpoints (CDP-12 , CDP-24 and CDI-12) were assessed in the pooled data set (Table 9 and Table 10). From the first p value that was above 0.05, all subsequent p values in the predetermined hierarchy were considered to be nonconfirmatory (i.e., descriptive only) (77).

All patients who received any study treatment were included in the safety population. All data collected during the double-blind, double-dummy treatment period and the safety follow-up were included in the main safety analyses. Data from patients who entered the safety follow-up earlier than week 96 were included in this analysis from the time that they entered the

safety follow-up until week 96. Safety outcomes are reported for the individual trials with the exception of herpes virus infections and neoplasms, for which pooled data are presented because of low incidences (77).

Table 9: Summary of statistical analyses in OPERA I and OPERA II

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
OPERA I and OPERA II	H_0 (null hypothesis): there was no statistically significant difference in protocol defined ARR at 2 years during the double-blind, double-dummy treatment period between ocrelizumab group and the IFNB-1a group H_1 (alternative hypothesis): there was a statistically significant difference in protocol defined ARR at 2 years during the double blind, double-dummy treatment period between the ocrelizumab group and the IFNB-1a group	Primary endpoint – negative binomial model testing (two-sided alpha of 0.05) All statistical hypotheses for the primary and secondary endpoints and treatment comparisons were tested at the 5% significance level (α=0.05) against two-sided alternatives	For ARR, a two-sided t-test, sample size of 400 patients per group, 84% statistical power to maintain type I error of 0.05 For CDP, a two group log-rank test, with the assumption of exponential survival and exponential dropout was used. A sample size of 400 patients per group, 80% statistical power to maintain type I error of 0.05 based on two RMS trials*	ITT population (all the patients who underwent randomisation) or, for the end point of NEDA, the analysed population was restricted to patients with an EDSS score of ≥2 at baseline.

Source: (78, 79)
ARR, annualised relapse rate; CDP, confirmed disability progression; ITT, intent-to-treat; NEDA, no evidence of disease activity
*800 patients treated with ocrelizumab and 800 patients treated with IFNB-1a

Table 10: Statistical model and stratification factors in OPERA I and OPERA II

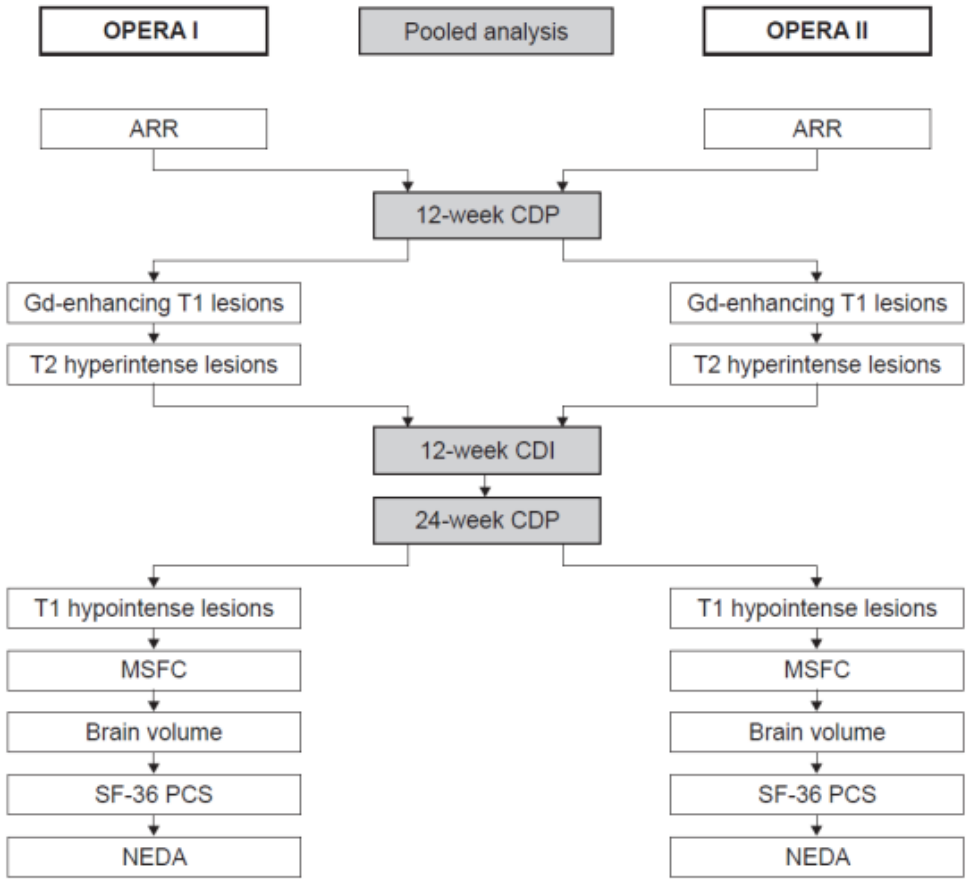
Endpoint	Statistical model	Stratification/adjusting factors
Primary: ARR	NBR (offset=log-transformed exposure time)	Baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)
Secondary: Time to onset of CDP for at least 12 weeks / 24 weeks	Log-rank test, Cos regression (for estimation of HR)	Baseline EDSS (<4.0 vs. ≥4.0), geographical region (US vs. ROW)

Source: (78, 79)
ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale, HR: hazard ratio; NBR: negative binomial regression; ROW, rest of the world

Hierarchical order

Pre-specified confirmatory analyses were those which were pre-specified in the statistical analysis plan and embedded in the hypothesis testing hierarchy (i.e. under type I error control). Although OPERA I and OPERA II were sufficiently powered for their respective primary analysis, testing of secondary endpoints based on the EDSS, specifically CDP and CDI, necessitated a pooling of data from the two trials to maintain sufficient power to detect relevant treatment differences. A hierarchical testing approach based on clinical meaning (i.e. importance to treating physicians and patients), regulatory requirements, and likelihood of positive outcome was used for this assessment (Figure 3). Established endpoints were generally given higher priority over novel endpoints within the hierarchy. The hierarchical analysis was to be undertaken only once the primary endpoint of ARR had been shown to be positive in both trials. Following that, the secondary endpoints were to be tested in the sequence presented in Figure 3, all at the α=0.05 level. Subsequent endpoints could only be tested in a confirmatory manner if the immediately preceding endpoint had reached a significance level of α=0.05 (78, 79).

Figure 3: Pre-defined hierarchical order of key efficacy endpoints



ARR, annualised relapse rate; CDI, confirmed disability improvement; CDP, confirmed disability progression; Gd, Gadolinium; MSFC, Multiple Sclerosis Functional Composite score; NEDA, no evidence of disease activity; SF-36 PCS, 36-item Short-Form Health Survey Physical Component Summary

Other types of analyses were also conducted; see section B.2.7 and Appendix E for subgroup analyses:

Pre-specified exploratory analyses

Pre-specified exploratory analyses were those foreseen in the statistical analysis plan, but for which hypothesis testing is not under type I error control (i.e. p values are reported as a measure of uncertainty rather than for formal confirmation of treatment effect). Example of pre-specified exploratory analyses include 12-week CDP in the individual OPERA I and OPERA II trials, and ARR in the pooled analysis (78, 79).

Post-hoc exploratory analyses

Post hoc exploratory analyses were those which were not foreseen within the statistical analysis plan, with p-values reported as a measure of uncertainty rather than for formal confirmation of treatment effect. An example of a post-hoc exploratory analysis is NEDA assessed in the ITT population (78, 79).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trials (RCTs) was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D.

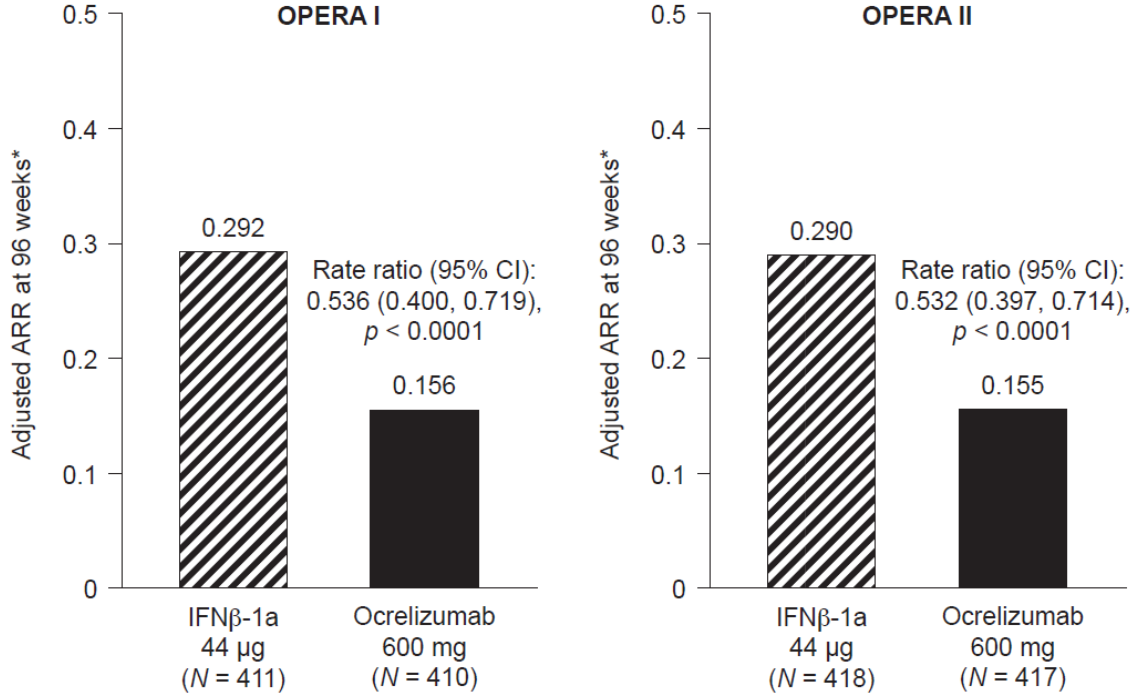
B.2.6 Clinical effectiveness results of the relevant trials

The data discussed in this section has been taken from the primary analysis for OPERA I and OPERA II (clinical cut-off dates 2nd April 2015 and 12th May 2015), in which a total of 821 and 835 patients were randomised, respectively.

Primary endpoint: ARR at 96 weeks in OPERA I and OPERA II

OPERA I and OPERA II met their primary endpoints, with ocrelizumab demonstrating a statistically significant reduction in ARR over 2 years compared with IFNB-1a (Rebif®). In OPERA I, ARR was reduced by 46.4% at 96 weeks in the ocrelizumab group compared with IFNB-1a (adjusted ARR 0.156 vs. 0.292 respectively; adjusted ARR ratio, 0.536; 95% CI: 0.400–0.719, p<0.0001), and in OPERA II by 46.8% (adjusted ARR 0.155 vs 0.290 respectively; adjusted ARR 0.532; 95% CI: 0.397–0.714; p<0.0001) (Figure 4) (77-79).

Figure 4: ARR results in OPERA I and OPERA II



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

Secondary endpoint: Pooled CDP-12 and CDP-24

In the OPERA trials, disability progression was defined as an increase in the EDSS score of:

- ≥1.0 point from the baseline EDSS score when the baseline score was ≤5.5
- ≥0.5 point from the baseline EDSS score when the baseline score was >5.5

This definition is in line with other RRMS studies (70, 71, 81, 82).

Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening. The initial event of neurological worsening had to occur during the 96-week, double-blind, double-dummy treatment period (83).

In the pre-specified pooled analysis, the proportion of patients with 12-week CDP was lower in the ocrelizumab group than in the IFNB-1a (Rebif®) group (9.1% had an event in the ocrelizumab group vs 13.6% in the IFNB-1a group). Ocrelizumab was associated with a 40% reduction in the risk of 12-week CDP compared with IFNB-1a (HR: 0.60; 95% CI: 0.45–0.81; p=0.0006) (Figure 5). Results for 24-week CDP were almost identical to those for 12-week CDP: 6.9% had 24-week CDP in the ocrelizumab group vs 10.5% in the IFNB-1a group. This represents a 40% reduction in risk of CDP for ocrelizumab versus IFNB-1a (HR: 0.60; 95% CI: 0.43–0.84; p=0.0025) (Figure 6) (77, 83).

Figure 5: CDP-12 results (OPERA pooled analysis)

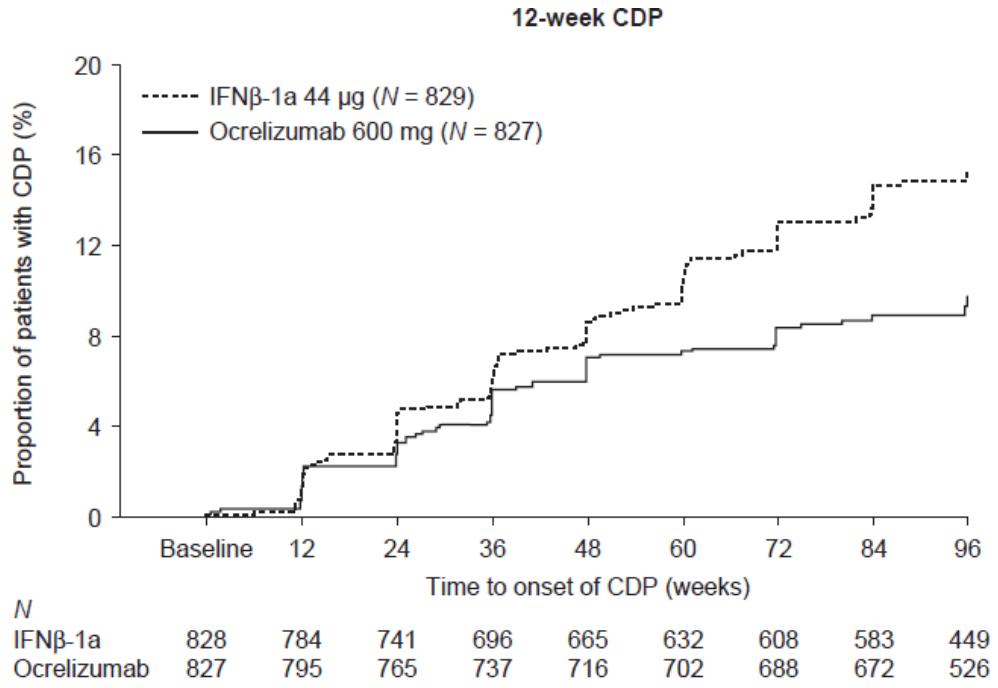
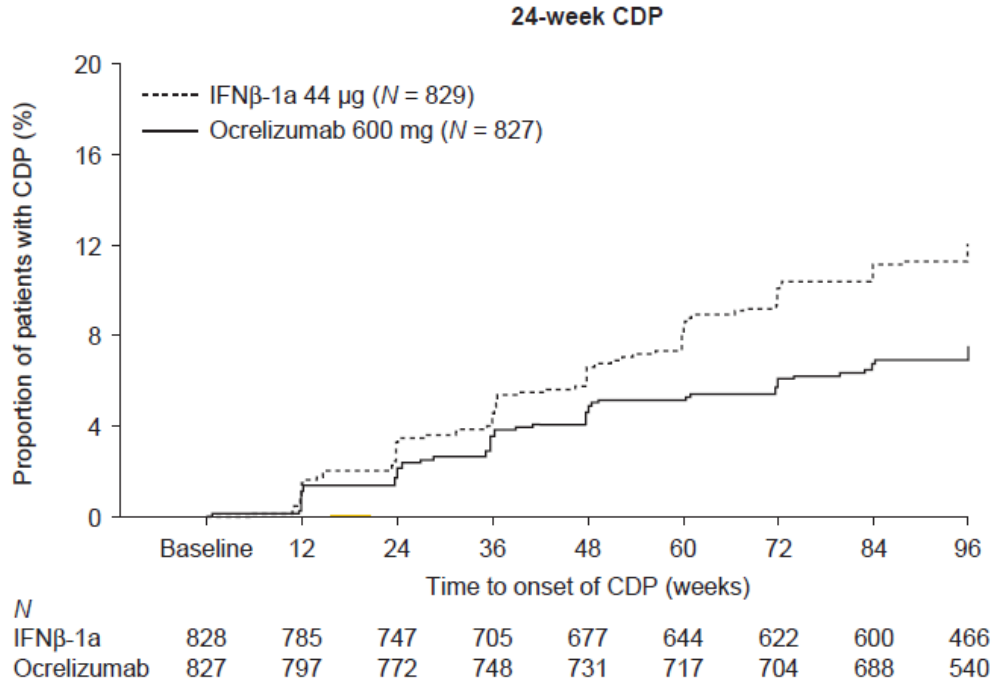


Figure 6: CDP-24 results (OPERA pooled analysis)



The pooled analysis of CDP-12 and CDP-24 is consistent with the findings in the individual OPERA trials. A significant reduction in 12-week CDP was observed for ocrelizumab versus IFNB-1a, with a 43% reduction in OPERA I (HR: 0.57; 95% CI: 0.37–0.90; p=0.0139) and a 37% reduction in OPERA II (HR: 0.63; 95% CI: 0.42–0.92; p=0.0169). A 43% risk reduction for 24-week CDP was observed in OPERA I (HR: 0.57; 95% CI: 0.34–0.95; p=0.0278), and 37% in OPERA II (HR: 0.63; 95% CI: 0.40–0.98; p=0.0370).

Summary of primary and secondary efficacy endpoints at Week 96 in OPERA I and OPERA II

Table 11: Clinical Results from OPERA I, OPERA II and the Pooled Analysis

Endpoint at week 96	Ocrelizumab 600 mg	IFNB-1a 44 µg	Difference	*p* value
OPERA I				
Primary Endpoint: Relapse Rate				
ARR at week 96 (95% CI)	*n* = 410 0.156 (0.122–0.200)	*n* = 411 0.292 (0.235–0.361)	Rate ratio (95% CI): 0.536 (0.400–0.719)	< 0.0001[a]
Secondary Endpoint: MRI Outcomes				
Gd-enhancing T1 lesions; mean number per MRI scan (95% CI)	*n* = 388[c] 0.016 (0.009–0.030)	*n* = 377[c] 0.286 (0.200–0.409)	Rate ratio (95% CI): 0.058 (0.032–0.104)	< 0.0001[a]
New and/or enlarged T2 hyperintense lesions; mean number per MRI scan (95% CI)	*n* = 390[c] 0.323 (0.256–0.407)	*n* = 378[c] 1.413 (1.123–1.777)	Rate ratio (95% CI): 0.229 (0.174–0.300)	< 0.0001[a]
New T1 hypointense lesions; mean number per MRI scan (95% CI)	*n* = 388[c] 0.420 (0.337–0.524)	*n* = 377[c] 0.982 (0.780–1.237)	Rate ratio (95% CI): 0.428 (0.328–0.557)	< 0.0001[a]
Brain volume; mean % decrease from week 24 to week 96 (95% CI)	*n* = 281[d] 0.572 (0.660–0.485)	*n* = 267[d] 0.741 (0.830–0.651)	Mean difference (95% CI): 0.168 (0.053–0.283)	0.0042
Secondary Endpoint: Disease Activity				
NEDA[e]; proportion of patients with NEDA (95% CI)	*n* = 289 47.4 (41.5–53.3)	*n* = 291 27.1 (22.1–32.6)	Relative risk: 1.74 (1.39–2.17)	< 0.0001
Secondary Endpoint: Disability				
MSFC score; mean change from baseline to week 96 (95% CI)	*n* = 322[b] 0.213 (0.153–0.273)	*n* = 308[b] 0.174 (0.113–0.235)	Mean difference (95% CI): 0.039 (–0.039–0.116)	0.3261
Secondary Endpoint: SF-36 PCS				
SF-36 PCS; mean change from baseline to week 96 (95% CI)	*n* = 331[b] 0.036 (–0.860–0.931)	*n*= 309[b] –0.657 (–1.590–0.275)	Mean difference (95% CI): 0.693 (–0.414–1.800)	0.2193

OPERA II				
Primary Endpoint: Relapse Rate				
ARR at week 96 (95% CI)	*n* = 417 0.155 (0.121–0.198)	*n* = 418 0.290 (0.234–0.361)	Rate ratio (95% CI): 0.532 (0.397–0.714)	< 0.0001[a]
Secondary Endpoint: MRI Outcomes				
Gd-enhancing T1 lesions; mean number per MRI scan (95% CI)	*n* = 389[c] 0.021 (0.012–0.036)	*n* = 375[c] 0.416 (0.309–0.561)	Rate ratio (95% CI): 0.051 (0.029–0.089)	< 0.0001[a]
New and/or enlarged T2 hyperintense lesions; mean number per MRI scan (95% CI)	*n* = 390[c] 0.325 (0.259–0.409)	*n* = 376[c] 1.904 (1.536–2.359)	Rate ratio (95% CI): 0.171 (0.130–0.225)	< 0.0001[a]
New T1 hypointense lesions; mean number per MRI scan (95% CI)	*n* = 389[c] 0.449 (0.359–0.560)	*n* = 375[c] 1.255 (1.003–1.571)	Rate ratio (95% CI): 0.357 (0.272–0.470)	< 0.0001[a]
Brain volume; mean % decrease from week 24 to week 96 (95% CI)	*n* = 287[d] –0.638 (–0.734,–0.543)	*n* = 259[d] –0.750 (–0.851,–0.649)	Mean difference (95% CI): 0.112 (–0.018–0.241)	0.0900
Secondary Endpoint: Disease Activity				
NEDA[e]; proportion of patients with NEDA (95% CI)	*n* = 289 43.9 (38.1–49.9)	*n* = 270 24.1 (19.1–29.6)	Relative risk (95% CI): 1.81 (1.41–2.32)	< 0.0001
Secondary Endpoint: Disability				
MSFC score; mean change from baseline to week 96 (95% CI)	*n* = 308[b] 0.276 (0.222–0.331)	*n* = 269[b] 0.169 (0.112–0.226)	Mean difference (95% CI): 0.107 (0.034–0.180)	0.0040[a]
Secondary Endpoint: SF-36 PCS				
SF-36 PCS; mean change from baseline to week 96 (95% CI)	*n* = 315[b] 0.326 (–0.545–1.198)	*n* = 276[b] –0.833 (–1.760–0.094)	Mean difference (95% CI): 1.159 (0.051–2.268)	0.0404
Pooled Analysis				
Secondary Endpoint: Disability				
12-week CDP; Kaplan–Meier estimate for proportion of patients with events at 96 weeks (95% CI)	*n* = 827 9.75 (7.63–11.87)	*n* = 829 15.18 (12.55–17.81)	Hazard ratio (95% CI): 0.60 (0.45–0.81)	0.0006

24-week CDP; Kaplan–Meier estimate for proportion of patients with events at 96 weeks (95% CI)	*n* = 827 7.58 (5.68–9.48)	*n* = 829 12.03 (9.63–14.44)	Hazard ratio (95% CI): 0.60 (0.43–0.84)	0.0025
12-week CDI[e]; Kaplan–Meier estimate for proportion of patients with improvement (95% CI)	*n* = 628 20.70 (17.60–24.08)	*n* = 614 15.64 (12.85–18.75)	Relative risk (95% CI): 1.33 (1.05–1.68)	0.0194

ARR annualised relapse rate; CDI confirmed disability improvement; CDP confirmed disability progression; Gd gadolinium; MSFC Multiple Sclerosis Functional Composite; NEDA No evidence of disease activity; SF-36 PCS Short Form 36 Physical Component Summary

[a]Indicates confirmatory statistically significant p values controlled by the hierarchical order of efficacy endpoints.

[b]Number of patients with measurements at baseline and week 96.

[c]Number of patients with MRI scans at week 96.

[d]Number of patients with MRI scans at weeks 24 and 96.

[e]In patients with baseline EDSS score ≥ 2.0.

A summary of all p values within the hierarchical structure is provided below and indicates those which should be considered non-confirmatory since they follow a non-signficant test result within the hierarchial structure (shaded cells). The primary and secondary endpoints showing efficacy of ocrelizumab on both clinical and subclincal measures (ARR, T1 Gd-enhancing lesions and new and/or enlarging T2 hyperintense lesions) and on measures of disease progression (CDP, new T1 hypointense lesions) were all met.

Table 12: Summary of hierarchical significance testing of efficacy endpoints

Endpoint	OPERA I p value	OPERA II p value
Protocol-defined ARR by 2 years	<0.0001	<0.0001
12-week CDP (pooled data)	0.0006	
T1 Gd-enhancing lesions	<0.0001	<0.0001
New and/or enlarging T2 hyperintense lesions	<0.0001	<0.0001
12 week CDI (pooled data)	0.0194	
24 week CDP (pooled data)	0.0025	
New T1 hypointense lesion	<0.0001	<0.0001
MSFC	0.3261	0.004
Brain volume	0.0042	0.09
SF-36 PCS	0.2193	0.0404
NEDA	<0.0001	<0.0001

B.2.7 Subgroup analysis

Subgroup analyses assessed ARR, CDP12 and CDP24 endpoints across various baseline patient demographics and disease characteristics in OPERA I and OPERA II. In summary, patients receiving ocrelizumab consistently showed a greater reduction of ARR, CDP12, and CDP24 compared with IFNB-1a across all subgroups (for more details see appendix E).

Subgroup analyses assessed ARR, CDP12 and CDP24 endpoints across various baseline patient demographics and disease characteristics in OPERA I and OPERA II. In summary, patients receiving ocrelizumab consistently showed a greater reduction of ARR, CDP12, and CDP24 compared with IFNB-1a across all subgroups (for more details see appendix E).

Subgroup analyses were also performed for disease activity subgroups based on payer-relevant definitions in the pooled OPERA I and II population. Analyses in patients who are highly active inadequate responders (HA) or have rapidly evolving severe (RES) disease are presented below as these are in line with the NICE decision problem and included in the economic analysis.

Highly active inadequate responders (HA) (pre-specified):

Patients treated with interferons or glatiramer acetate for at least 1 year, and

- Had at least one relapse in the previous year, and
- Had at least one T1 Gd-enhancing lesion on brain MRI at baseline, or
- Had at least nine T2 hyperintense lesions on brain MRI at baseline

Rapidly evolving severe (RES) (post hoc):

- Patients had at least two relapses in the previous year, and
- Had at least one T1 Gd-enhancing lesion on brain MRI at baseline, or
- Had an increase in T2 hyperintense lesion count on brain MRI at baseline (changing from 0-5 to 6-9, >9 lesions or 6-9 lesions to >9 lesions), compared to previous MRI

Subgroup analysis indicated that ARR results were different in HA and RES subgroups compared with the ITT population (Table 13). The treatment effect of ocrelizumab in reducing relapse was improved in the HA and RES subgroups compared with ITT. The treatment effects on CDP12 or CDP24 in the subgroups of interest were consistent with ITT (Table 14 and Table 15).

Table 13: ARR in HA and RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Rate ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	ARR	N (patients)	n (event)	ARR				
ITT	829	334	0.291	827	194	0.156	0.535	0.435–0.659	<0.0001	-
HA	140	64	0.313	143	23	0.099	0.317	0.181–0.556	<0.0001	0.0346
RES	140	78	0.394	150	40	0.151	0.384	0.243–0.607	<0.0001	0.0811

ARR: annualised relapse rate; CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

Table 14: CDP12 in HA and RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Hazard ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	% (event)	N (patients)	n (event)	% (event)				
ITT	829	113	13.6	827	75	9.1	0.60	0.45–0.81	0.0006	-
HA	140	22	15.7	143	12	8.4	0.47	0.23–0.95	0.0311	0.5109
RES	140	20	14.3	150	15	10.0	0.65	0.33–1.29	0.2163	0.8490

CDP: confirmed disability progression; CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

Table 15: CDP24 in HA and RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Hazard ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	% (event)	N (patients)	n (event)	% (event)				
ITT	829	87	10.5	827	57	6.9	0.60	0.43–0.84	0.0025	-
HA	140	17	12.1	143	10	7.0	0.50	0.23–1.09	0.0763	0.6898
RES	140	20	14.3	150	14	9.3	0.61	0.31–1.22	0.1566	0.9853

CDP: confirmed disability progression; CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

B.2.8 Meta-analysis

Three studies evaluated ocrelizumab in adult patients with relapsing forms of MS (Table 6). The proof-of-concept Phase II study was a dose finding study with primary endpoint the number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain. Secondary endpoints included ARR but disease progression was not evaluated. The Phase II study evaluating ocrelizumab was excluded from the MTC because no data was available for this study beyond 24 weeks.

The two Phase III OPERA studies were identical in terms of design, endpoints, inclusion and exclusion criteria, active comparator and statistical analysis plan. Pre-planned pooled analyses are presented in Section B.2.6.

B.2.9 Indirect and mixed treatment comparisons

MTCs were conducted for the outcomes of ARR, CDP-12, CDP-24 and all-cause discontinuation in both ITT populations and HA and RES subgroups. 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 for each outcome in ITT population to evaluate the assumptions of the base-case MTC (see Appendix D.1.4):

- applying an alternative prior for the between-study variance
- fixed effect model
- meta-regression on follow-up time.

In addition, the impact of restricting the networks to comparator treatments matching the NICE scope was evaluated in ITT and subgroup populations.

Included studies

A systematic review (SR) was conducted to identify RCTs of treatments for RRMS. The SR was designed with multi-country HTA submissions in mind and comparators were included based on having, or expected to have by the time of ocrelizumab launch, a FDA or EMA licence for treatment in RRMS. As a result, the scope of the SR is broader than the NICE decision problem, e.g. it includes cladribine. Due to geometry of the networks, inclusion of comparators outside of the NICE scope has negligible impact on the overall MTC results and conclusions for the comparators in scope (see Appendix D.1.4).

The SR and subsequent ad-hoc updates identified a total of 46 eligible studies, with 33 of these providing appropriate data for MTC based on ITT populations. Studies included in the ITT MTC are summarised in Table 16.

Subgroup MTCs were conducted for patients with highly active disease despite prior treatment (HA) and rapidly evolving severe disease (RES). Of the 33 studies providing appropriate data for the MTC based on ITT populations, subgroup data were identified for only 16 studies (either pooled or individual). Studies included in the subgroup MTC are summarised in Table 17.

Due to the limited number of studies and data available for the subgroup MTCs, the networks were disconnected. In order to connect the networks, ITT data from studies investigating ABCR treatments (IFNB-1a [Avonex], IFNB-1b [Betaferon], glatiramer acetate [Copaxone], and IFNB-1a [Rebif]) were included. 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.

Excluded studies

Following a feasibility assessment 13 studies originally identified in the SR were excluded from the MTC (see Appendix D.1.1). Two studies were excluded due to use of unlicensed doses or treatment regimens, and a number of treatment arms were excluded from other studies for the same reason. In addition, eleven studies were excluded due to short trial duration. Across the studies, patient follow-up varied from 12 to 240 weeks. Most trials that reported on the outcomes of interest were 96 weeks long. In order to be as inclusive of evidence as possible while still considering trials of similar length, data from 48 weeks or longer was eligible for the base-case analysis. 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 disease characterised by periods of exacerbations and remissions like RRMS.

Finally, the INCOMIN trial (84), investigating IFNB-1b compared to IFNB-1a, was excluded from the base case analysis for CDP-24 as it is widely considered an outlier by clinical experts (85). In general, there is a high correlation between CDP-12 and CDP-24 endpoints. However, CDP-12 and CDP-24 MTC outputs for IFNB-1b are inconsistent (INCOMIN is the only study informing CDP-24 for IFNB-1b) (see Figure in Appendix D.1.1). The approach of excluding INCOMIN is supported by the MTC published by Tolley et al, which concluded that INCOMIN was a source of inconsistency for ARR and CDP-24 and was thus excluded from their MTC (86).

Table 16: Summary of trials included in ITT MTC

Study reference / ID	ALEM	CLAD*	DAC	DMF	FINGO	GA	IFNB-1a (Avonex)	IFNB-1a (Rebif)	IFN-B 1b (Betaferon)	IFNB-1a (Extavia)	NAT	OCR	pegIFNB-1a	Placebo	TERI
ADVANCE (44)													✓	✓	
AFFIRM (47)											✓			✓	
BEYOND (87)						✓			✓						
Bornstein et al, 1987 (88)						✓								✓	
BRAVO (82)							✓							✓	
Calabrese et al, 2012 (89)						✓	✓	✓							
CAMMS223 (90)	✓							✓							
CARE-MS I (45)	✓							✓							
CARE-MS II (74)	✓							✓							
CLARITY (91)		✓												✓	
CombiRx (92)						✓	✓							✓	
CONFIRM (93)				✓		✓								✓	
Copolymer 1 MS trial (94)						✓								✓	
DECIDE (72)			✓				✓								
DEFINE (95)				✓										✓	
Etemadifir et al, 2006 (96)							✓	✓	✓						
EVIDENCE (97)							✓	✓							
FREEDOMS (46)					✓									✓	

FREEDOMS II (71)					✓									✓	
GALA (98)						✓								✓	
IFNB MS (99)									✓					✓	
INCOMIN (84)							✓		✓						
MSCRG (100)							✓							✓	
OPERA I (79)								✓				✓			
OPERA II (78)								✓				✓			
PRISMS (101)								✓						✓	
REGARD (102)						✓		✓							
SELECT (103)			✓											✓	
Stepien et al, 2013 (104)							✓		✓						
TEMSO (70)														✓	✓
TENERE (105)								✓							✓
TOWER (68)														✓	✓
TRANSFORMS (81)					✓		✓								

* Outside of NICE decision problem scope. Evidence included in network meta-analysis but results not presented.
** Sensitivity analysis only for CDP-24
Abbreviations: ALEM, alemtuzumab; DAC, daclizumab; DMF, dimethyl fumarate; FINGO, fingolimod; GA, glatiramer acetate; OCR, ocrelizumab; NAT, natalizumab; TERI, teriflunomide.

Table 17: Summary of the trials included in subgroup MTC, by outcome

treatments / trials	ALEM		DAC		DMF*		FINGO			NAT	OCR		TERI*	
	CARE MS I	CARE MS II	SELECT	DECIDE	CONFIRM	DEFINE	TRANSFORMS	FREEDOMS	FREEDOMS II	AFFIRM	OPERA I	OPERA II	TEMSO	TOWER
HA														
ARR		✓[1]	✓	✓			✓	✓[2]			✓[2]			
CDP-12					✓[2]		✓	✓[1,2]			✓[2]		✓[2]	
CDP-24		✓[1]	✓	✓				✓[2]			✓[2]		✓[2]	
RES														
ARR	✓	✓	✓	✓			✓	✓		✓	✓[2]			
CDP-12			✓		✓[2]		✓	✓		✓	✓[2]		✓	
CDP-24		✓								✓	✓[2]			

Only treatments and trials reporting subgroups are included; ABCRs are not included to avoid redundancies.
Legend: [1] IFN + GA summed; [2] pooled analysis
* Outside of NICE decision problem scope. Evidence included in network meta-analysis but results not presented.
Abbreviations: ALEM, alemtuzumab; DAC, daclizumab; DMF, dimethyl fumarate; FINGO, fingolimod; HA, highly active despite prior treatment with ABCR; NAT, natalizumab; OCR, ocrelizumab; RES, rapidly evolving severe; TERI, teriflunomide.

MTC results for ARR - ITT

The network for ARR includes 17 treatments including placebo, and 30 studies (Figure 7). The results for the base-case analysis are provided in Figure 8 and tabulated in Appendix D.1.4.

The results suggest that ocrelizumab is more effective than nine of the comparator treatments relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), pegIFBB-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod and daclizumab. There is no evidence of a difference between ocrelizumab and natalizumab or alemtuzumab as the credible intervals cross 1.

The results of the sensitivity analyses are provided in Appendix D.1.4. Each of the choice of models provides a similar fit to the data (the DIC values are within 3 of each other), suggesting that the alternative models support the conclusions of the base-case analysis. The network meta-regression on trial duration suggest that the meta-regression does not provide a better fit than the meta-analysis (the meta-regression increased the DIC by more than 3). Finally, the restricted network meta-analyses that exclude comparators not in the NICE scope suggest similar results and support the conclusions of the base-case analysis with the full network.

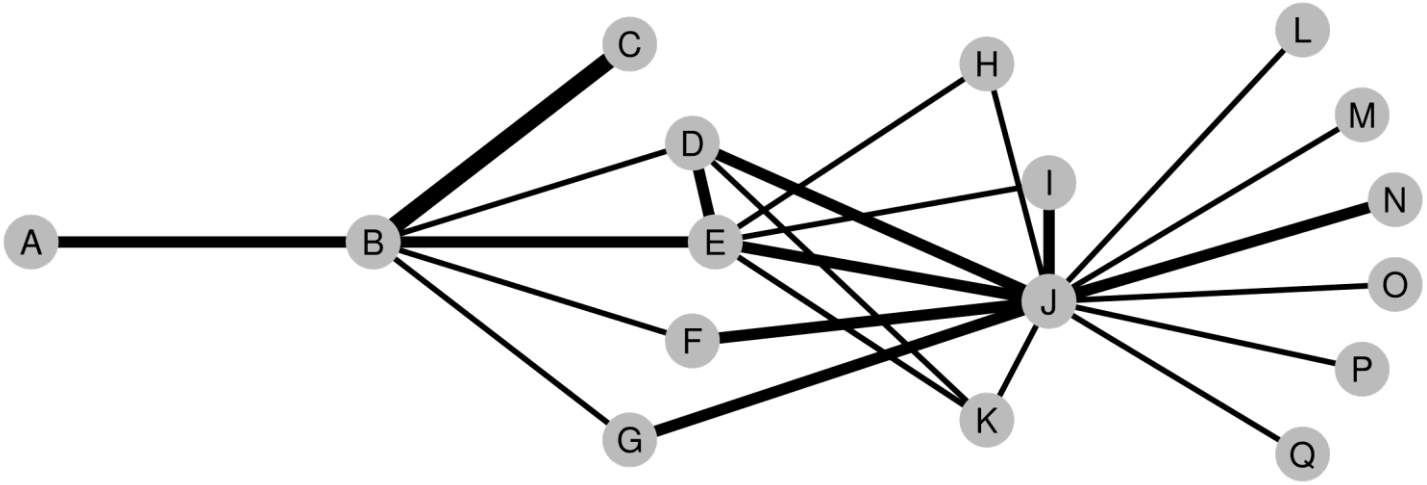
MTC results for ARR – subgroups

The network diagrams for the HA and RES subgroups are given in Figure 9 and Figure 10, respectively. Due to disconnected subgroup networks, ITT links from ABCRs are applied to connect the network.

The results for the subgroup analyses are provided in Figure 11. The subgroup results lead to wider credible intervals than the ITT results due to smaller sample size of subgroups and sparsity of subgroup data. The results from the HA subgroup support the conclusions of the ITT analysis. The conclusions of the RES subgroup analysis differ in one case from those of the ITT population analysis: the RES subgroup analysis suggests that there is no evidence of a difference between ocrelizumab and daclizumab. The results for ocrelizumab compared with alemtuzumab in both subgroups are also in contrast to the ITT results, though none of the credible intervals clear the 1 threshold of no difference.

The results of the restricted network meta-analyses that exclude comparators not in the NICE scope suggest similar results and support the conclusions of the base-case analysis with the full network (Appendix D.1.4).

Figure 7: Network diagram for ARR ITT



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

E = IM IFNB-1a 30 mcg, QW

F = TERI 14 mg, QD

G = TERI 7 mg, QD

H = DAC 150 mg , Q4W

I = FINGO 0.5 mg, QD

J = Placebo

K = SC IFNB-1b 250 mcg, EOD

L = CLAD 3.5mg/kg

M = CLAD 5.25mg/kg

N = DMF 240 mg, BID

O = GA 40 mg, TIW

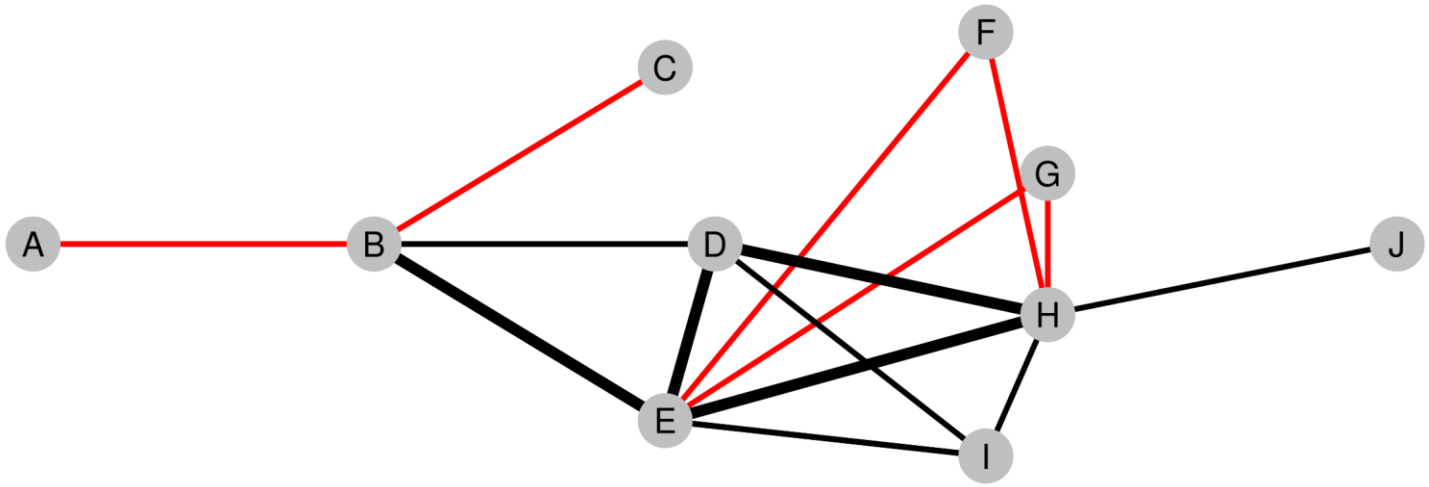
P = NAT 300 mg, Q4W

Q = PEG-INFB-1A 2W 125 mcg, Q2W

Edge width is proportional to the number of inputs for each comparison.

Figure 8: Forest plot of ARR ITT – Base case

Figure 9: Network Diagram for ARR – HA subgroup



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

E = IM IFNB-1a 30 mcg, QW

F = DAC 150 mg , Q4W

G = FINGO 0.5 mg, QD

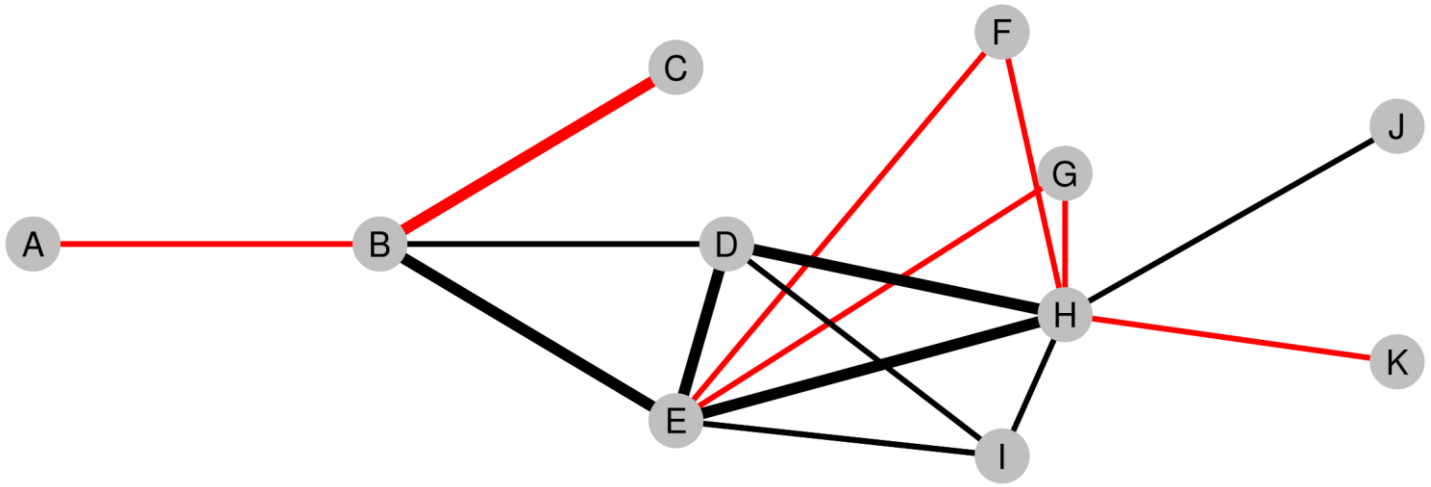
H = Placebo

I = SC IFNB-1b 250 mcg, EOD

J = GA 40 mg, TIW

Red lines depict comparisons that are informed by subgroup data inputs, while black lines are informed by ITT data inputs. Edge width is proportional to the number of inputs for each comparison.

Figure 10: Network Diagram for ARR – RES subgroup



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

E = IM IFNB-1a 30 mcg, QW

F = DAC 150 mg , Q4W

G = FINGO 0.5 mg, QD

H = Placebo

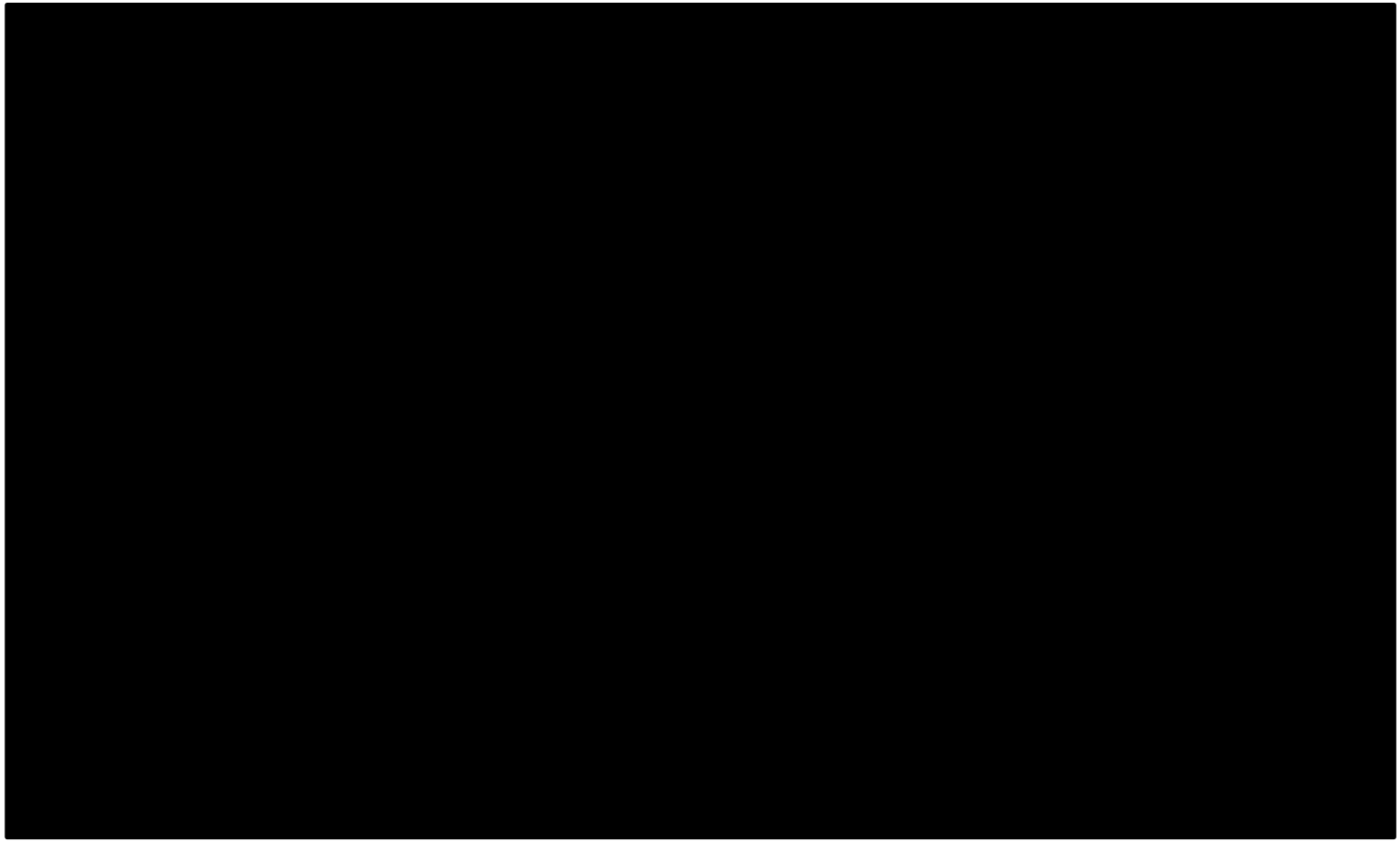
I = SC IFNB-1b 250 mcg, EOD

J = GA 40 mg, TIW

K = NAT 300 mg, Q4W

Red lines depict comparisons that are informed by subgroup data inputs, while black lines are informed by ITT data inputs. Edge width is proportional to the number of inputs for each comparison.

Figure 11: Forest Plot comparing ARR ITT and subgroups



MTC results for CDP-12 - ITT

The network for CDP-12 includes 17 treatments including placebo, and uses data from 22 sources (21 individual studies and 1 MTC, see below for further details). The network diagram is provided in Figure 12.

The results for the base-case analysis are provided in Figure 13 and tabulated in Appendix D.1.4. The results suggest that ocrelizumab is more effective than placebo and seven of the comparator treatments relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. There is no evidence of a difference between ocrelizumab and pegIFNB-1a, natalizumab, daclizumab, or alemtuzumab as the credible intervals cross 1.

The results of the sensitivity analyses are provided in Appendix D.1.4. Each of the choice of models provides a similar fit to the data (the DIC values are within 3 of each other). The alternative models broadly support the conclusions of the base-case analysis. In one case the conclusions differ from the base-case analysis: ocrelizumab is no longer more effective than dimethyl fumarate in the random effects model with a different choice of priors. The network meta-regression on trial duration suggest that either the meta-regression or the meta-analysis would be a good fit (the DIC values are very similar). Finally, the restricted network meta-analyses that exclude comparators not in the NICE scope suggest similar results and support the conclusions of the base-case analysis with the full network.

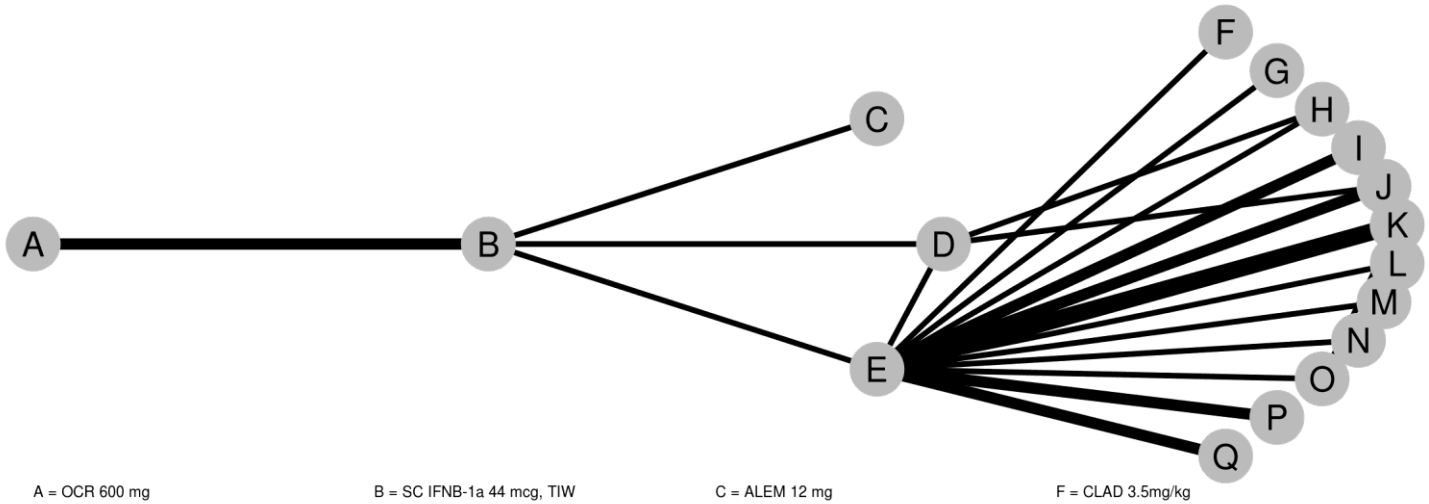
MTC results for CDP-12 – subgroups

The network diagrams for the HA and RES subgroups are given in Figure 14 and Figure 15, respectively. Due to disconnected subgroup networks, ITT links from ABCRs are applied to connect the network.

The results for the subgroup analyses are provided in Figure 16. The subgroup results are associated with wider credible intervals than the ITT results due to smaller sample size in subgroups and sparsity of subgroup data. In some cases the conclusions of the HA and RES subgroup analyses differ from those of the ITT analysis. For instance, the results for ocrelizumab compared to daclizumab are in contrast in the RES subgroup to what they were in the base-case ITT result, though none of the credible intervals clear the 1 threshold of no difference. The HA subgroup analysis suggests that there is no longer any evidence of a difference between ocrelizumab and fingolimod.

The results of the restricted network meta-analyses that exclude comparators not in the NICE scope suggest similar results and support the conclusions of the base-case analysis with the full network (Appendix D1.4).

Figure 12: Network diagram for CDP-12 ITT



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = IM IFNB-1a 30 mcg, QW

E = Placebo

F = CLAD 3.5mg/kg

G = CLAD 5.25mg/kg

H = DAC 150 mg , Q4W

I = DMF 240 mg, BID

J = FINGO 0.5 mg, QD

K = GA 20 mg, QD

L = NAT 300 mg, Q4W

M = PEG-INFB-1A 2W 125 mcg, Q2W

N = SC IFNB-1a 22 mcg, TIW

O = SC IFNB-1b 250 mcg, EOD

P = TERI 14 mg, QD

Q = TERI 7 mg, QD

Edge width is proportional to the number of inputs for each comparison.

Figure 13: Forest plot of CDP-12 ITT

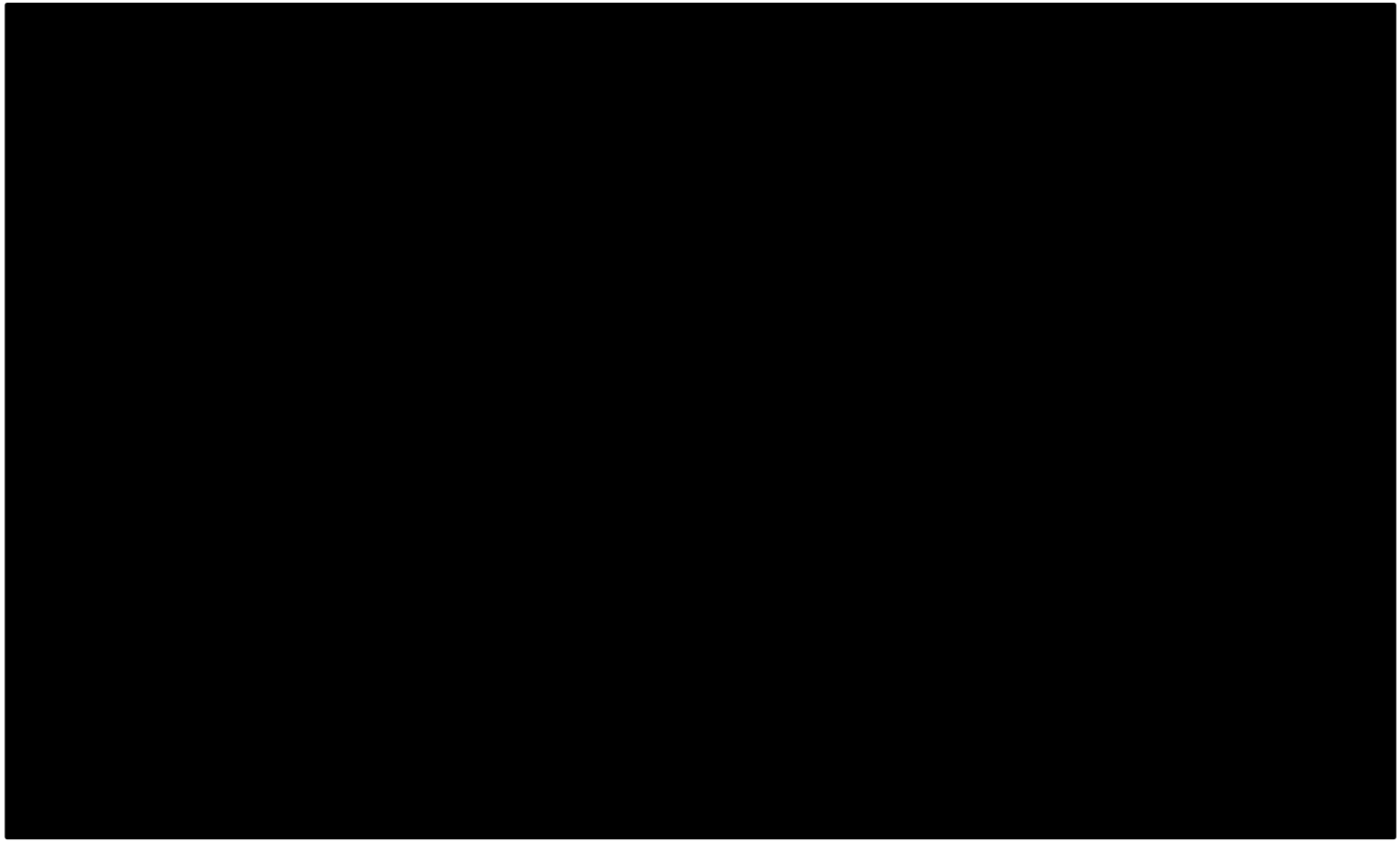
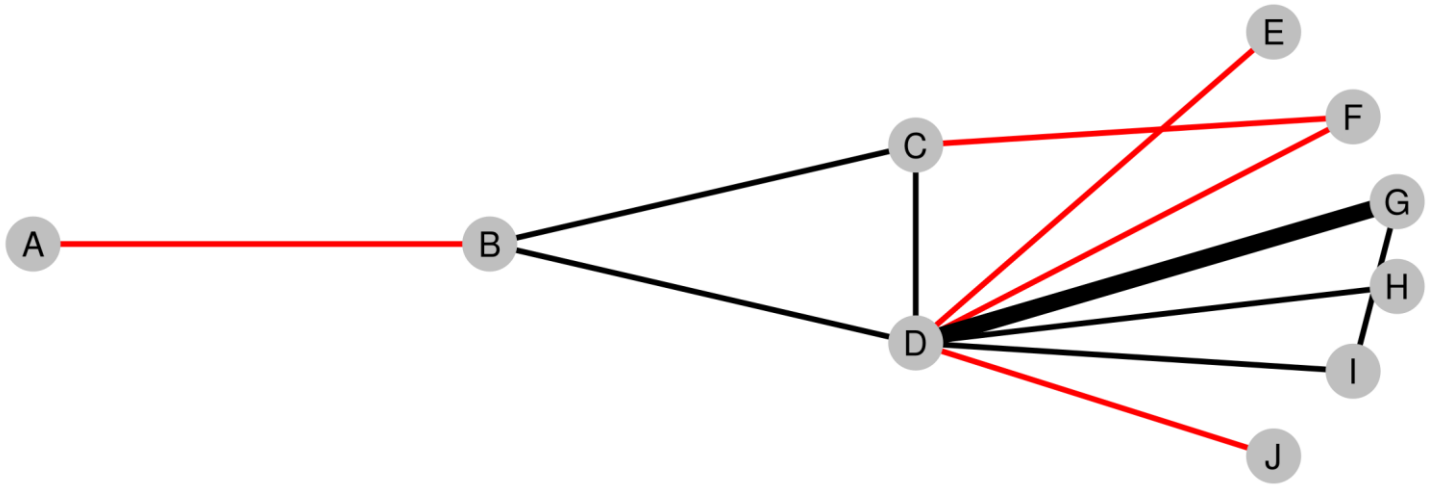


Figure 14: Network Diagram for CDP-12 – HA subgroup



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = IM IFNB-1a 30 mcg, QW

D = Placebo

E = DMF 240 mg, BID

F = FINGO 0.5 mg, QD

G = GA 20 mg, QD

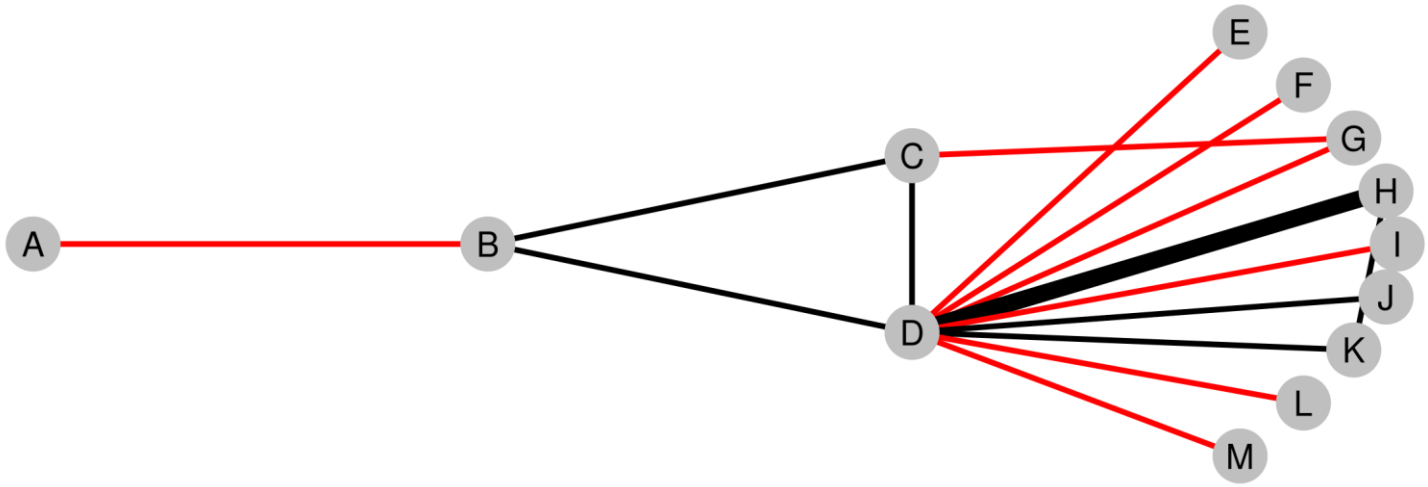
H = SC IFNB-1a 22 mcg, TIW

I = SC IFNB-1b 250 mcg, EOD

J = TERI 14 mg, QD

Red lines depict comparisons that are informed by subgroup data inputs, while black lines are informed by ITT data inputs. Edge width is proportional to the number of inputs for each comparison.

Figure 15: Network Diagram for CDP-12 – RES subgroup



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = IM IFNB-1a 30 mcg, QW

D = Placebo

E = DAC 150 mg , Q4W

F = DMF 240 mg, BID

G = FINGO 0.5 mg, QD

H = GA 20 mg, QD

I = NAT 300 mg, Q4W

J = SC IFNB-1a 22 mcg, TIW

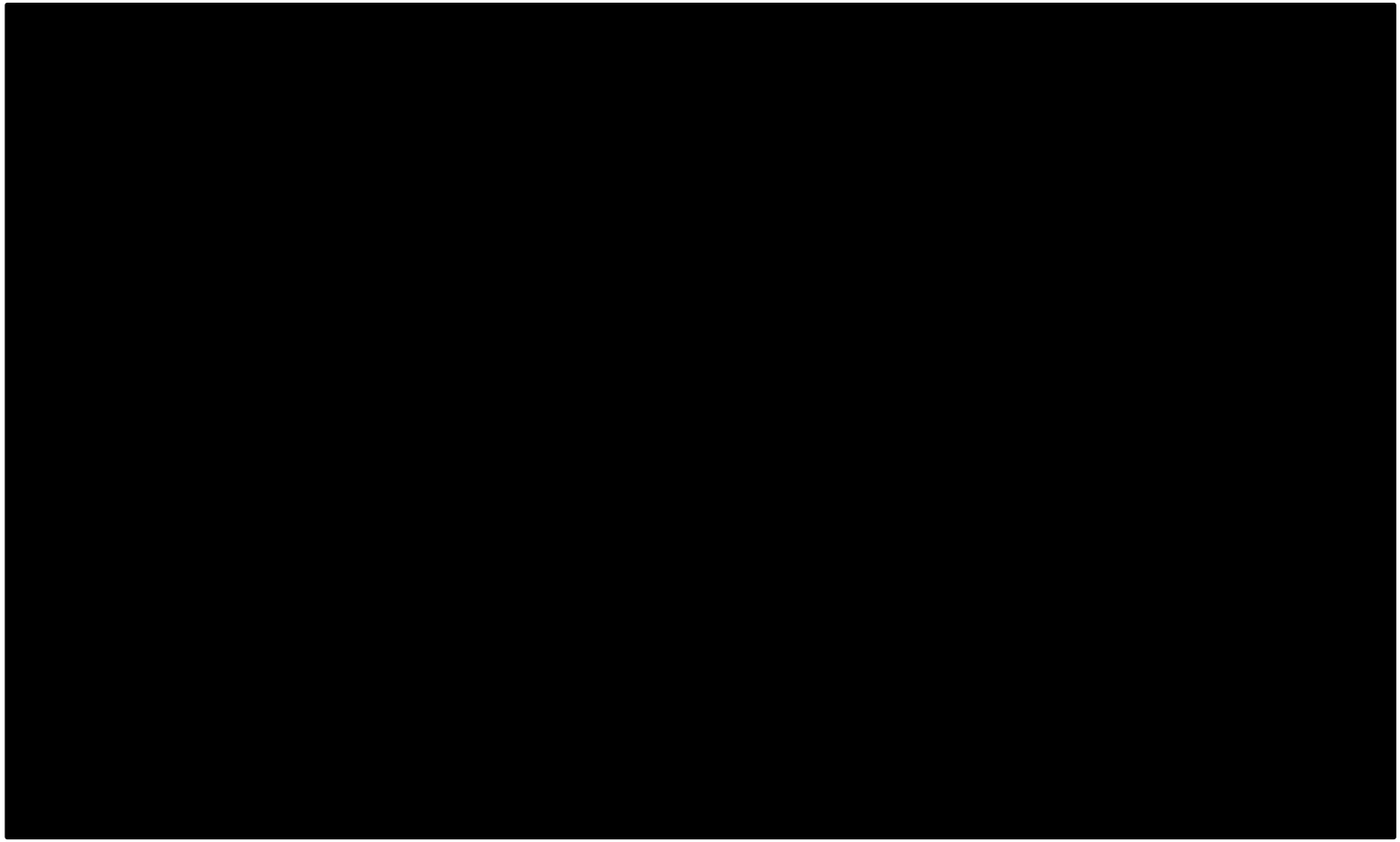
K = SC IFNB-1b 250 mcg, EOD

L = TERI 14 mg, QD

M = TERI 7 mg, QD

Red lines depict comparisons that are informed by subgroup data inputs, while black lines are informed by ITT data inputs. Edge width is proportional to the number of inputs for each comparison.

Figure 16: Forest Plot comparing CDP-12 results in base case and subgroups



MTC results for CDP-24 – ITT

The base-case network for CDP-24 includes 15 treatments including placebo, and 21 studies (Figure 17).

The results for the base-case analysis are provided in Figure 18 and tabulated in the Appendix D.1.4. The results suggest that ocrelizumab is more effective than placebo and the trial comparator IFNB-1a (Rebif). There is no evidence of a difference between ocrelizumab and any of the other treatments as the credible intervals cross 1.

The results of the sensitivity analyses are provided in Appendix D.1.4. Each of the choice of models provides a similar fit to the data (the DIC values are within 3 of each other). The alternative models support the conclusions of the base-case analysis. The network meta-regression on trial duration suggest that the meta-regression does not provide a better fit than the meta-analysis (the meta-regression increased the DIC). Finally, the restricted network meta-analyses that exclude comparators not in the NICE scope suggest similar results and support the conclusions of the base-case analysis with the full network.

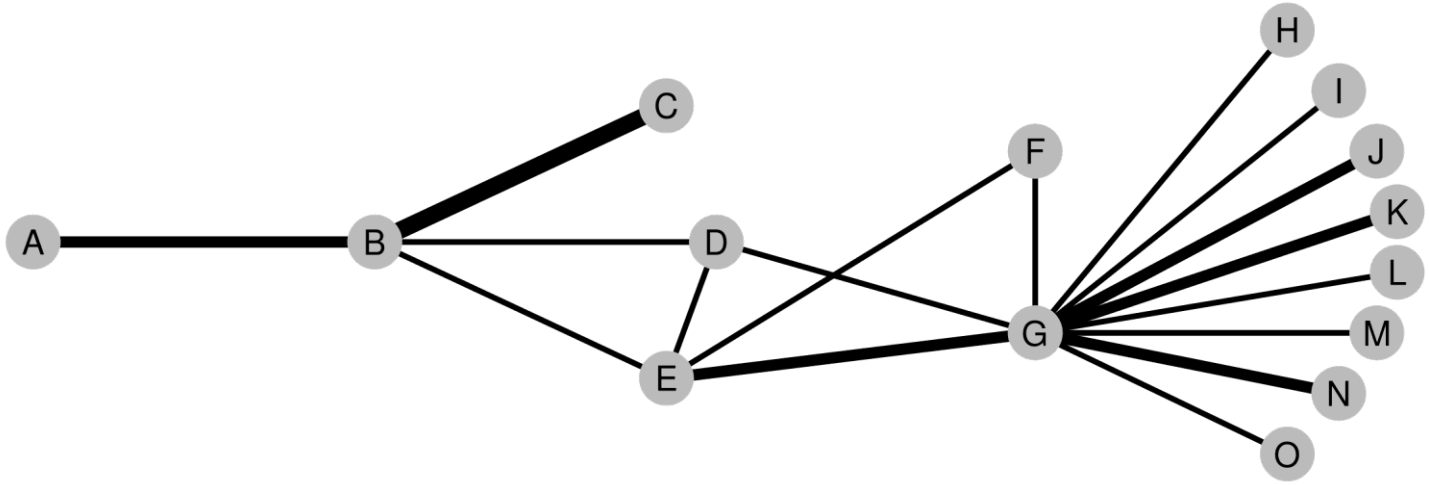
MTC results for CDP-24 – subgroups

The network diagrams for the HA and RES subgroups are given in Figure 19 and Figure 20 respectively. Due to disconnected subgroup networks, ITT links from ABCRs are applied to connect the network.

The results for the subgroup analyses are provided in Figure 21. The subgroup results are associated with wider credible intervals than the ITT results due to smaller sample size of subgroups and sparsity of subgroup data. In some cases the conclusions of the HA and RES subgroup analyses differ from those of the ITT analysis. The results for ocrelizumab compared to alemtuzumab are in contrast in the HA subgroup to what they were in the base-case ITT result, though none of the credible intervals clear the 1 threshold of no difference; similarly with ocrelizumab compared to natalizumab in the RES subgroup. The HA and RES subgroup analysis suggests that there is no longer any evidence of a difference between ocrelizumab and IFNB-1a (Rebif) or placebo.

The results of the restricted network meta-analyses that exclude comparators not in the NICE scope suggest similar results and support the conclusions of the base-case analysis with the full network.

Figure 17: Network Diagram for CDP-24 – ITT



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

E = IM IFNB-1a 30 mcg, QW

F = DAC 150 mg , Q4W

G = Placebo

H = CLAD 3.5mg/kg

I = CLAD 5.25mg/kg

J = DMF 240 mg, BID

K = FINGO 0.5 mg, QD

L = NAT 300 mg, Q4W

M = PEG-INFB-1A 2W 125 mcg, Q2W

N = TERI 14 mg, QD

O = TERI 7 mg, QD

Edge width is proportional to the number of inputs for each comparison.

Figure 18: Forest plot of CDP-24 – ITT

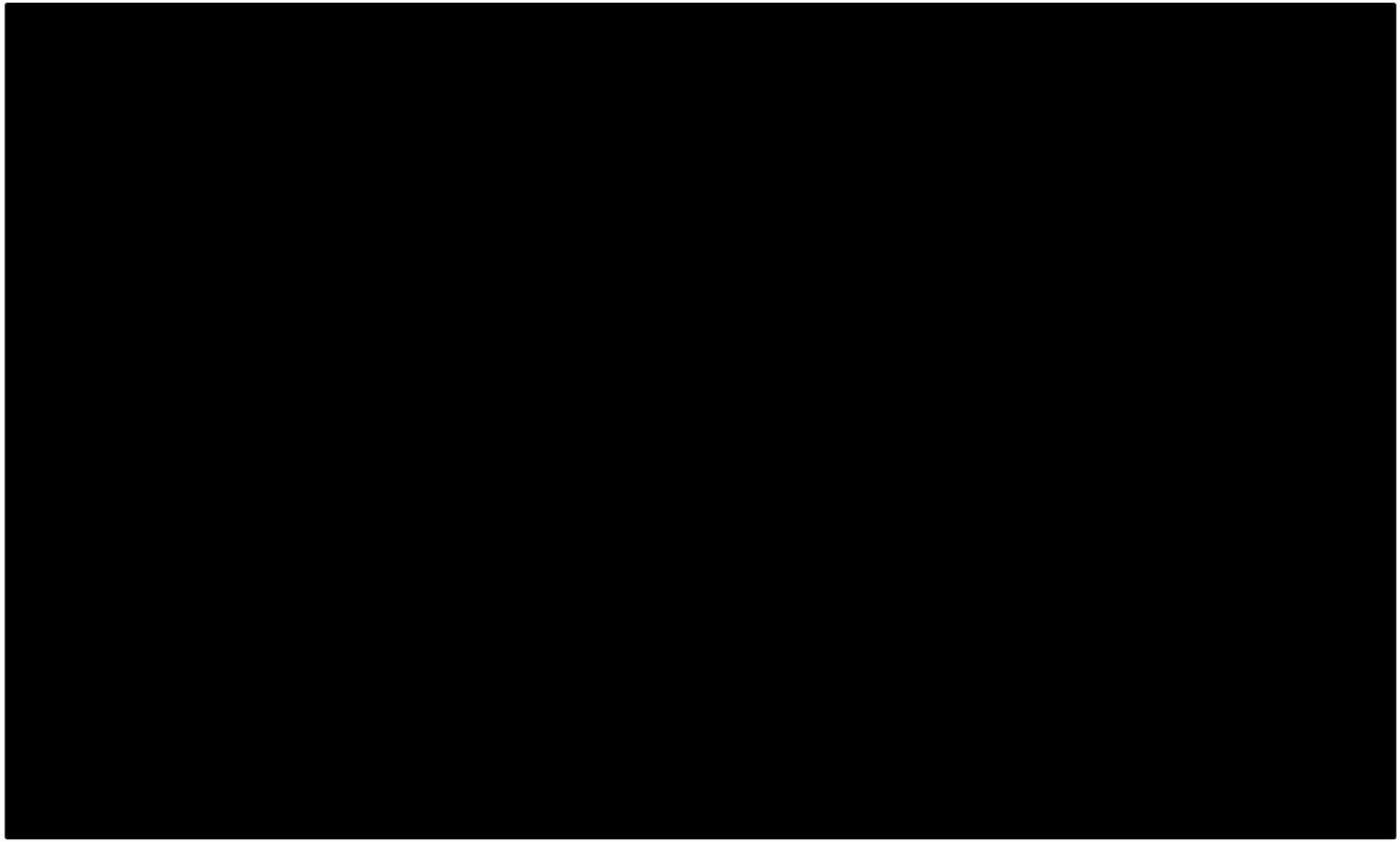
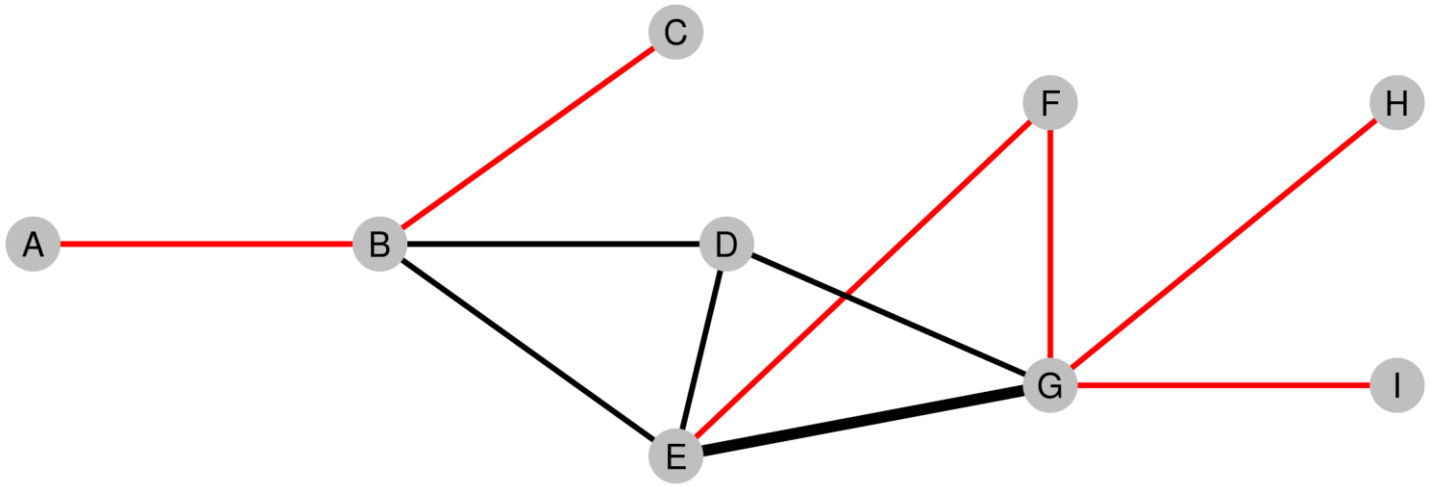


Figure 19: Network Diagram for CDP-24 – HA subgroup



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

E = IM IFNB-1a 30 mcg, QW

F = DAC 150 mg , Q4W

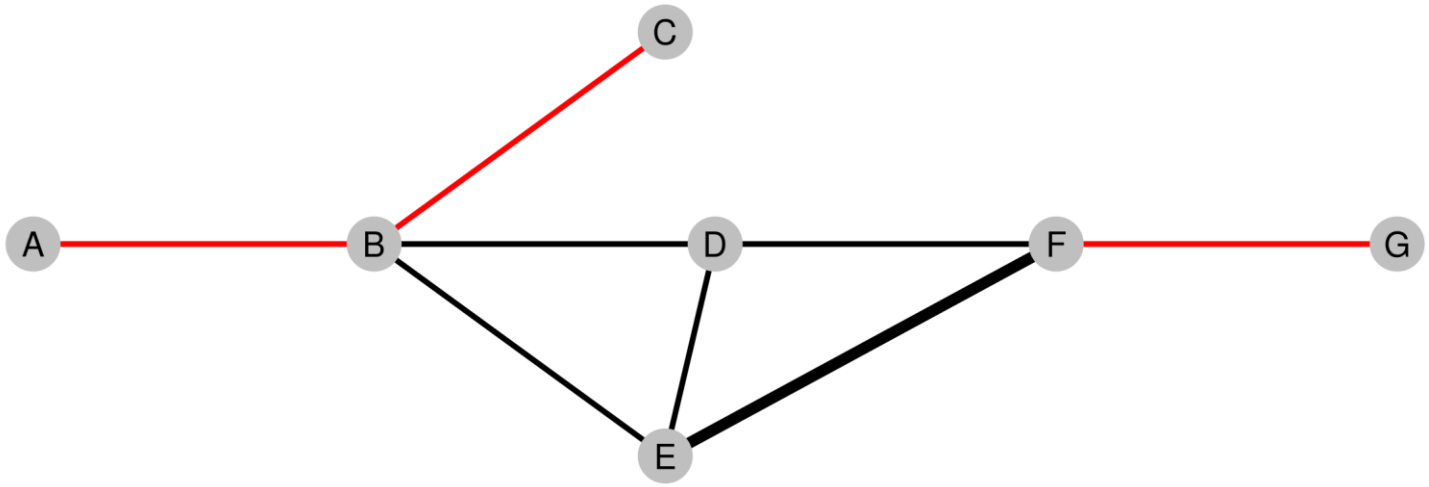
G = Placebo

H = FINGO 0.5 mg, QD

I = TERI 14 mg, QD

Red lines depict comparisons that are informed by subgroup data inputs, while black lines are informed by ITT data inputs. Edge width is proportional to the number of inputs for each comparison.

Figure 20: Network Diagram for CDP-24 – RES subgroup



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

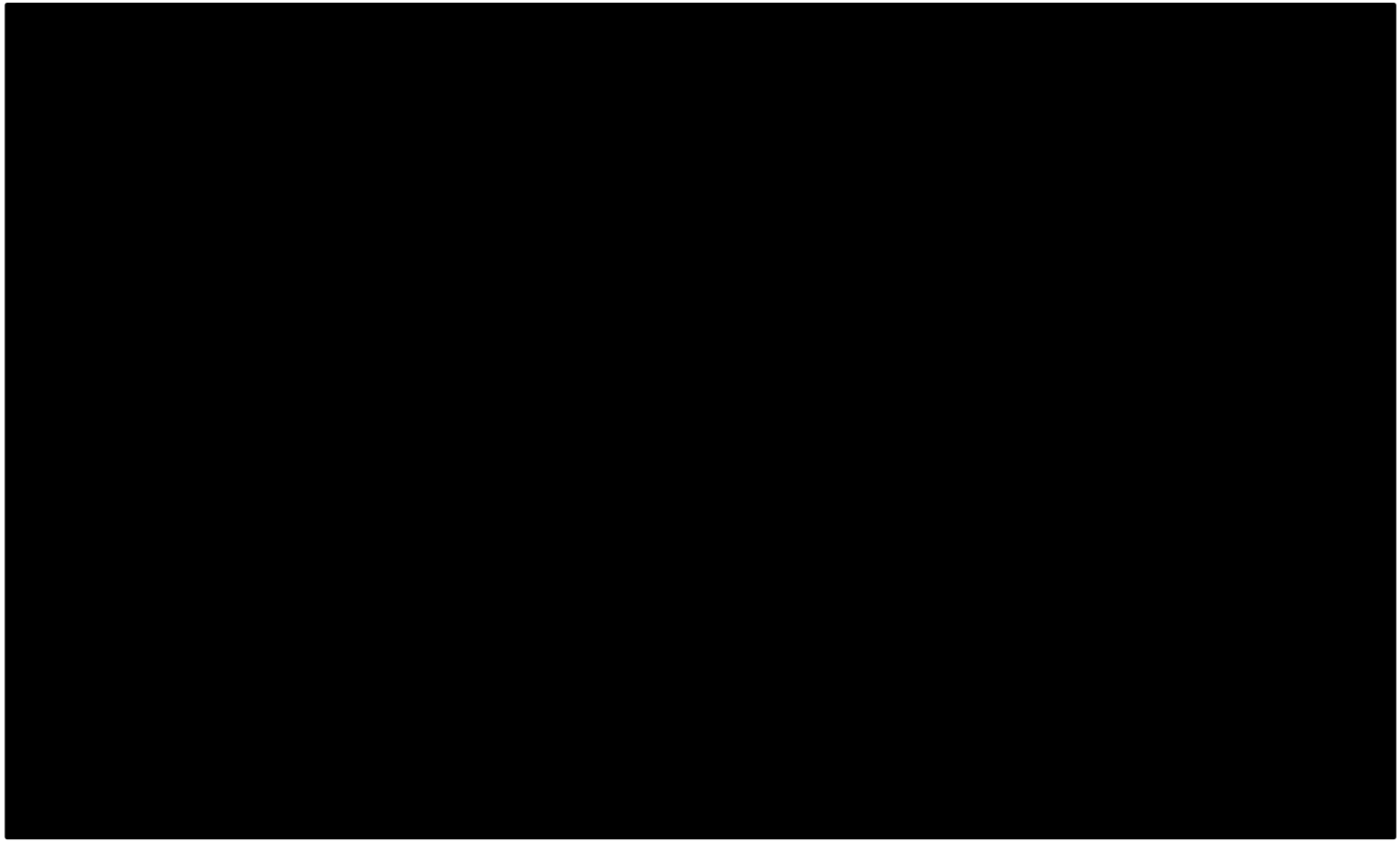
E = IM IFNB-1a 30 mcg, QW

F = Placebo

G = NAT 300 mg, Q4W

Red lines depict comparisons that are informed by subgroup data inputs, while black lines are informed by ITT data inputs. Edge width is proportional to the number of inputs for each comparison.

Figure 21: Forest plot comparing CDP-24 base case and subgroups



MTC results for all-cause discontinuation – ITT

The network for all cause discontinuation of treatment includes 17 treatments including placebo, and 26 studies (Figure 22).

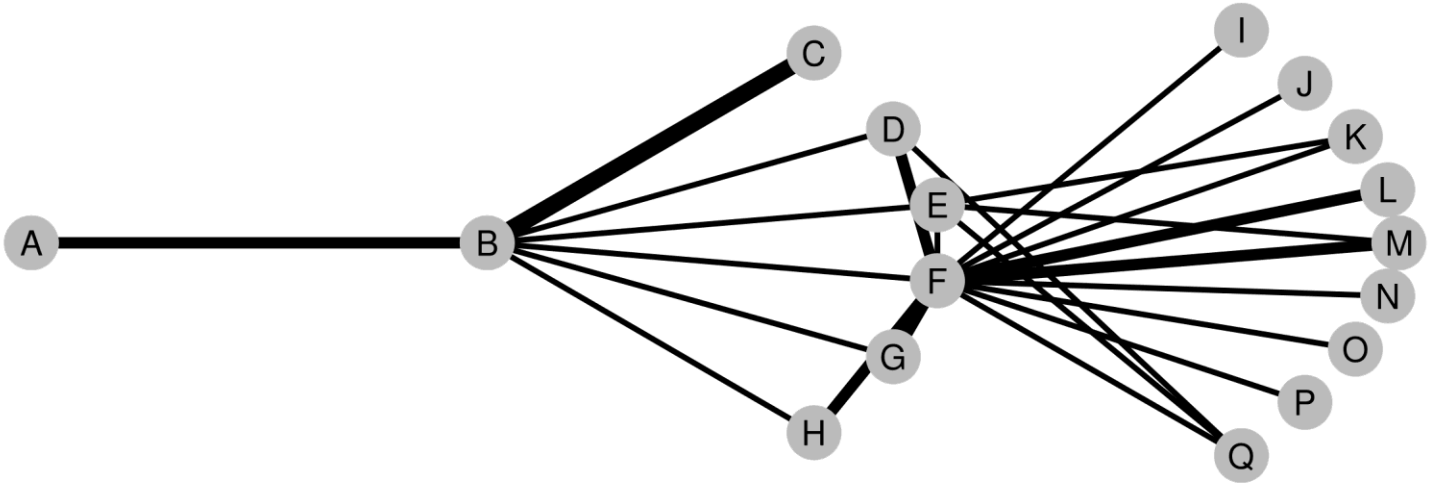
The results for the base-case analysis are provided in Figure 23 and tabulated in appendix D1.4. The results suggest that there are greater odds of all-cause discontinuation in patients who receive ocrelizumab compared to alemtuzumab and natalizumab, and lower odds of all-cause discontinuation in patients who receive ocrelizumab compared to pegIFNB-1a and IFNB-1a (Rebif).

The results of the sensitivity analyses are provided in Appendix D.1.4. Each of the choice of models provides a similar fit to the data (the DIC values are within 3 of each other). The alternative models broadly support the conclusions of the base-case analysis. In one case this has caused the conclusions to differ from the base-case analysis: the fixed effect model suggests that there are lower odds of all-cause discontinuation in patients who receive ocrelizumab compared to IFNB-1a (Avonex). The network meta-regression on trial duration suggests that the meta-regression does not provide a better fit than the meta-analysis (the meta-regression increased the DIC).

The impact of restricted network meta-analyses that exclude comparators not in the NICE scope was not evaluated for all-cause discontinuation. The results of a restricted network were assumed to be similar to the full network ITT results, based on sensitivity analyses with restricted networks for ARR, CDP-12 and CDP-24 suggesting no impact of including additional comparators.

A MTC for the HA and RES subgroups was not attempted for the all-cause discontinuation outcome as these data are usually not reported for subgroups specifically. The underlying assumption here is that all-cause discontinuation rates are no different in the subgroups from ITT.

Figure 22: Network diagram for all-cause discontinuation – Base case ITT



A = OCR 600 mg

B = SC IFNB-1a 44 mcg, TIW

C = ALEM 12 mg

D = GA 20 mg, QD

E = IM IFNB-1a 30 mcg, QW

F = Placebo

G = TERI 14 mg, QD

H = TERI 7 mg, QD

I = CLAD 3.5mg/kg

J = CLAD 5.25mg/kg

K = DAC 150 mg , Q4W

L = DMF 240 mg, BID

M = FINGO 0.5 mg, QD

N = NAT 300 mg, Q4W

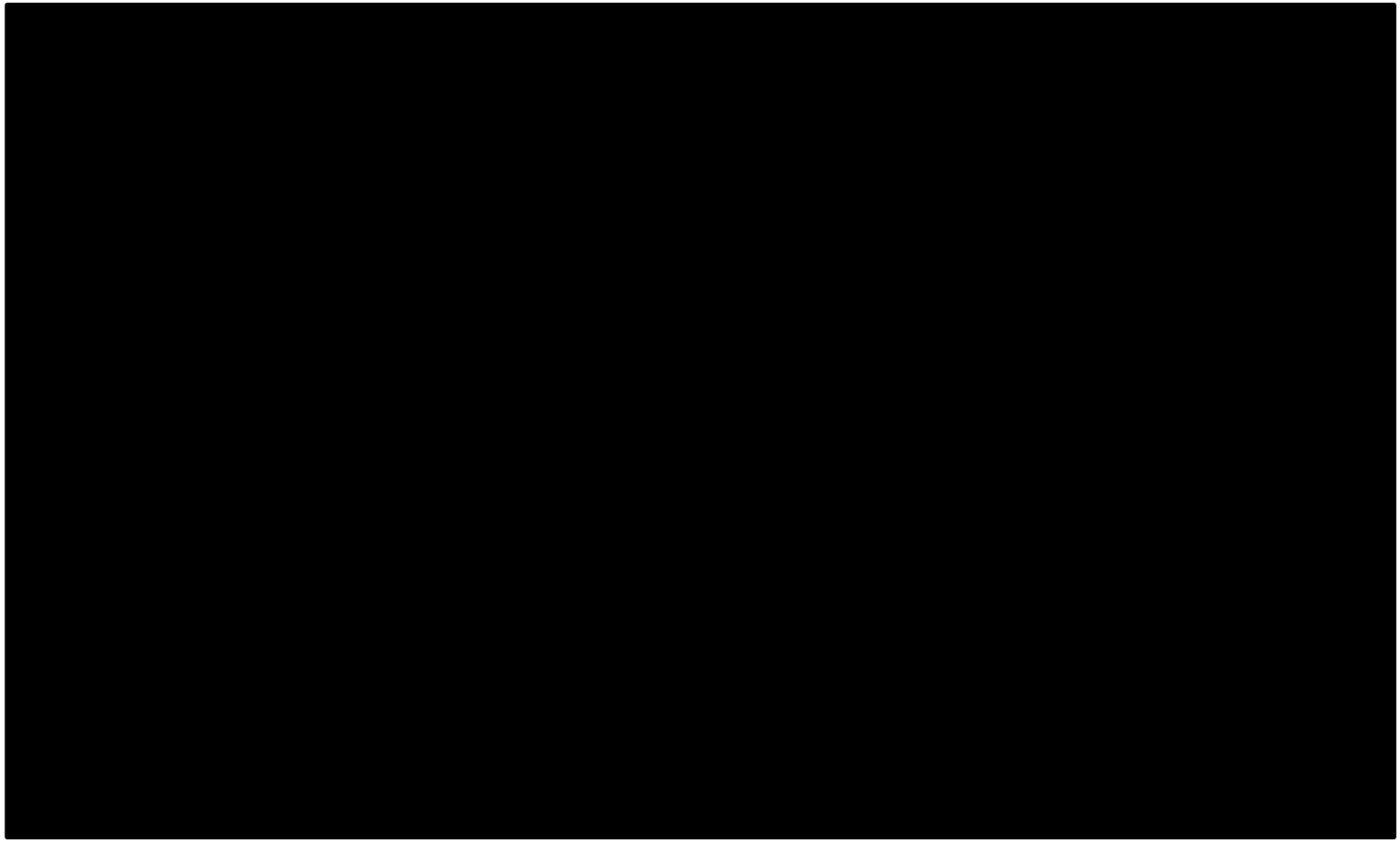
O = PEG-INFB-1A 2W 125 mcg, Q2W

P = SC IFNB-1a 22 mcg, TIW

Q = SC IFNB-1b 250 mcg, EOD

Edge width is proportional to the number of data inputs for each comparison.

Figure 23: Forest plot of all-cause discontinuation – Base case ITT



Comparison of CDP-12 and CDP-24 results

When assessing a treatment's comparative efficacy with respect to delaying disability progression, the overall robustness of the MTCs is a function not only of the outcome definition used (CDP-12 versus CDP-24), but also of the quantity and quality of the trial or data informing the models. In this case, the CDP-12 network provides better comparative estimates of sustained disability progression than the CDP-24 network (see Appendix D.1.4).

The CDP-12 MTCs contains better quality data than the CDP-24 MTCs: CDP-12 was pre-specified as a primary or secondary endpoint in 71% of the trials included in the CDP-12 ITT MTC while CDP-24 was pre-specified in only 48% of the trials included in the CDP-24 ITT MTC. When outcomes are not pre-specified, there is no regulatory requirement to report results, leading to possible publication bias (i.e. bias which ensues when favourable results are more likely to be reported than unfavourable ones).

The CDP-12 network also contains more data than the CDP-24 MTC: the ITT analysis is informed by 27 hazard ratio data inputs from 24 studies, for a total of 38 000 person-years, and includes 25 pairwise comparisons and 6 loops of evidence. Conversely, the CDP-24 ITT network is informed by 23 data inputs from 21 trials for a total of 31 000 person-years, 18 pairwise comparisons and 3 loops, fewer than CDP-12 MTC on every measure.

Beyond the benefit to precision of estimates of MTCs based on more rather than less data, including multiple trials with replicated results on a given comparison also adds significant robustness to any conclusions drawn from such an MTC, as it down weighs any possible outlier trial result. As shown in appendix D.1.4, it is indeed possible to have multiple studies for the same treatment yield different conclusions in terms of CDP-12 or CDP-24 (for example, DEFINE and CONFIRM for dimethyl fumarate). But when results are based on just one trial as they are for confirmed disability results for pegIFNB-1a (1-year ADVANCE trial, peg-interferon vs placebo) or daclizumab (1-year SELECT trial, daclizumab vs placebo), no adjustment for outlier results can be made, and conclusions based on those comparisons should be drawn with caution.

There is one caveat to the guiding principle that more data is better in MTC: that is that the additional information must not add more heterogeneity to the network (for instance by adding trials which enrolled patients with different severity of disease) or more inconsistency to the network (for example, by adding in new information to a MTC that contradicts existing information already in the network). To investigate the latter point, the MTC model was re-run without the assumption of consistency for each MTC outcome. The purpose of this

'inconsistency model' was to provide a comparison with the standard MTC model, and hence allow an evaluation of whether the consistency assumption is valid or not.

These inconsistency assessments found no evidence of inconsistency for 3 out of the 4 ITT MTCs including the CDP-12 ITT MTC (Appendix D.1.4). This means that the consistency model typically had a better model fit (by deviance information criterion (DIC)) than the new inconsistency model which relaxes the assumption of consistency (DIC of 1.6 vs 6.5, where a lower DIC demonstrating a better model fit and DIC differences ≥3 considered meaningful).

The only MTC to suggest inconsistency was the CDP-24 ITT NMA. Indeed the CDP-24 base-case model was marginally worse than the inconsistency model in terms of model fit (DIC of 14.9 vs 14.1). Exploring the possible source of this inconsistency led to the SELECT, REGARD and EVIDENCE trials (which form a loop) which were identified as inconsistent with each other with respect to definitions of CDP, and the time period of evaluations of CDP. Note that a key limitation of this assessment is that inconsistency can only be evaluated where there are loops in the network – of which there are fewer in the CDP-24 due to poorer connectivity (see Appendix D.1.4 for full details of the heterogeneity and inconsistency assessment).

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

The Cochrane Risk of Bias tool was used to evaluate the risk of bias for each of the eligible studies (see Appendix D.1.3). For the studies included in the MTC, where reported, randomization, concealment of the treatment allocation and the balance in the prognostic factors at the outset of the study were generally acceptable. There was little evidence to suggest that authors measured more outcomes than they reported, with notable exception of CARE-MS II. There is some risk of bias due to studies that were not double blind, unexpected drop-outs and missing or inappropriate intention-to-treat analyses. The risk of bias evaluation was limited by the availability of information for each of the studies.

A limitation of this MTC is that it synthesizes results from different time points. In order to combine data from different time points it is necessary to make the following assumptions.

- For ARR, the Poisson NMA model accounts for the length of the observation period. The assumption is that the relapse rate is constant over time.
- The CDP outcomes were analysed as survival outcomes. For these outcomes, the assumption is that the proportional hazards assumption holds.
- The binomial outcomes were analysed on the odds ratio scale. Hence it was necessary to assume that the odds ratios are constant over time.

The validity of the base-case analyses depends on the appropriateness of these assumptions. Sensitivity analyses using network meta-regression to adjust for time point suggested that these assumptions are valid.

For the relapse and CDP outcomes, another limitation is that studies used different definitions of relapse and progression. It was assumed that the definitions were sufficiently similar for MTC.

The MTCs have limited power to detect differences between treatments. Each of the base-case MTCs includes between 15 and 18 treatments. These NMAs are informed by between 21 and 31 studies. Where the number of studies is low, relative to the number of treatments, MTCs may lead to uncertain results. The further apart two treatments are in the network, the less precision there will be in their relative treatment effect. Thus, the uncertainty in comparisons between ocrelizumab and the other treatments will depend on the quality and quantity of the linking trials and the distance between ocrelizumab and the other treatments in network.

For ARR, CDP-12 and CDP-24, subgroup analyses were conducted to explore the effectiveness of the treatments in patients with HA and RES disease. The strength of these analyses was that data on specific patient populations corresponding to subgroups described in the EMA label for several comparators was identified. However, this analysis has several major limitations, beyond those already noted above for the base-case analyses.

The key limitation of the subgroup analyses is that analyses were not pre-specified for subgroups meaning that there is a high likelihood of publication bias, e.g. only favourable subgroup results being published. Indeed, Table 17 shows key outcomes data in subgroups are missing from comparator studies, e.g. disability data (CDP12 or CDP24) in RES subgroup from the daclizumab phase 3 study (DECIDE) and from the alemtuzumab phase 3 study CARE MS I are unpublished. The consequence of missing key study results is that comparisons for several treatments in the subgroup MTCs are based on one study only, which may or may not be consistent with the unpublished subgroup results of the other study. Thus the subgroup results are associated with a high level of uncertainty and should be interpreted with caution.

Another consequence of subgroup analyses not being pre-specified is that for some studies (particularly in the case of fingolimod) many different post hoc analyses were reported for a subgroup based on different definitions. The subgroups that most closely resembled the EMA definition of HA and RES were selected for inclusion in the MTC.

Furthermore, none of the included trials randomised patients based on subgroups, and thus the subgroup analyses should be regarded only as observational data. The presence and impact of any confounding factors in post hoc subgroup analyses could not be assessed due to lack of fully reported patient characteristics. Furthermore, heterogeneity and consistency of subgroup evidence could not be assessed due to low number of studies and absence of loops based on subgroup data.

Another key issue with the subgroup MTCs was disconnected networks due to sparsity of evidence. In order to connect the networks, ITT data from studies investigating ABCR treatments were included. The underlying assumption here is that results of treatment with ABCRs in ITT population do not differ from results in subgroup populations.

To assess the validity of this approach, the ITT and subgroup data was compared in the OPERA studies. As described in Section B2.7, there was no difference in subgroup versus ITT results for the confirmed disability progression outcomes. These data confirmed that ocrelizumab treatment effect was broadly consistent between subgroups and ITT for CDP-12 or CDP-24 and that the use of ABCR ITT links to connect the subgroup networks for these outcomes is likely to be valid. However, the subgroup results of ocrelizumab for the outcome ARR are different from those in the ITT population (Table 13). Using ABCR ITT data to supplement the subgroup networks for ARR is therefore a limitation, as treatment effect of ABCRs may differ between ITT and subgroups for this outcome.

Finally, subgroup analysis of all-cause discontinuation was not attempted due to lack of reported data.

In summary, the subgroup MTCs are associated with considerably more limitations than the ITT MTCs. The ITT MTCs rely on better quality data less prone to publication bias, are more populated networks leading to more plausible outputs, and do not break randomization as subgroup MTCs do. For these reasons we recommend interpreting the subgroup MTCs with caution and considering the ITT MTCs alongside the subgroups MTCs even for comparators that are only recommended in subgroups (i.e., natalizumab, fingolimod, and daclizumab). This allows for consideration of both relevance and robustness of evidence in decision making.

B.2.10 Adverse reactions

Adverse events from OPERA I and OPERA II are presented in this section. The safety population included all patients who received any study drug. Randomised patients who received incorrect therapy different from that intended were summarised in the group

according to the therapy actually received. Patients who were not randomised, but who received study drug, were included in the safety population and summarised according to the therapy actually received (77).

A total of 327 of 408 patients (80.1%) in the ocrelizumab group reported AE in the OPERA I trial, compared with 331 of 409 (80.9%) in the IFNB-1a group. A total of 360 of 417 patients (86.3%) in the ocrelizumab group reported an AE in the OPERA II trial, compared with 357 of 417 (85.6%) in the IFNB-1a group (Table 18). The most common AEs in patients treated with ocrelizumab were infusion-related reaction (IRR), nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection. Three deaths occurred, including one death in the ocrelizumab group (suicide in the OPERA II trial) and two in the IFNB-1a group (one suicide in the OPERA I trial, and one death due to mechanical ileus in the OPERA II trial) (77). All deaths were considered unrelated to study drug by investigators.

Table 18: Summary of adverse events in OPERA I and OPERA II

Variable, n (%)	OPERA I Trial		OPERA II Trial	
	Ocrelizumab n=408	IFNB-1a (Rebif®) n=409	Ocrelizumab n=417	IFNB-1a (Rebif®) n=417
Any adverse event	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection[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)
Neoplasm[b]	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death[c]	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse event	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)

[a]Infections were identified either as adverse events as defined in the Medical Dictionary for Regulatory Activities infections system organ class "infections and infestations" or as an adverse event with pathogen information provided.
[b]The neoplasms reported in the OPERA I trial were ductal breast carcinoma (in two patients) and renal cancer (in one) in the ocrelizumab group and mantle-cell lymphoma (in one) in the interferon beta-1a group. The neoplasms reported in the OPERA II trial were malignant melanoma (in one patient) in the ocrelizumab group and squamous-cell carcinoma (in one) in the IFNB-1a group.
[c]Deaths occurring during the trials were due to suicide (one in the ocrelizumab group in the OPERA II trial and one in the IFNB-1a group in the OPERA I trial) and mechanical ileus (one in the IFNB-1a group in the OPERA II trial).

Table 19: Pooled OPERA I and II safety data

Event, n (%)	Ocrelizumab n=825	IFNB-1a (Rebif®) n=826
Any adverse event	688 (83.4)	689 (83.4)
Total number of events	4194	4141
Total number of deaths	1 (0.1)	2 (0.2)

All-cause discontinuation from study treatment	99 (12.0)	166 (20.1)
Total number of patients with at least one		
AE with fatal outcome	1 (0.1)	2 (0.2)
Serious AE	57 (6.9)	72 (8.7)
Serious infection	11 (1.3)	24 (2.9)
AE leading to withdrawal from treatment	29 (3.5)	51 (6.2)
AE leading to dose modification/interruption	38 (4.6)	85 (10.3)
IRRs leading to withdrawal at first infusion	11 (1.3)	0

Source: (83)

Treatment exposure

Overall, there was good compliance regarding administration of IFNB-1a injections and ocrelizumab infusions, as well as their equivalent placebo treatments, in both treatment groups.

More than 80% of patients in the IFN group and 89% of patients in the ocrelizumab group received four doses of ocrelizumab/placebo. The mean cumulative ocrelizumab dose was 2240 mg over 2 years of exposure.

Table 20: Exposure to ocrelizumab during the controlled treatment period – treatment duration

	Ocrelizumab n=825	**IFNB-1a (Rebif®) n=826**
Treatment duration, weeks, n (%)		
0–23	37 (4.5)	50 (6.1)
24–47	18 (2.2)	55 (6.7)
48–71	22 (2.7)	37 (4.5)
72–95	32 (3.9)	33 (4.0)
96–110	716 (86.8)	650 (78.8)
Number of doses, n (%)		
1	46 (5.6)	74 (9.0)
2	20 (2.4)	49 (5.9)
3	27 (3.3)	39 (4.7)
4	732 (88.7)	663 (80.4)
Mean number of doses (SD)	3.8 (0.8)	3.6 (1.0)
Mean cumulative dose, mg (SD)	2240.0 (489.9)	0.0 (0)

Source: (83)

Common AEs

Common AEs, reported with frequency ≥ 5% of patients in either treatment group, are summarised by preferred term below. The most common AEs were IRR, headache, influenza-like illness, upper respiratory tract infection, and nasopharyngitis. Influenza like illness and injection site erythema were more frequently reported in the IFN group. IRR, upper respiratory tract infection, and nasopharyngitis were more common in the ocrelizumab group.

Table 21: Adverse events reported in ≥ 5% of patients by preferred term during the controlled treatment period

n, (%)	Ocrelizumab n=825	IFNB-1a (Rebif®) n=826
Total number of patients with at least one AE occurring at relative frequency ≥5%	544 (659)	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: (83)

Adverse events by intensity (including fatal adverse events)

During the controlled treatment period, the majority of patients reported AEs of Grade 1 or 2 in intensity (83). Among patients who experienced AEs of Grade ≥3 there were:

- Grade 3: IFNB-1a 111 patients (152 events) and ocrelizumab 110 patients (156 events). With the exception of 28 patients (IFNB-1a 19 patients and ocrelizumab 9 patients), all recovered or were recovering at time of last contact
- Grade 4: IFNB-1a nine patients (nine events; AE PTs of acute myocardial infarction, angina, unstable, multiple injuries, overdose, blood creatinine phosphokinase increased, hypertriglyceridemia, MS relapse, depression suicidal, or pulmonary embolism) and ocrelizumab ten patients (12 events; AE PTs of acute myocardial infarction, appendicitis, biliary sepsis, infusion-related reaction, invasive ductal breast carcinoma, seizure, hydrocephalus, depression, suicide attempt, and pneumonia aspiration). With the exception of one patient with the breast cancer in the ocrelizumab group, all patients recovered or were recovering at the time of last contact
- Grade 5: IFNB-1a two patients (AE preferred terms of mechanical ileus and completed suicide) and ocrelizumab one patient (AE preferred term completed suicide). All were considered unrelated to study drug by investigators.

Serious adverse events

The total number of patients reporting SAEs during the controlled treatment period was low, relative to the total number of patients reporting AEs, and similar between the IFNB-1a and ocrelizumab treatment groups (8.7% and 6.9% of patients with an SAE, respectively) (83).

Most frequently, patients reported SAEs belonging to the following SOCs:

- Infections and Infestations (IFNB-1a 2.9% and ocrelizumab 1.3%)
- Nervous System Disorders (IFNB-1a 1.3% and ocrelizumab 1.0%)
- Injury, Poisoning and Procedural Complications (IFNB-1a 1.2% and ocrelizumab 0.7%)

Adverse events that led to withdrawal of study treatment

During the controlled treatment period, the proportion of patients withdrawn from study treatment due to a non-fatal AE was low overall. However, the incidence was higher in the IFNB-1a group (6.2%; 51 patients) compared with the ocrelizumab group (3.5%; 29 patients) (83).

The primary AEs leading to withdrawal reported with a higher incidence in the IFNB-1a group were:

- Withdrawals due to influenza-like illness, fatigue, and injection site reaction (15 patients)
- Withdrawals due to liver function test abnormalities or abnormalities in creatinine phosphokinase levels (increased) or in platelet or leukocyte counts (11 patients)
- Withdrawals due to neutropenia or leukopenia (4 patients)

With the exception of creatinine phosphokinase elevation, all AEs are known side effects, typically associated with IFNB-1a treatment.

There were 11 patients in the ocrelizumab group and none in the IFNB-1a group who were withdrawn from treatment due to IRRs.

Anti-drug antibodies

Out of 807 patients who received ocrelizumab and had an anti-drug antibody (ADA) assay result from a post-baseline sample during the controlled treatment period, three patients (0.4%) showed treatment-induced ocrelizumab ADAs. Of these, one patient (0.12%) tested

positive for neutralising antibodies to ocrelizumab. In contrast, out of the 796 patients who received IFNB-1a and had an ADA assay result from a post-baseline sample, 170 patients (21.3%) showed treatment-induced IFNB-1a ADAs.

Table 22: Baseline prevalence and post-baseline incidence of anti-drug antibodies during the controlled treatment period

n, (%)	Ocrelizumab n=825	IFNB-1a (Rebif®) n=826
Anti-ocrelizumab neutralising antibodies		
Baseline prevalence of ADAs, n Positive sample at baseline, n (%)	798 5 (0.6)	804 4 (0.5)
Post-baseline incidence of ADAs, n Positive for ADA, n (%)	807 3 (0.4)	804 7 (0.9)
Anti-IFNB-1a neutralising antibodies		
Baseline prevalence of ADAs, n Positive sample at baseline, n (%)	800 42 (5.3)	800 35 (4.4)
Post-baseline incidence of ADAs, n Positive for ADA, n (%)	796 67 (8.4)	796 170 (21.3)

Source: (83)

Safety profile summary

Overall, ocrelizumab had a similar safety profile to IFNB-1a over the 96-week study period in OPERA I and II; the number of patients who experienced any AE and the total number of AEs were similar between the two treatment groups. Results of the pooled safety analyses from 1651 patients (826 patients in the IFNB-1a group and 825 patients in the ocrelizumab group) did not indicate any unexpected safety findings over the controlled treatment period from what was known originally from the Phase II study WA21493 with ocrelizumab in patients with RRMS.

The number of patients who experienced any AE and the total number of AEs was well balanced between the two treatment groups. The total number of patients reporting SAEs was similarly well balanced between groups and low relative to the overall number of patients reporting AEs.

The most common AE associated with ocrelizumab treatment was IRR which occurred most frequently at the first ocrelizumab infusion. Their incidence markedly decreased with subsequent infusions, consistent with the typical pattern for IRRs associated with anti-CD20 drugs. The majority of IRRs were Grade 1 or 2 in intensity with a few patients experiencing Grade 3 IRRs. The severity of IRR symptoms markedly decreased with subsequent dosing.

The low incidence of treatment-emergent ADA (<1%) in patients receiving ocrelizumab is in line with expectations given that ocrelizumab, as a humanised antibody, carries a low risk for inducing immune responses.

B.2.11 Ongoing studies

There is an open-label extension study for OPERA I and II in patients with RRMS (NCT01247324 and NCT01412333) (106). Data from this phase will be presented at a scientific meeting in 2018 and are described in Appendix L. There are no other additional studies which are likely to be available in the next 12 months.

B.2.12 Innovation

Ocrelizumab is a glycoengineered humanised monoclonal antibody specifically for chronic administration that selectively targets circulating B cells expressing CD20, a cell-surface antigen that is expressed on mature B cells but not B cell progenitor cells in the bone marrow or terminally differentiated plasma cells. Adaptive immune responses to antigen challenge remain largely intact despite the depletion of circulating B cells (107).

- Ocrelizumab is the only DMTs to consistently demonstrate **efficacy** across all disease outcomes in RRMS (Table 23). Furthermore, ocrelizumab is the only DMT to demonstrate delays in disability progression in patients with PPMS (108) and therefore has the potential to establish a new standard of care in this form of the disease.

Table 23: Overview of ocrelizumab and comparator Phase III results in delaying CDP

DMT	Study	Trial duration, yrs	Comparator	12-week CDP HR (95% CI)	24 week CDP HR (95% CI)
Ocrelizumab	OPERA I (79)	2	IFNB-1a (Rebif®)	0.57 (0.37, 0.90)	0.57 (0.34, 0.95)
	OPERA II (78)	2	IFNB-1a (Rebif®)	0.63 (0.42, 0.92)	0.63 (0.40, 0.98)
Dimethyl fumarate (69)	DEFINE	2	Placebo	0.62 (0.44, 0.87)	0.77 (0.52, 1.14)
	CONFIRM	2	Placebo	0.79 (0.52, 1.19)	0.62 (0.37, 1.03)
Fingolimod	FREEDOMS (46)	2	Placebo	0.70 (0.52, 0.96)	0.63 (0.44, 0.90)
	FREEDOMS II (71)	2	Placebo	0.83 (0.61, 1.12)	0.72 (0.48, 1.07)
	TRANSFORMS (81)	1	IFNB-1a (Avonex®)	NR	NR
Alemtuzumab	CARE-MS I (45)	2	IFNB-1a (Rebif®)	NR	0.70 (0.40, 1.23)

	CARE-MS II (74)	2	IFNB-1a (Rebif®)	NR	0.58 (0.38, 0.87)
Natalizumab	AFFIRM (47)	2	Placebo	0.58 (0.43, 0.77)	0.46 (0.33, 0.64)
Daclizumab	DECIDE (72)	2	IFNB-1a (Avonex®)	0.84 (0.66, 1.07)	0.73 (0.55, 0.98)
	SELECT (103)	1	Placebo	0.43 (0.21, 0.88)	NR
Teriflunomide	TEMSO (70)	2	Placebo	0.70 (0.51, 0.97)	NR
	TOWER (68)	2	Placebo	0.68 (0.47, 1.00)	NR

NR, not reported
Green shading indicates upper limit of 95% CI ≤1
Red shading indicates upper limit of 95% CI >1

- Ocrelizumab is administered as a single 600 mg IV infusion every six months (5). The **frequency of administration** over a 12 month period is less than other DMTs and may mitigate the risk of non-adherence as seen with other DMTs that have logistical and resource intensive administration schedules. It has been previously reported that injectable DMTs and oral drugs are associated with low adherence rates due to the frequency of administration (67). Less frequent administration is also expected to result in NHS efficiencies in relation to service provision and resource utilisation compared to other intravenously infused DMTs like natalizumab and alemtuzumab.
- In addition, the **safety profile** of ocrelizumab in the OPERA trials was similar to IFNB-1a (Rebif®) with a distinct absence of burdensome and complex safety monitoring requirements. Patients receiving ocrelizumab are not expected to require additional routine JCV, cardiovascular or laboratory tests, or other safety monitoring like MRI screening compared to other intravenously infused and orally administered DMTs for the treatment of RMS (5). Less frequent monitoring may reduce the logistic, administrative and resource associated burdens of safety monitoring for MS-related healthcare services in the UK (109).
- There is a low probability of long-term **treatment waning** with ocrelizumab compared to other DMTs. This is based on the identification and assessment of all relevant biologically plausible contributory factors and the associated evidence following literature review and repeated consultation with clinical experts:
    - As a humanised antibody, the immunogenicity of ocrelizumab is significantly reduced compared to other biological MS DMTs like alemtuzumab and IFNB-1a preparations (Table 24). This is likely to reduce the probability of long-term treatment waning effects due to the formation of neutralising and inhibitory anti-drug antibodies.

    - Furthermore, data from pre-clinical investigations suggest that ocrelizumab decreases inflammation of the innate immune system which may also reduce the probability of a treatment waning effect. In the EAE model, a widely accepted animal model of human MS disease, anti-CD20 therapy reduced microglial activation and lesion formation, with immunohistochemistry for MHCII also demonstrating a reduced volume of brain microglial activation which was accompanied by a reduction in T-cell recruitment and demyelination (110). This is in contrast to the lack of effect seen in relation to microglial activation with other DMTs (like alemtuzumab (111)).
- Given the complex therapeutic options currently available in RRMS, the **reversibility of pharmacodynamic effects** in order to facilitate the transition to another DMT in the event of treatment-limiting adverse events or efficacy failure becomes clinically important. The half-life (t1/2) of ocrelizumab is 26 days. A Phase II study (WA21493, N=51) indicated that the median time to B cell repletion (return to baseline or LLN, whichever occurred first) was 72 weeks (range 27–175 weeks). The reversibility of the pharmacodynamic effect therefore does not prejudice the patient's ability to receive any future therapy, as and when newer more innovative and safer treatment options become available. The rate of B cell repletion also does not result in disease rebound phenomena on drug discontinuation, as seen with other DMTs like fingolimod and natalizumab (112, 113). Furthermore the inter- and intrapatient variability in the rate and nature of immune reconstitution post induction treatments like alemtuzumab and cladribine, and the lack of evidence of managing breakthrough disease in patients after the use of these agents, further necessitates the need for an efficacious treatment with more predictable reversibility of pharmacodynamic effect that does not prejudice patient eligibility for subsequent treatment options.

There is currently no cure for MS. The aim of treatment with DMTs is to reduce relapses, delay disability progression and preserve mobility while diminishing the impact on HRQoL (114). The MTC indicates that ocrelizumab is a highly efficacious DMT, and coupled with the

lower healthcare utilisation due to patients only needing two infusions per year with less frequent monitoring than the other high efficacy DMTs, this demonstrates that the introduction of ocrelizumab will lead to a step-change in treatment for all RRMS patients and may lead to earlier treatment with a high efficacy DMT.

B.2.13 Interpretation of clinical effectiveness and safety evidence

OPERA I and OPERA II were randomised, double-blind, double-dummy active-controlled, parallel-group phase 3 trials in patients with RMS. The two studies were identical in terms of design, endpoints, inclusion and exclusion criteria, and active comparator (IFNB-1a 44 µg, Rebif®). The duration of treatment was 96 weeks.

The internal validity of these studies is supported by the rigid adherence to the EMA guidance on recommended study design and endpoints in the clinical investigation of medicinal products for the treatment of MS (115). There is a very low risk of bias with trials of ocrelizumab. In all trials, randomisation was carried out appropriately, using a validated interactive voice response system with OPERA I and OPERA II having double-blind, double-dummy designs. Furthermore, the trial population in OPERA I and OPERA II is reflective of UK clinical practice, with relevant endpoints investigated to address the unmet need for patients with RRMS.

The primary endpoint was reached in both OPERA I and OPERA II, where ARR was significantly lower with ocrelizumab than IFNB-1a (Rebif®). In OPERA I in the ocrelizumab group, adjusted ARR was reduced by 46.4% at 96 weeks compared with the IFNB-1a group (rate ratio, 0.536; 95% CI: 0.400–0.719; p<0.0001), and in OPERA II by 46.8% (rate ratio, 0.532; 95% CI: 0.397–0.714; p<0.0001). In addition, ocrelizumab was associated with a lower rate of disability progression; in the pre-specified pooled analysis, the percentage of patients with CDP at 12 and 24 weeks was 9.1% vs 13.6% (40% lower risk with ocrelizumab; HR, 0.60; 95% CI: 0.45–0.81; p<0.001) (77). In OPERA I and OPERA II, a significant reduction in 12-week CDP was observed for ocrelizumab versus IFNB-1a, with a 43% reduction in OPERA I (HR: 0.57; 95% CI: 0.37–0.90; p=0.0139) and a 37% reduction in OPERA II (HR: 0.63; 95% CI: 0.42–0.92; p=0.0169). Relapses have a substantial impact on the health-related quality HRQoL of patients with RMS (116, 117) and can lead to the accumulation of disability (32, 118). The OPERA I and II trials demonstrated that ocrelizumab can lead to a reduction in patient and health care burden associated with symptoms arising from relapses and disability progression. The efficacy of ocrelizumab was observed across all payer-relevant subgroups, suggesting that they will all benefit from ocrelizumab treatment (Appendix E).

In OPERA I and OPERA II, the total proportions of patients reporting AEs during the clinical trials were similar in the ocrelizumab treatment groups and the comparator groups. Most AEs (approximately 80%) were grade 1 or 2 intensity and the proportions of patients reporting grade 3 or 4 AEs were comparable between the ocrelizumab and the comparator treatment groups. In the MTC, no statistically significant difference was found between ocrelizumab and the other DMTs with respect to all-cause discontinuation. IRRs were more common in patients treated with ocrelizumab than in those treated with IFNB-1a and included one life-threatening (grade 4) bronchospasm. The most likely mechanism for an IRR is a type 2 hypersensitivity reaction, in which cytokines are released from an effector cell after the ligation of low-affinity Fc receptors by ocrelizumab-opsonised B cells.

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 (77, 119).

The limited immunogenicity of ocrelizumab was shown by the low incidence of antidrug antibodies among patients treated with ocrelizumab (77); this is in contrast to that seen with other DMTs.

Table 24: Immunogenicity of DMTs for RRMS

DMT	Incidence of ADAs
Alemtuzumab (66)	Approximately **85%** of patients tested positive for anti-alemtuzumab antibodies during a controlled clinical study; **92%** of these patients tested positive also for antibodies that inhibited alemtuzumab binding in vitro
Natalizumab (59)	Neutralising ADAs to natalizumab were detected in **10%** of patients in 2-year controlled clinical trials. Persistent antibodies developed in approximately **6%** of patients and were associated with a substantial decrease in efficacy and increased incidence of hypersensitivity reactions
Daclizumab (65)	Treatment-emergent ADAs and neutralising antibodies were observed in **19%** and **8%** of patients in the DECIDE study respectively. The majority of neutralising antibodies were transient (6%); 2% of patients had persistent responses
IFNB-1a (Avonex®) (120)	Data from patients treated up to two years suggests that approximately **8%** develop neutralising antibodies
IFNB-1a (Rebif®) (121)	Clinical data suggest that after 24 to 48 months of treatment (Rebif 22µg), approximately **24%** of patients develop persistent serum antibodies to IFNB-1a
PEG-IFNB-1a (Plegridy) (60)	Data from patients treated up to 2 years with Plegridy suggests that **less than 1%** developed persistent-neutralising antibodies to the IFNB-1a portion of PEG-IFNB-1a

There is unmet need for a DMT that has a benefit–risk profile which supports initiation at any time during the disease course of MS, which preserves neurological function, inhibits the

accumulation of irreversible disability and improves HRQoL. Despite the availability of different types of DMTs, most patients with RRMS continue to experience disease activity. The OPERA I and II studies demonstrate that ocrelizumab is an efficacious treatment that reducess the ARR in this patient population by almost half compared with IFNB-1a (Rebif®) while also delaying disability progression (12-week and 24-week CDP). Preventing relapses and delaying disability progression offers substantial benefits to patients in terms of HRQoL and health status (122-124) and is likely to reduce healthcare utilisation (125), therefore ocrelizumab not only addresses the unmet medical need for patients with RRMS but also provides benefits to other stakeholders.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic review (SR) was conducted to identify cost-effectiveness studies in RRMS. Thirty-three unique studies were identified (see Appendix G), as well as seven previous NICE appraisals in RRMS. No studies modelling the cost-effectiveness of ocrelizumab were identified in the literature search.

Separate from the SR, one report was identified from the website of the US organisation the Institute for Clinical and Economic Review assessing the cost-effectiveness of DMTs in MS (126). As this report includes cost-effectiveness analysis for ocrelizumab it is relevant to the decision problem and summarised here.

The economic evaluation was conducted from a US payer perspective and a Markov model consisting of 20 health states and a lifetime horizon was used. Treatment sequencing was allowed; after discontinuation of the initial DMT in an RRMS or SPMS state, patients continued to a second-line treatment before transitioning to BSC. Treatment effect on CDP-24 was preferentially applied in the model, when not available, CDP-12 was used.

The MTC results indicated that ocrelizumab was the second-most efficacious DMT after alemtuzumab, with 10.94 QALYs gained on ocrelizumab over a lifetime compared with 7.92 for the least efficacious DMT, IFNB-1a (Avonex), and 12.46 for alemtuzumab. No ICER was calculated for ocrelizumab as the drug price was not available at time of analysis. For the other DMTs the ICERs ranged from $38,277 (alemtuzumab) to $327,639 (IFNB-1a [Avonex]) versus best supportive care (BSC).

B.3.2 Economic analysis

The previous NICE appraisals and the combined literature on economic analyses in RRMS informed the development of the economic model for this submission, which is in line with established model structure in RRMS.

B.3.2.1 Patient population

The current draft SmPC states that ocrelizumab is indicated for adult patients with relapsing forms of MS (RMS) with active disease defined by clinical or imaging features (5). Full details regarding inclusion/exclusion criteria and patient characteristics of the OPERA studies are presented in Section B.2.3.

Patients with RRMS are the population of interest in the economic analysis. The NICE scope also requested analysis in people with SPMS with active disease, evidenced by relapses. However as explained in Section B.1.1, no data is available for this specific sub-population.

Analyses were conducted in the following (sub-)populations in line with the NICE scope:

- in people with RRMS
- in people with RES RRMS
- in people with HA RRMS despite previous treatment

B.3.2.2 Model structure

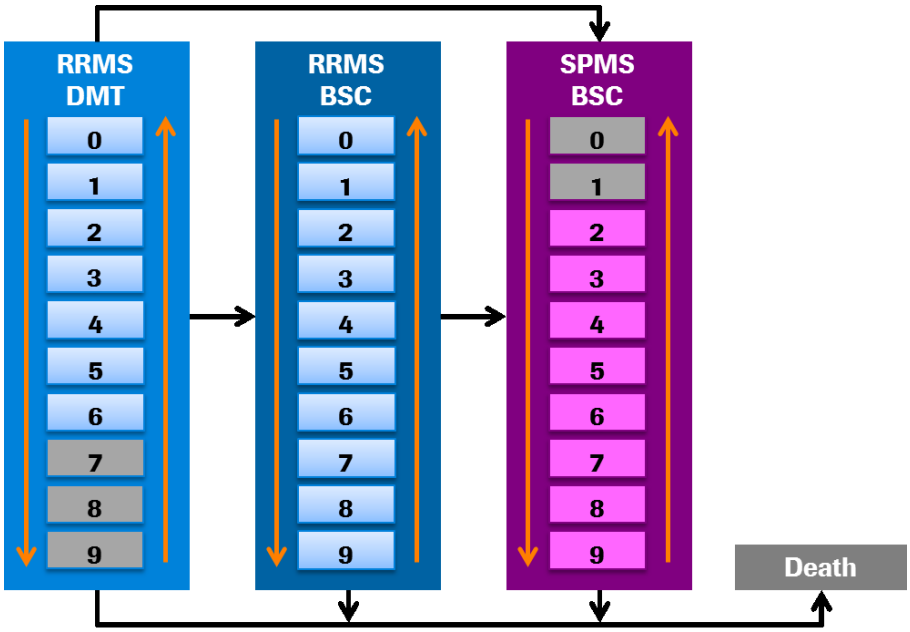
A cohort multi-state Markov model was developed which reflect health states based on disease classification and severity. Two key clinical manifestations are reported in RRMS and SPMS, an exacerbation of symptoms (known as relapses) and progressing disability over time. The prominence of these clinical manifestations can vary in the different forms of MS. The prevention of relapses and the avoidance of disability progression are two of the main clinical objectives of treatment in these patients. Therefore, the model structure has been designed to account for both relapses and disability progression.

Characterisation of disability progression in MS is most commonly based on the Kurtzke Expanded Disability Status Scale (EDSS) (127). Accordingly, health states in the model are defined by the EDSS, giving rise to ten states (EDSS 0 - 9). While the EDSS scale permits patients to be rated at 0.5-point increments (for example, EDSS 1.5: no disability, minimal signs in more than one functional system), health states have been collapsed to integer EDSS values for modelling tractability and consistency with reported data in MS and previous NICE appraisals.

The EDSS measure has well recognised limitations. It is based on neurological examination which is inherently subjective, and due to time constraints in MS clinics may not be fully implemented in practice. As a result, the scale has poor reliability within and between raters thereby creating considerable “noise” in real world measurements (128). Furthermore, the EDSS is driven mainly by ambulatory function (scores 4–7 are based primarily on ability to walk a certain distance and need for assistive device), and captures cognitive impairment poorly (129). Finally, EDSS is a non-linear ordinal scale, such that increments do not have the same level of impact depending on where on the scale they occur. The upper end of the scale (scores 7–9) is less sensitive to change, i.e. a 1-point increase between 7 and 8 (‘essentially restricted to wheelchair’ to ‘essentially restricted to bed’) has a much larger impact on a patient’s HRQoL and costs than a 1-point increase between 3 and 4 (‘fully ambulatory’ to ‘able to walk without aid for 500 metres’).

The model structure and inputs are, by design, similar to the models used in previous NICE appraisals in RRMS (Figure 24 and Table 25).

Figure 24: Diagram of model structure



Transitions between health states

Patients enter the model in a baseline RRMS disease-course state on active treatment and start in one of the ten EDSS states.

In each annual cycle patients may:

1) transition between EDSS states in RRMS;
2) withdraw from active treatment and continue to receive BSC;
3) convert to SPMS and then transition between EDSS states in SPMS;
4) transition to death.

Relapse rate, conversion from RRMS to SPMS, and mortality are all EDSS-dependent, as are costs and health-related quality of life (HRQoL). As per previous NICE appraisals in RRMS, caregiver disutilities per EDSS state were also accounted for in the model.

The probability of changing EDSS state (disability progression) was determined by natural history data (underlying disease progression of patients not on therapy). Treatments were assumed to delay the progression of disease and reduce the frequency of relapses in RRMS. Treatment effects in the form of hazard ratios were derived from the MTC, using CDP-12 in the base case, and applied to the natural history data probabilities of worsening in EDSS. The probabilities of improving EDSS are assumed to be unaffected by treatment.

In line with several previous NICE appraisals, a partial treatment effect on the probability of a patient progressing from RRMS to SPMS is assumed. No direct treatment effect on transitions between SPMS states and mortality were assumed.

The annual relapse rate (ARR) within each RRMS and SPMS EDSS health state was determined using natural history, in line with previous appraisals. Relapse rates are applied to the EDSS health state distribution of patients in RRMS and SPMS to estimate the number of relapses. Treatment effects (relative risks) for patients within RRMS were taken from the MTC.

Treatment withdrawal due to all-causes is included in the economic model and is derived from the OPERA trials and MTC. Patients receiving active treatment for MS may experience tolerability issues; therefore the most frequently experienced AEs associated with each treatment were included in the model and incurred costs and disutilities.

The time horizon in the model is 50 years, in line with previous NICE appraisals in RRMS, and a half cycle correction is applied. Induction therapy like alemtuzumab is given at the beginning of each year and treatment-related costs should not be half cycle corrected. As such a 5% increase is applied to alemtuzumab drug costs and administration costs.

Table 25: Features of the economic analysis

	Previous appraisals (Committees' stated or implicit preferences)							Current appraisal	
Factor	**TA32**	**TA127**	**TA254**	**TA303**	**TA312**	**TA320**	**TA441**	**Chosen values**	**Justification**
Time horizon	20 years	20 years, but Committee considered longer time horizon more appropriate	50 years	50 years	50 years	30 years	50 years	50 years	In line with majority of previous appraisals
Source of natural history EDSS	London Ontario	- Trial placebo arm for EDSS 0-6 - London Ontario for EDSS 7-9	London Ontario	- Trial placebo arm for EDSS 0-6 - London Ontario for EDSS 7-9 Committee considered EDSS improvements more appropriate	- Trial placebo arm for EDSS 0-6 - London Ontario for EDSS 7-9 Committee considered EDSS improvements more appropriate	- Trial placebo arm for EDSS 0-7 - London Ontario for EDSS 8-9	- Trial placebo arm for EDSS 0-7 - British Columbia for EDSS 8-9 - placebo arm from different trials for HA subgroup - as per TA127 for RES subgroup	British Columbia - as per TA127 for HA and RES subgroup	Long-term registry data was considered most robust in reflecting chronic disease course, and EDSS improvements are allowed in British Columbia dataset. Lack of placebo arm in OPERA studies meant that trial data from TA127 was used to adjust for HA and RES subgroups.
Source of natural history relapse	Patzold et al 1982, adjusted for EDSS distribution	Patzold et al 1982, combined with UK MS survey data - adjusted for RES using trial data	Patzold et al 1982, combined with UK MS survey data	Held 2005, combined with Orme et al 2007 data, divided by assumption about hospitalise	Held 2005, combined with Orme et al 2007 data, divided by assumption about hospitalise	As per TA254	- Trial data for EDSS 0-5 Patzold et al 2005, combined with UK MS survey data	As per TA254 - adjusted for HA and RES using TA127 trial data	In line with majority of previous appraisals. Lack of placebo arm in OPERA studies meant that trial data from TA127 was used to adjust for HA and RES subgroup.

				d vs non-hospitalised	d vs non-hospitalised		for EDSS 6-9		
Source of MS mortality multiplier	Not applied	Pokorski et al	Pokorski et al, extrapolated for EDSS states	As per TA254	As per TA254	As per TA254	As per TA254	As per TA254	In line with majority of previous appraisals
Application of treatment effect	NR	- ARR - CDP-24 - SPMS transition (50%)	- ARR - CDP-12	- ARR - CDP-12 - SPMS transition (50%)	- ARR - CDP-24 - SPMS transition (50%)	- ARR - CDP-24	- ARR - CDP-24 (if available, otherwise CDP-12)	- ARR - CDP-12 - SPMS transition (50%)	CDP-12 was considered more robust than CDP-24 due to quality and amount of data in MTC (see Section B.2.9).
Treatment waning effect	Not applied	Not applied	50% waning after 5 yrs	25% waning after 2 yrs and 50% after 5 yrs	25% waning after 2 yrs and 50% after 5 yrs, time-dependent rate of re-treatment	25% waning after 2 yrs and 50% after 5 yrs	25% waning after 2 yrs and 50% after 5 yrs	Not applied	See argumentation in Sections B.2.12 and B.3.3 for not applying treatment waning in the base case. Impact of potential treatment waning is explored in scenario analyses.
Application of treatment withdrawal	Trial data, assumed higher for yr 1-2 than yr 2+	Trial data, constant annualised rates for 10 years	Trial data (discontinuation due to AEs), constant annualised rates	Trial data (all-cause discontinuation), constant annualised rates for yr 1-2, 50% applied for yr 2+	Trial data (all-cause discontinuation), constant annualised rates for yr 1-2, 50% applied for yr 2+	Trial data (all-cause discontinuation), constant annualised rates	Trial data (all-cause discontinuation rates yr 1, 2, 3), yr 3+ based on yr 3 rate	As per TA320	Constant withdrawal rates were assumed based on long-term nature of safety concerns with majority of DMTs.

Stopping rule	- EDSS ≥7 - SPMS transition (scenario)	- EDSS ≥7 - SPMS transition	As per TA127	As per TA127	As per TA127	As per TA127	As per TA127	As per TA127	In line with ABN clinical guidelines and previous appraisals
Source of patient utilities	Kobelt et al 2000	UK MS Survey 2005 (later published by Orme et al, 2007)	As per TA127	Trial data and Orme et al, 2007	Trial data and Orme et al, 2007	Trial data and UK MS Survey 2005 (published by Orme et al, 2007)	BOI study, 2015 (not published)	Trial data and Orme et al, 2007	In line with majority of previous appraisals
Source of relapse disutility	Parkin et al, 2000	UK MS Survey 2005 (later published by Orme et al, 2007), adjusted with trial data for EDSS specific disutilities	Orme et al, 2007	Orme et al, 2007 (non-hospitalised), Prosser et al 2003 (hospitalised)	Orme et al, 2007 (non-hospitalised), Prosser et al 2003 (hospitalised)	UK MS survey, 2005 (published by Orme et al, 2007)	BOI study, 2015 (not published)	Orme et al, 2007	In line with majority of previous appraisals
Source of caregiver disutility	Not applied	Loveman et al, 2006 and UK MS survey data	As per TA127	As per TA127	As per TA127	As per TA127	Maximum disutility reduced	As per TA127	In line with majority of previous appraisals
Source of EDSS cost	Kobelt et al 2000, direct costs for EDSS 0-7, direct + indirect costs for EDSS 8-9	UK MS Survey 2005, direct medical and non-medical (NHS & PSS) (later published by Tyas et al, 2007)	As per TA127	Tyas et al, 2007 (direct medical and mid-point of non-medical)	Tyas et al, 2007 (direct medical only)	UK MS survey, 2005 (direct medical only)	BOI study, 2015 (not published), direct medical and partial non-medical)	Tyas et al, 2007 (direct medical and partial non-medical)	In line with majority of previous appraisals
Source of relapse cost	NR	UK MS survey, 2005 (later published by	Tyas et al, 2007	Dee et al, 2012	Dee et al, 2012	NR	BOI study, 2015 (not published)	As per TA254	In line with majority of previous appraisals

		Tyas et al, 2007)							

NR, not reported

B.3.2.3 Intervention technology and comparators

As per the NICE scope for ocrelizumab, the economic model allows comparisons with the following technologies:

- IFNB-1a (Avonex, Rebif)
- pegIFNB-1a (Plegridy)
- IFNB-1b (Betaferon)
- glatiramer acetate (Copaxone)
- teriflunomide (Aubagio)
- dimethyl fumarate (Tecfidera)
- fingolimod (Gilenya) [in ITT and HA subgroup]
- alemtuzumab (Lemtrada) [in ITT, HA, and RES subgroups]
- natalizumab (Tysabri) [in ITT and RES subgroup]
- daclizumab (Zinbryta) [in ITT, HA, and RES subgroups, subject to EMA restriction]

The intervention and comparators are implemented in the economic analysis as per their marketing authorisation.

Discontinuation rules

The ABN clinical guideline and the NHS England Commissioning Policy for DMTs in MS states that treatment should be stopped if patients have confirmed SPMS or are unable to walk (56, 58). The economic analysis therefore applies a stopping rule at EDSS 7 (patients restricted to wheelchair) or conversion to SPMS, in line with previous NICE appraisals in RRMS (Table 25).

The point at which a patient is considered to have progressed to SPMS can be difficult to define in routine practice. It is commonly defined in retrospect due to the unpredictable nature of the MS disease course. A majority of patients experience a period of overlap between relapsing-remitting and relapsing progressive disease and even at an individual patient level the duration of relapses and the rate of disease progression can vary substantially.

The economic model does not differentiate between relapsing and non-relapsing SPMS health states, due to lack of data in these disease sub-types. Therefore, the model assumes that DMT treatment is discontinued upon progression to SPMS, in line with the clinical guidance described above.

B.3.3 Clinical parameters and variables

Whenever possible, patient level data from the OPERA I and II trials were used to inform clinical parameters and variables in the economic analysis. Further information regarding these trials is presented in depth in Section B.2.6.and Appendix D.1.4.

Baseline patient characteristics

Patient level data from the pooled OPERA I and II trials were used for baseline EDSS distribution, age, and gender (Table 26). Demographic data for the HA and RES subgroups were also assessed and found to be similar to the intention-to-treat (ITT) data. These data are reported below, however, given the similarity between the subgroups and ITT, baseline demographic data for the subgroups have not been incorporated into the model.

The impact of applying UK specific baseline patient characteristics from the MS Risk Sharing Scheme is explored in scenario analysis.

Table 26: Baseline patient characteristics used in model (ITT)

Characteristic		ITT population n=1656	HA subgroup n=283	RES subgroup n=221
Age (years)		37	38	35
Gender (% male)		34	35	32
EDSS (%)	0	3.1	1.8	2.4
	1	18.8	15.2	19.3
	2	30.4	30.4	30.7
	3	23.5	23.0	23.1
	4	14.7	17.3	15.2
	5	8.8	11.7	8.6
	6	0.6	0.7	0.7
	7	0.0	0.0	0.0
	8	0.0	0.0	0.0
	9	0.0	0.0	0.0

* Numbers may not sum up to 1 due to rounding.

Disability progression in RRMS

Due to the chronic, lifetime nature of MS and the relatively short duration of trials, the most robust way to estimate natural history is to use real-world longitudinal observational data, i.e. registry data. The most commonly used sources of long-term natural history on disease progression in MS are the British Columbia and the London Ontario datasets, both from Canada (Table 27). The British Columbia dataset is more recent and more complete, but does not differentiate between RRMS and SPMS patients. The key limitation of the London Ontario dataset is that disability data had been retrospectively smoothed to remove

improvements in EDSS. Clinical expert opinion confirms that improvements in EDSS are seen in routine practice in RRMS and SPMS patients.

The British Columbia dataset was the preferred source of natural history in the most recent NICE appraisals and is applied in the model base case for transition probabilities in RRMS (Table 28). The impact of using the London Ontario dataset is explored in scenario analysis (Table 29). As the OPERA studies were both active-controlled studies there is no trial evidence from a placebo arm available to supplement the registry data in scenario analysis.

Table 27: Key differences between natural history datasets

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

For the purpose of the risk sharing scheme (RSS), patients with active disease as per British clinical guidelines (defined as: EDSS≤6.5; ≥18 years old; two relapses in the last 2 calendar-years) were identified in the British Columbia database (Palace et al, 2014). Patient data was not truncated if SPMS was reached. Furthermore, patients with a SPMS diagnosis at baseline (15.7%) were not removed from the analysis set, nor was a covariate for MS diagnosis added to the statistical model. The UK RSS group believe that SPMS is a later stage of the relapsing remitting form of disease and the transition has considerable overlap and, therefore, data from both RRMS and SPMS patients are used to inform the transition matrix.

Table 28: Natural history RRMS and SPMS disability progression transition matrix (ITT, British Columbia dataset, base case)

		EDSS state in following year									
	EDSS	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. Underlined values have been adjusted to allow rows to sum up to 1.

Table 29: Natural history RRMS disability progression transition matrix (ITT, London Ontario dataset, scenario analysis)

		EDSS state in following year									
	EDSS	0	1	2	3	4	5	6	7	8	9
Current EDSS state	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	N/A	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	N/A	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	N/A	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	N/A	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	N/A	0	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
	7	N/A	0	0	0	0	0	0	[redacted]	[redacted]	[redacted]
	8	N/A	0	0	0	0	0	0	0	[redacted]	[redacted]
	9	N/A	0	0	0	0	0	0	0	0	[redacted]

In line with the preference of previous NICE committees, a transition probability matrix reflecting more active/severe patients was applied in the model for the RES and HA subgroups. The manufacturer submission for the natalizumab NICE appraisal (57) includes a natural history matrix for the subgroup of patients with RES based on the placebo arm of the AFFIRM phase 3 study. Due to lack of a published transition matrix for the HA subgroup, the RES matrix from the natalizumab manufacturer submission is also applied to the HA subgroup in the model. As data for EDSS states 7 onwards are not available from the AFFIRM study, these have been imputed using data from the British Columbia matrix.

It should be noted that the subgroup transition matrix is informed by very few patients/EDSS measurements (given the size of the subgroup in the clinical trial) and is considered less robust than the ITT analysis. The impact of using ITT transition matrices for the subgroups is explored in scenario analysis.

Table 30: Natural history RRMS disability progression transition matrix for RES subgroup

		EDSS state in following year									
	EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Current EDSS state	0	0.2299	0.1670	0.4250	0.1040	0.0600	0.0120	0.0020	0.0001	0.0000	0.0000
	1	0.0700	0.1084	0.5110	0.1560	0.1190	0.0280	0.0070	0.0005	0.0001	0.0000
	2	0.0300	0.0860	0.4997	0.1730	0.1560	0.0420	0.0110	0.0017	0.0005	0.0000
	3	0.0170	0.0600	0.3930	0.1619	0.2410	0.0820	0.0310	0.0103	0.0036	0.0003
	4	0.0070	0.0320	0.2530	0.1710	0.2999	0.1360	0.0680	0.0258	0.0067	0.0006
	5	0.0030	0.0120	0.1710	0.1480	0.3460	0.1254	0.1360	0.0388	0.0188	0.0010
	6	0.0010	0.0070	0.0760	0.0930	0.2830	0.2210	0.1620	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: (57)

The MTC (Section B2.9) is the source for treatment effect on disease progression. The effects of treatment are handled in the model by an instantaneous hazard rate relative to that of patients not on treatment in the RRMS natural history dataset. The MTC was conducted for both ITT population and HA and RES subgroups; subgroup MTC data is applied to the RES subgroup natural history.

In line with several previous NICE appraisals in RRMS (Table 25), treatment effect as expressed by CDP-12 is applied in the base case economic model. MTC data for CDP-12 is more robust than CDP-24 due to it being reported in more studies (see Section B.2.9). The effect of using CDP-24 is explored in sensitivity analysis.

Conversion from RRMS to SPMS

In clinical practice, many patients transition from an RRMS disease course to an SPMS disease course as duration of disease increases. This is an important aspect of the disease to capture as these patients experience different outcomes to RRMS patients. In previous NICE appraisals conversion to SPMS is a DMT stopping rule. As per clinical definition and understanding of SPMS, once a patient has become an SPMS patient, conversion back to RRMS is not possible in the model. Similarly to previous NICE appraisals in RRMS, it is assumed that a patient's EDSS state increases by 1 when a patient transitions from RRMS to SPMS and this is applied to both ITT and HA and RES subgroups.

The London Ontario dataset has been used to generate estimates of patients progressing from RRMS to SPMS by EDSS state (Table 25). These data have also informed previous NICE appraisals in RRMS. Transitions from EDSS 0 are not available in the London Ontario

dataset. The risk of conversion from RRMS to SPMS is assumed to be dependent on EDSS, and is therefore assumed to be similar in ITT, HA, and RES populations.

Table 31: Natural history transition probabilities for RRMS - SPMS (London Oratorio dataset)

EDSS	Probability of conversion to SPMS during following year
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]

Consistent with the natalizumab NICE appraisal, 50% of the CDP treatment effect is applied to the conversion from RRMS to SPMS in the ITT population and HA and RES subgroups. No treatment effect is applied to transitions between EDSS states in SPMS as active treatment is assumed to be discontinued in SPMS patients.

Disability progression in SPMS

The British Columbia dataset included both RRMS and SPMS (15.7% at baseline) patients to inform the transition matrix. Separate transitions for SPMS patients are not available from the Palace et al 2014 study. In the base case model the British Columbia transition matrix is used to reflect transitions between EDSS states in both RRMS and SPMS patients (Table 28).

Due to lack of evidence to the contrary, disability progression in SPMS was assumed to be similar regardless of rate of progression in RRMS prior to conversion to SPMS, i.e. active or HA / RES RRMS.

In scenario analysis the London Ontario dataset is used to explore the impact of using different estimates of transition probabilities for RRMS versus SPMS patients (Table 32).

Table 32: Natural history SPMS disability progression transition probabilities (London Ontario dataset, scenario analysis)

		EDSS state in following year									
	EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Current EDSS state	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	N/A	N/A	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	N/A	N/A	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	N/A	N/A	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	N/A	N/A	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
	7	N/A	N/A	0	0	0	0	0	[redacted]	[redacted]	[redacted]
	8	N/A	N/A	0	0	0	0	0	0	[redacted]	[redacted]
	9	N/A	N/A	0	0	0	0	0	0	0	[redacted]

Relapse rates

As the OPERA studies were active-controlled trials, there is no trial data available for relapse rate in a placebo arm, and neither was data collected retrospectively on relapse rate during 12 months prior to enrolment in the studies. For natural history on relapse rates by EDSS stage, the most commonly used approach in previous NICE appraisals is to combine data from (130) and the UK MS Survey reported in the natalizumab NICE submission (TA127) (57) , and this methodology is followed here. The relapse rates by disease duration from Patzold et al 1982 (Table 33) are multiplied with EDSS distribution by disease duration from the UK MS Survey (Table 34) to derive ARR per EDSS state (Table 35). In general, as EDSS increases patients experience fewer relapses and SPMS patients have lower relapse rates than RRMS patients.

Table 33: ARR per year since diagnosis

Years since diagnosis	ARR
1	1.85
2	1.10
3	1.00
4	0.85
5	0.65
6-7	0.75
8-9	0.25
10-11	0.60
12-13	0.28
14-15	0.30
16+	0.20

Source: reproduced from TA127 manufacturer submission (Patzold et al 1982) (57)

Table 34: Number of patients per EDSS state by year since diagnosis

Years since diagnosis	1	2	4	4	5	6-7	8-9	10-11	12-13	14-15	16+
RRMS											
EDSS 0	2	2	1	2	6	6	3	2	0	1	3
EDSS 1	11	16	18	11	16	22	15	10	3	10	18
EDSS 2	11	16	7	17	14	13	19	19	9	5	22
EDSS 3	6	4	4	5	7	9	4	1	5	6	6
EDSS 4	6	15	7	12	13	24	8	13	6	2	17
EDSS 5	2	5	12	9	13	18	11	10	4	7	23
EDSS 6	2	3	3	5	2	6	11	2	2	6	20
EDSS 6.5	1	0	2	0	3	3	4	1	2	2	9
EDSS 7	1	0	0	0	0	0	1	1	1	0	3
EDSS 8	0	0	0	0	1	2	1	0	0	0	1
EDSS 9	1	0	0	0	0	0	0	0	0	0	1
SPMS											
EDSS 2	0	0	0	1	2	2	0	0	0	0	5
EDSS 3	2	0	1	1	0	4	0	1	1	0	1
EDSS 4	1	2	3	3	0	6	6	2	6	1	7
EDSS 5	6	6	5	6	7	14	17	15	10	11	35
EDSS 6	3	5	8	14	11	20	23	21	17	14	74
EDSS 6.5	2	1	3	4	5	18	16	11	19	12	78
EDSS 7	0	1	0	0	3	8	10	9	7	8	63
EDSS 8	0	0	0	0	3	5	4	7	4	5	46
EDSS 9	0	0	0	0	0	1	2	1	2	0	2

Source: reproduced from TA127 manufacturer submission (MS Survey 2005) (57)

Table 35: ARR by EDSS state (ITT analysis)

EDSS	RRMS	SPMS
0	0.709	0
1	0.729	0
2	0.676	0.465
3	0.720	0.875
4	0.705	0.545
5	0.591	0.524
6	0.490	0.453
7	0.508	0.340
8	0.508	0.340
9	0.508	0.340

Source: reproduced from TA127 manufacturer submission (57)

In line with the natalizumab appraisal, different relapse rates per EDSS state are applied to the HA and RES subgroups which are defined by more active disease in terms of frequency of relapses. In the natalizumab AFFIRM study the average relapse rate in the placebo arm in the RES subgroup was 1.98 times higher than in the ITT population. The relapse rates in the

RES subgroup are multiplied accordingly to derive rates that reflect more active disease (Table 36).

Table 36: ARR by EDSS state in RES and HA subgroups

EDSS	RRMS	SPMS
0	1.407	0
1	1.448	0
2	1.343	0.923
3	1.430	1.738
4	1.400	1.083
5	1.173	1.041
6	0.972	0.900
7	1.009	0.676
8	1.009	0.676
9	1.009	0.676

Source: reproduced from TA127 manufacturer submission (57)

The MTC is the source for treatment effect on relapse rates (Section B2.9). Relative risks derived from the MTC were applied (multiplicatively) to the natural history relapse rate to give a treatment relapse rate per EDSS per patient.

The duration of a relapse, 46 days, was sourced from the ScHARR model for the appraisal of beta interferons and glatiramer acetate (131) and has been used by the majority of appraisal since.

Mortality

Mortality was based on the general population, with the application of adjustable MS-specific mortality multipliers by EDSS. All-cause mortality rates for the general population were obtained from national life tables for England and Wales from 2013–2015 (132). A weighted average of the general population all-cause mortality rate is calculated based upon the female to male ratio of MS patients used in the model.

Mortality multipliers are taken from those used in previous NICE submissions. The original data are from a Canadian study (133) as reported by (134). The Canadian study included 2,348 patients followed in MS specialty clinics between 1972 and 1985. MS patients were categorised as mild (EDSS ≤3.5), moderate (EDSS 4-7) and severe (EDSS ≥7.5) and reported a 160%, 184% and a 444% increase in the mortality, respectively. The fingolimod manufacturer submission to NICE (135) generated an equation to predict excess mortality for individual EDSS scores and this has been used in NICE MS appraisals ever since.

The resulting relative risks by EDSS state are provided in Table 29. The mortality multipliers are applied to the all-cause weighted average mortality rates to derive the risk of mortality of RRMS and SPMS patients in different EDSS states. The assumption was made that mortality per EDSS would not differ for SPMS patients or for patients with more active disease (HA and RES subgroups). Finally, mortality rates are converted to annual probabilities of mortality by EDSS. The probability of mortality per cycle is dependent on the starting age of the cohort.

No direct treatment effect on mortality is assumed; however, there will be an indirect impact on mortality of applying treatment effects to disability progression as mortality is EDSS dependent.

Table 37: MS mortality multipliers by EDSS

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

Source: TA254 manufacturer submission (135)

Treatment withdrawal

The MTC (Section B2.9) is the source for all-cause discontinuation of treatment. All-cause discontinuation includes withdrawal due to adverse events or lack of efficacy. The output of the MTC for treatment withdrawal is an odds ratio. The following process is used to generate annual probabilities of withdrawal for each treatment (Table 38):

1. Baseline withdrawal probability for ocrelizumab, converted to odds ratio
    a. As a reference point the probability of withdrawal from ocrelizumab was taken from the OPERA studies: 99 out of 825 patients treated with ocrelizumab withdrew from study drug by the end of the 96 week controlled period (12% withdrawal probability) (see Appendix D.1.2)
2. Apply the relative treatment odds ratios to baseline odds ratio
    a. Odds ratios for each treatment versus ocrelizumab were sourced from the MTC and multiplied with the baseline odds ratio for ocrelizumab
3. Convert odds ratios for each treatment back to probabilities, adjust to annual probabilities

The annual withdrawal rates were assumed to be constant and were applied to each year of the model time horizon. This assumption is considered valid because experience with DMTs has shown that intolerance / AEs can occur either soon after start of treatment (e.g. infusion related reactions) or can develop years later (e.g. thyroid disease). Furthermore, withdrawal due to lack of efficacy is suggested to show a similar dynamic, with early withdrawal

occurring in non-responders and late withdrawal occurring after development of drug resistance.

All-cause discontinuation data from the ITT MTC data was applied to the HA and RES subgroups due to lack of published subgroup data. The underlying assumption is that treatment withdrawal does not differ in these patient populations.

Table 38: Annual probabilities of treatment withdrawal

DMT	All-cause discontinuation (%)
PegIFNB-1a	13.11
IFNB-1a (Rebif)	10.64
IFNB-1a (Avonex)	9.34
Teriflunomide	7.89
Dimethyl fumarate	6.98
Glatiramer acetate	6.48
Fingolimod	6.30
Ocrelizumab	6.19
IFNB-1b (Betaferon)	5.39
Alemtuzumab	3.00
Natalizumab	2.21

On withdrawal patients are assumed to follow the same transition probabilities as those assigned to BSC.

Treatment effect waning

Waning of long-term treatment effect has been the topic of long-standing discussion at NICE appraisals ever since the first DMTs were approved. The relatively short trial durations compared with a lifetime of disease, and the occurrence of anti-drug neutralising antibodies in a considerable proportion of patients in the early DMT trials has often led NICE committees to consider a scenario or base case with waning of treatment effect due to drug resistance or other factors. Most previous NICE committees have concluded that the plausible ICER range is somewhere between excluding and including waning assumptions. The usual treatment waning assumptions applied across several appraisals is 25% waning after end of trial duration [usually 2 years], and 50% waning after 5 years. No treatment waning scenario was considered in the natalizumab appraisal.

No waning of long-term treatment effect has been assumed in the base case model due to the following reasons (see Section B.2.12):

1. Ocrelizumab generates negligible neutralising antibodies, unlike other DMTs (see Table 24).

2. Ocrelizumab has demonstrated sustained treatment effect across different timepoints and different outcomes in the open label extension study (see Appendix D.1.4).

3. Pre-clinical investigations suggest that ocrelizumab also decreases inflammation of the innate immune system which, together with the effects of ocrelizumab seen on the adaptive immune system, may reduce the probability of a treatment waning effect.

In addition, as various treatment options with different mechanisms of action are available to patients with RRMS today, patients in routine practice are assumed to switch to a different therapy if lack of durable response becomes apparent in the long-term instead of staying on the same treatment. Assumptions about treatment waning therefore do not reflect what would likely happen in routine practice if a patient perceives a reduction in clinical benefit from a DMT. Due to lack of an established treatment pathway in RRMS, economic models for submission to NICE have generally not been designed to enable sequencing of treatments, and instead patients are assumed to receive BSC after treatment discontinuation due to any cause including perceived lack of efficacy.

For the above reasons a scenario that includes waning of treatment effect lacks clinical plausibility for ocrelizumab. Nonetheless it is included in scenario analysis for comparison due to the precedents set by previous NICE appraisals. As OLE data shows sustained effect of ocrelizumab up to 4 years, 25% waning is applied in years 5-7 and 50% in years 8+.

Adverse events

Similar to the daclizumab submission to NICE, AEs with occurrence of ≥5% in either arm in the pooled analysis of OPERA I and II were included in the economic analysis (Table 21). The rates of AEs in the 2-year studies were converted to annual risk of AEs (Table 39). The recent daclizumab manufacturer submission to NICE conducted a MTC for AEs and these data were used to source the annual risk of AEs for the comparators. As IFNB-1a (Rebif) is common between the OPERA studies and the daclizumab MTC, the ocrelizumab AE rates were adjusted using an AE rate ratio estimated from AE rates for IFNB-1a (Rebif) from the daclizumab submission and pooled analysis of OPERA I and II (Table 40).

In the daclizumab appraisal PML was added as an AE because it has an occurrence of ≥2% with natalizumab treatment and is a high-cost complication resulting in considerable disutility. Other AEs resulting in high costs and disutilities with alemtuzumab treatment, like renal failure, were not included as the rates were low and the ERG report concluded that these had little impact on the cost-effectiveness results.

The annual risk of AEs is assumed to be constant and applied to each year of the model time horizon. This assumption is supported by long-term experience with DMTs which has shown that AEs can occur either soon after start of treatment (e.g. infusion related reactions) or can develop years later (e.g. PML or thyroid disease).

Due to lack of reported safety data in HA and RES subgroups, the assumption is made that adverse events are no different in subgroup populations compared with ITT.

Table 39: Adverse events for ocrelizumab included in model

	Ocrelizumab		IFNB-1a	
AE, %	**2-year probability**	**Yearly probability**	**2-year probability**	**Yearly probability**
Arthralgia	5.6	2.8	6.2	3.1
Back pain	6.4	3.3	4.5	2.3
Bronchitis	5.1	2.6	3.5	1.8
Depression	7.8	4.0	6.5	3.3
Fatigue	7.8	4.0	7.7	4.0
Headache	11.3	5.8	15.0	7.8
Influenza-like illness	4.6	2.3	21.4	11.4
Infusion related reaction	34.3	18.9	9.7	5.0
Injection site pain	0.1	0.2	5.4	11.0
Insomnia	5.6	2.8	4.6	2.3
Nasopharyngitis	14.80	7.7	10.2	5.2
Upper respiratory tract infection	15.20	7.9	10.5	5.4
Urinary tract infection	11.60	6.0	12.1	6.2
Sinusitis	5.6	2.8	5.4	2.8

Table 40: Summary of adverse events applicable in economic analysis

AEs	ALEM	DAC	DMF	FINGO	GA*	IFNB-1a (Avonex)	IFNB-1a (Rebif)	IFNB-1b	NAT	OCR	pegIFNB-1a	TERI
Arthralgia	-	3.4	-	3.5	5.1	3.8	6.2	7.2	10.0	2.3	12.1	-
Back pain	-	4.1	5.4	5.5	5.0	4.1	4.5	6.0	-	5.2	12.9	5.3
Bronchitis	-	2.9	-	4.2	-	2.3	3.5	-	-	5.1	-	-
Depression	-	3.8	3.7	4.3	5.3	7.5	6.5	9.0	10.0	13.1	-	-
Fatigue	8.4	3.2	5.7	8.1	8.4	10.3	7.7	13.1	14.5	12.0	10.8	6.4
Headache	22.5	8.1	8.2	16.6	9.7	15.0	15.0	16.9	21.2	7.7	46.6	11.3
Influenza-like illness	1.5	4.3	-	3.5	-	24.4	21.4	-	-	2.6	-	-
Infusion related reaction	-	-	-	-	-	-	9.7	-	-	34.3	-	-
Injection site pain	-	4.7	-	-	15.6	5.0	20.8	4.3	-	0.4	-	-
Insomnia	-	-	-	-	-	-	4.6	-	-	5.6	-	-
Nasopharyngitis	13.4	11.9	9.8	16.1	9.4	13.3	10.2	9.6	-	10.8	11.2	13.3
PML	-	-	-	-	-	-	-	-	2.1	-	-	-
Sinusitis	-	-	-	-	-	-	5.4	-	-	5.6	-	-
Upper respiratory tract infection	8.2	7.5	5.6	16.6	4.7	6.1	10.5	4.5	-	6.4	-	-
Urinary tract infection	10.2	4.6	8.2	5.9	5.2	4.9	12.1	5.3	10.5	3.1	-	3.6

Source: MTC from daclizumab manufacturer submission (53) and pooled analysis OPERA I and II (83)
*Based on 20mg dose.
Abbreviations: AEs, adverse events; ALEM, alemtuzumab; ALT, alanine aminotransferase; DAC, daclizumab; DMF, dimethyl fumarate; FINGO, fingolimod; GA, glatiramer acetate; IFNB, interferon beta; NAT, natalizumab; OCR, ocrelizumab; PML, progressive multifocal leukoencephalopathy; TERI, teriflunomide

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life data collected in the trials was consistent with the NICE reference case. EQ-5D-3L was collected in OPERA I and II at baseline and at weeks 48 and 96. No statistically significant differences were observed between treatment arms and EQ-5D data was therefore pooled. The UK value set as described by Dolan et al (136) was used to translate the patient measurements into preferences from the perspective of the UK general public. For the purpose of the economic analysis the EQ-5D values were linked to EDSS states by regression analysis (Table 32). The regression model included EDSS state, relapse event within the 30 days prior to assessment, region of world, age and gender as variables (see Appendix H.1.5 for details).

The distribution of EDSS states during the duration of the OPERA studies ranged from 0-7. However, EQ-5D data for EDSS state 7 are associated with considerable uncertainty due to the small number of observations at this advanced state (n=4). No EQ-5D data is available from the OPERA studies for EDSS states 8 and 9 as patients with advanced disease were not included in the study. Further details on the application of utilities for advanced EDSS states and SPMS are described in B.3.4.5.

The HA and RES subgroups were assumed to have similar HRQoL by EDSS states as ITT population.

Table 41: Utility values from OPERA studies

Health state	Mean	95% CI	Standard error	Assessments / patients (n)
EDSS 0	0.8809	0.851, 0.911	0.0154	197 / 102
EDSS 1	0.8438	0.830, 0.858	0.0072	1145 / 481
EDSS 2	0.7699	0.758, 0.782	0.0061	1524 / 673
EDSS 3	0.7048	0.691, 0.718	0.0069	1135 / 540
EDSS 4	0.6438	0.627, 0.661	0.0088	714 / 333
EDSS 5	0.6003	0.575, 0.626	0.0130	307 / 157
EDSS 6	0.4909	0.451, 0.531	0.0205	100 / 54
EDSS 7	0.4387	0.245, 0.633	0.0989	4 / 2
Relapse	–0.1006	-0.140, -0.061	0.0201	64

Regression model settings: mix of 75% rest of world and 25% USA, 66% Female - 34% Male population, Age 37, no relapse

B.3.4.2 Mapping

Mapping was not required as EQ-5D was collected in the OPERA studies and various other sources of EQ-5D values in MS were identified in the literature.

B.3.4.3 Health-related quality-of-life studies

A SR was conducted in March 2016 and updated in March 2017 to identify health-related quality of life studies appropriate for application in economic analysis. A total of 51 studies were identified reporting health state utility values (HSUV) for patients with MS according to EDSS score (43 full publications and 8 abstracts). Of these, 28 studies were consistent with the NICE reference case; however 4 of these only contained two EDSS data points and are not further described here (see appendix H).

The majority of relevant studies included a mixed population of patients with RRMS, SPMS, and PPMS (n=20 studies). A further two studies considered patients with RRMS only, and two studies included HSUV in RRMS, SPMS and PPMS patients separately.

Eight studies reported utility data for pooled EDSS health states, most commonly EDSS 0-3 (mild disability), EDSS 4-6 (moderate disability), and EDSS 7-9 (severe disability). A further 13 studies reported data for parts of the EDSS spectrum only. Only three studies reported data for the entire EDSS spectrum, two in the UK (123, 137) and one in Ireland (138). The 24 relevant studies with sufficient health-related quality of life data are summarised in Appendix H.

A clear pattern was observed across the evidence base of decreasing overall utility with increasing EDSS score (Figure 34). Declining health-related quality of life was observed in mild disability health states (EDSS 0–3), relative stability or mild fluctuation in moderate disability health states (EDSS 4-6), and a significant decline in severe disability health states (EDSS 7–9), to the point of negative values corresponding to worse than death at EDSS 9.

Key differences between utilities from OPERA studies and the literature

As shown below, the trajectory of decreasing utility values per EDSS score in the pooled EQ-5D analysis of the OPERA studies was consistent with other studies that reported data for the same EDSS spectrum (EDSS 0–7 or more).

For the last 10 years there has been precedent in previous NICE appraisals in RRMS to use EQ-5D data elicited from patients via the MS Trust survey (123). To date this is the largest and most complete study among 2,048 patients with MS in the UK, and it includes separate

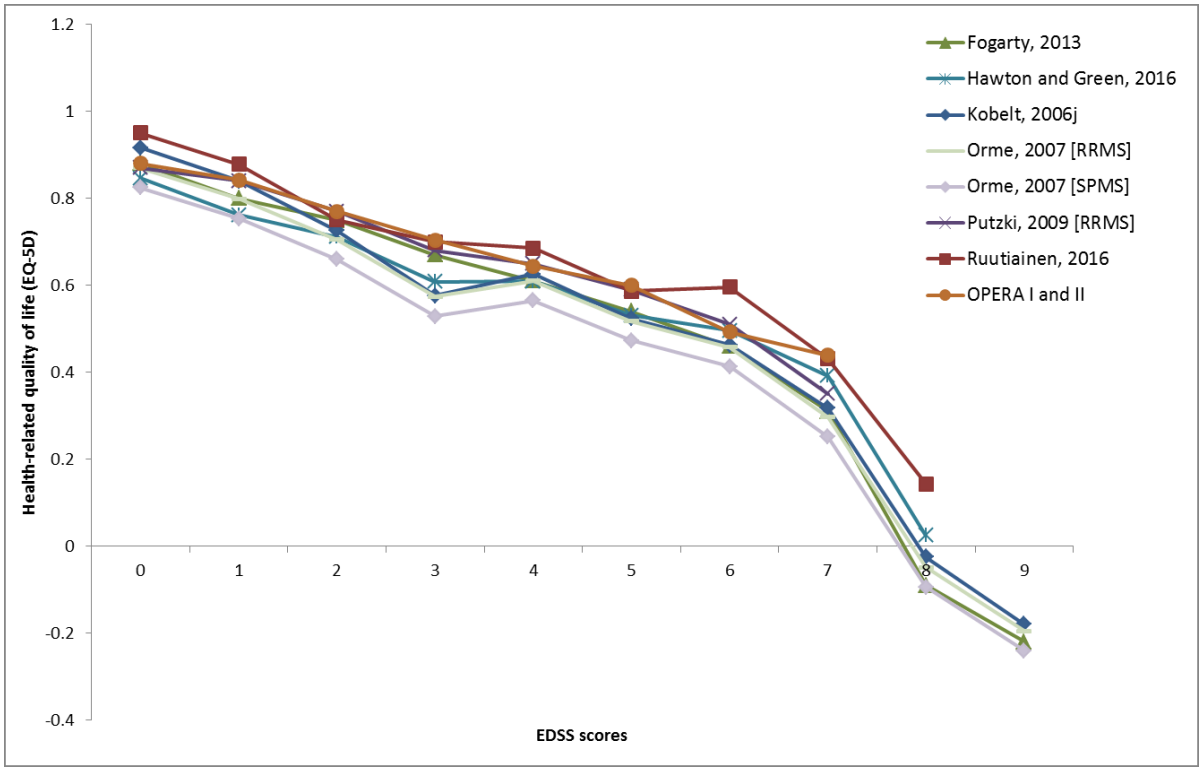
utilities for patients with RRMS versus SPMS. Its limitations have been well described in previous NICE appraisals.

The health state utility values (HSUV) from the OPERA studies are at the higher end of values found in the literature, but confidence intervals overlap with those of Orme et al which are at the lower end of the values found in the literature. This is likely due to the younger age at baseline in the OPERA trials (37 years) compared with patients included in the MS Trust survey reported by Orme et al (51 years).

In line with previous appraisals, utilities from the upper end of the EDSS spectrum were derived from Orme et al to supplement trial data (see Section B.3.4.5).

In scenario analysis the impact of using HSUV for RRMS and SPMS entirely derived from the MS Trust survey (Orme et al, 2007) is explored.

Figure 25: Consistency of EDSS-dependent utility values



B.3.4.4 Adverse reactions

Most of the disutilities associated with AEs and the duration of AEs were sourced from the recent daclizumab manufacturer submission to NICE. To supplement missing data, disutilities and duration of infusion related reactions, insomnia, and sinusitis were derived from the alemtuzumab manufacturer submission to NICE.

Table 42: Disutilities associated with adverse events

	Non-serious		Serious		
AE	**Disutility**	**Duration (days)**	**Disutility**	**Duration (days)**	**Average disutility***
Arthralgia	-0.25	10.5	-0.25	24.5	-0.0079
Back pain	-0.25	10.5	-0.5	24.5	-0.009
Bronchitis	-0.01	14	-0.01	14	-0.0004
Depression	-0.165	75	-0.56	365	-0.0702
Fatigue	0	182.5	0	182.5	0
Headache	-0.14	10.5	-0.493	24.5	-0.006
Influenza-like illness	-0.08	1	-0.08	1	-0.0002
Infusion related reaction	-0.0002	1	-0.0002	1	-5E-07
Injection site pain	0	7	0	7	0
Insomnia	-0.0002	1	-0.0002	1	-5E-07
Nasopharyngitis	0	7	0	14	0
PML	-0.3	365	-0.3	265	-0.3
Sinusitis	0	1	0	1	0
Upper respiratory tract infection	-0.2	7	-0.2	14	-0.0041
Urinary tract infection	-0.1	5	-0.1	5	-0.0014

Reproduced from daclizumab manufacturer submission (53) and alemtuzumab manufacturer submission (55)
* It is assumed that for each type of AE 93.1% are non-serious and 6.9% are serious, based on average proportion of SAEs in OPERA I and II pooled analysis.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Trial-based HRQL data were used to derive HSUV for RRMS in the base case economic analysis (Table 43). For the advanced health states that lack robust trial data (EDSS 7–9), utility decrements from the regression analysis of the MS Trust survey were applied (e.g. for EDSS 7, a decrement of -0.573 was applied to reference EDSS 0 [0.881] to derive 0.308) (123).

To derive HSUV for SPMS, the SPMS utility decrement (-0.045) from the regression analysis of the MS Trust survey was applied to the RRMS HSUV (123).

HRQoL impact per EDSS was assumed to be the same in HA, RES, and ITT populations.

In sensitivity analysis the impact of using HSUV for RRMS and SPMS entirely derived from the MS Trust survey (Orme et al, 2007) is explored.

Table 43: Health state utility values in economic analysis

	OPERA studies (pooled analysis), adjusted using Orme et al 2007	
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

Disutility associated with a relapse is important to incorporate in the economic analysis as it can have a profound impact on patients' HRQoL. Disutility for relapse (-0.071) was sourced from the literature (123) in line with previous appraisals and is applied in the economic analysis for the average duration of a relapse, 46 days, according to the original ScHARR model for the appraisal of beta interferons and glatiramer acetate (131). The average duration of a relapse is not assumed to vary in subgroups with more active disease (HA and RES).

The impact of applying disutility for relapse identified in regression analysis of the OPERA studies (-0.1006) is explored in scenario analysis. In addition, the impact of applying different relapse duration (1 or 2 months) is assessed in scenario analysis.

Caregivers of patients with MS experience a substantial burden, particularly as the patient become progressively more disabled. Previous NICE appraisals in RRMS have applied disutility for caregivers (Table 25). A maximum utility decrement of 0.014 was derived from studies in Alzheimer's disease and adjusted according to time spent by friends and family caring for a person with MS at different EDSS health states as derived from the UK MS survey (Table 44). As would be expected, disutility is minimal for EDSS states 0–6 but once a patient becomes reliant on a wheelchair (EDSS 7) and particularly once a patient is bed-bound (EDSS 8-9), the impact on the caregiver's HRQoL increases significantly.

Table 44: Caregiver disutility by EDSS state

EDSS	Caregiver disutility
0	0.000
1	-0.001
2	-0.003
3	-0.009
4	-0.009
5	-0.020
6	-0.027
7	-0.053
8	-0.107
9	-0.140

Source: TA127 manufacturer submission (57)

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

Several treatments in RRMS – daclizumab, dimethyl fumarate, fingolimod, teriflunomide, and ocrelizumab – are subject to confidential patient access schemes (PAS). In addition, several of the ABCRs – IFNB-1a (Rebif) and glatiramer acetate – are available to the NHS with commercial arrangements through the RSS. The drug acquisition costs listed in Table 45 are based on list prices for comparators and are therefore not a true reflection of the costs borne by the NHS.

Alemtuzumab is an induction therapy of two years, however 5-year follow up data of the pivotal phase 3 studies have shown that a considerable proportion of patients need additional courses of alemtuzumab or switch to other DMTs in subsequent years due to recurring disease activity (Table 46). Smaller scale observational studies in the UK have followed patients treated with alemtuzumab for longer term and show that some patients require re-treatment even after 10 years (139, 140).

The data presented in Tuohy et al 2015 was extracted to establish the follow-up time and re-treatment rates of 87 patients. To identify any trends in re-treatment rate per patient year varying over time, the rate of re-treatment per patient year of follow-up was estimated using varying amounts of follow-up through Poisson regression of the number of doses including log(patient years) as an offset. The results are illustrated in Figure 26 and suggest that the annualised re-treatment rate stabilizes after 6 years and stays constant for the remainder of the follow up period. Data recorded prior to 1.5 years of follow up was ignored as being part of the induction dosing regimen. Between 1.5–10 years of follow up there were 54 doses and

419 patient years; thus the re-treatment rate per 100 patient years for the entire period observed was 12.9 (95% CI 9.9, 16.8). This is broadly consistent with the rates observed in the extended follow up of Care MS I and Care MS II and supports application of alemtuzumab re-treatment rates for the entire model time horizon.

In line with the alemtuzumab manufacturer submission to NICE, the need for re-treatment has been taken into consideration in the base case model. For years 3-5 the average re-treatment rates from the CARE MS I and II follow up data were applied (19%, 16%, and 14% respectively), and for years 6+ the 13% re-treatment rate estimated from Touhy et al was used. Switching to other DMTs after failure on alemtuzumab was not accounted for in the model and adds to the uncertainty and likely underestimation of the long-term costs of alemtuzumab.

The treatments available in RRMS differ substantially in their modes of administration and monitoring requirements. A full description is provided in Table 47 and Table 48.

Resource use associated with administration and monitoring was based on the daclizumab manufacturer submission, supplemented with product-specific SmPC requirements and clinical expert opinion by a MS neurologist and MS nurse.

A summary of drug acquisition, drug administration, and monitoring costs for all interventions are provided in Table 49.

Table 45: Drug acquisition costs

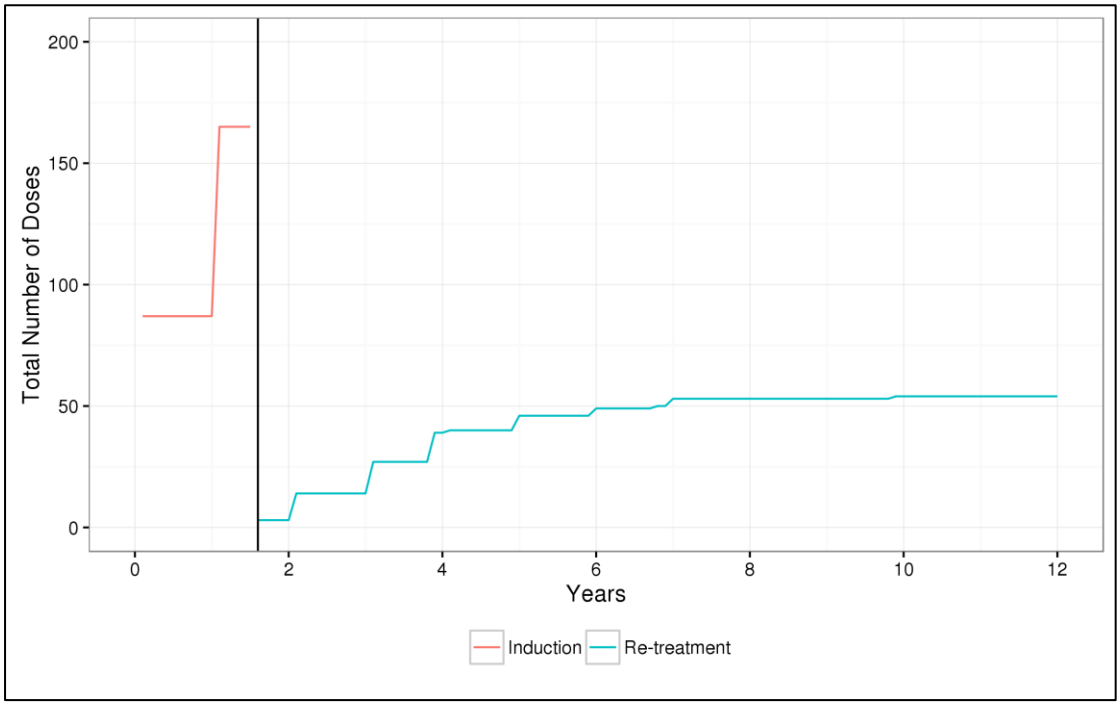
Drug	Dosage	Cost (£, list price)	
		Year 1	Year 2+
ALEM	12 mg/day for 5 days (year 1) or 3 days (year 2)	35225.00	21135.00
DAC	150 mg QM	19160.00*	19160.00*
DMF	120 mg BID for 7 days, then 240 mg BID	17898.00*	17898.00*
FINGO	0.5 mg QD	19162.50*	19162.50*
GA	20 mg QD or 40 mg TIW	6681.35*	6681.35*
IFNB-1a (Avonex)	30 mcg QW	8502.00	8502.00
IFNB-1a (Rebif)	44 mcg TIW	10571.73*	10571.73*
IFNB-1b	250 mcg QAD	7259.00	7259.00
NAT	300 mg Q4W	14690.00	14690.00
OCR	2 x 300 mg and then 600 mg Q6M	19160 [redacted]	19160 [redacted]
pegIFNB-1a	125 mcg Q2W	8502.00	8502.00
TERI	14 mg QD	13529	13529

Abbreviations: BID, twice daily; GA, glatiramer acetate; IFN, interferon; TIW, three times a week; QAD, every other day; QD, once daily; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; QM, every month; Q6M, every 6 months.
* Available with PAS or commercial access arrangement.

Table 46: Additional treatments required after alemtuzumab induction therapy

Source	CARE MS I 5-year follow up (75)		CARE MS II 5-year follow up (73)	
	Additional alemtuzumab courses	Other DMTs	Additional alemtuzumab courses	Other DMTs
Year 3	18.1%	0.6%	20.4%	2.8%
Year 4	12.3%	1.7%	18.9%	3.4%
Year 5	12.7%	1.2%	15.3%	3.0%

Figure 26: Long-term re-treatment with alemtuzumab



Source: (139)

Table 47: Resource use and cost associated with drug administration

Drug	Cost (£, year 1)	Resource use (year 1)	Cost (£, year 2+)	Resource use (year 2+)	Source
ALEM	2496.66	5 x IV administration (£494 day case each) Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95) Paracetamol 2x500 mg QD (£0.16) Aciclovir 200 mg BID for 28 days (£7.25)	1508.66	3 x IV administration (£494 day case each) Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95) Paracetamol 2x500 mg QD (£0.16) Aciclovir 200 mg BID for 28 days (£7.25)	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case British National Formulary MIMS
DAC	172.00	2 hours of MS nurse time to teach self-administration	0.00	None	Hospital based nurse band 5
DMF	130.00	1 hour of MS nurse time to answer telephone questions about AEs	0.00	None	Hospital based nurse band 7
FINGO	494.00	day case, 6 hours ECG and blood pressure monitoring	0.00	None	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case
IFNB-1a IFNB-1b pegIFNB-1a GA	172.00	2 hours of MS nurse time to teach self-administration	0.00	None	Hospital based nurse band 5
NAT	6422.00	13 x day case (£494 each)	6422.00	13 x day case (£494 each)	AA30F Day case Medical Care of Patients with Multiple Sclerosis, with CC score 0-1. Day case
OCR	1501.41	3x IV administration (£494 day case each) Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95)	1007.41	2x IV administration (£494 day case each) Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95)	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case British National Formulary MIMS

		Paracetamol 2x500 mg QD (£0.16)		Paracetamol 2x500 mg QD (£0.16)	
TERI	0.00	None (oral)	0.00	None	

Source: (141, 142)

Table 48: Resource use and cost associated with monitoring

Drug	Unit cost (£, year 1)	Resource use (year 1)	Unit cost (£, year 2+)	Resource use (year 2+)	Source
ALEM*	216.58 130.00 3.10 1.18 1.18 1.18 6.42 6.42 6.42 **1092.72**	1 neurology visit 12 MS nurse visits (30 min) 13 full blood counts 13 urinalysis 13 renal function tests 5 thyroid function tests 1 varicella zoster virus test 1 HPV test 1 tuberculin skin test **Total**	160.76 130.00 3.10 1.18 1.18 1.18 6.42 6.42 6.42 **1023.84**	1 neurology visit 12 MS nurse visits (30 min) 12 full blood counts 12 urinalysis 12 renal function tests 4 thyroid function tests 1 varicella zoster virus test 1 HPV test 1 tuberculin skin test **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 DAPS05, DAPS04, DAPS06
DAC	216.58 130.00 3.10 1.18 **374.32**	1 neurology visit 2 MS nurse visits (30 min) 4 full blood counts 13 liver function tests **Total**	160.76 130.00 3.10 1.18 **317.32**	1 neurology visit 2 MS nurse visits (30 min) 4 full blood counts 12 liver function tests **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 DAPS05, DAPS04
DMF	216.58 130.00 202.70 3.10 1.18 1.18 **574.22**	1 neurology visit 2 MS nurse visits (30 min) 1 MRI 5 full blood counts 4 liver function tests 4 urinary tests **Total**	160.76 130.00 3.10 1.18 1.18 **242.88**	1 neurology visit 1 MS nurse visits (30 min) 4 full blood counts 2 liver function tests 2 urinary tests **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 RD03Z. Magnetic Resonance Imaging Scan of one area, with pre and post contrast DAPS05, DAPS04

FINGO	216.58 130.00 202.70 3.10 1.18 90.64 6.42 **662.72**	1 neurology visit 2 MS nurse visits (30 min) 1 MRI 3 full blood counts 6 liver function tests 1 ophthalmology visit 1 varicella zoster virus test **Total**	160.76 130.00 3.10 1.18 **231.22**	1 neurology visit 2 MS nurse visits (30 min) 1 full blood counts 2 liver function tests **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 RD03Z. Magnetic Resonance Imaging Scan of one area, with pre and post contrast WF01B. Non-admitted Face to face attendance, first. 130 Ophthalmology. Consultant led outpatient attendance DAPS05, DAPS04, DAPS06
IFNB-1a (Avonex) IFNB-1b pegIFNB-1a	216.58 130.00 3.10 1.18 1.18 **368.42**	1 neurology visit 2 MS nurse visits (30 min) 4 full blood counts 4 liver function tests 4 urinary tests **Total**	160.76 130.00 3.10 1.18 1.18 **236.68**	1 neurology visit 2 MS nurse visits (30 min) 2 full blood counts 2 liver function tests 2 urinary tests **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 DAPS05, DAPS04
IFNB-1a (Rebif)	216.58 130.00 3.10 1.18 1.18 1.18 **369.60**	1 neurology visit 2 MS nurse visits (30 min) 4 full blood counts 4 liver function tests 4 urinary tests 1 thyroid test **Total**	160.76 130.00 3.10 1.18 1.18 **236.68**	1 neurology visit 2 MS nurse visits (30 min) 2 full blood counts 2 liver function tests 2 urinary tests **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 DAPS05, DAPS04
GA	216.58 130.00 **346.58**	1 neurology visit 2 MS nurse visits (30 min) **Total**	160.76 130.00 **225.76**	1 neurology visit 2 MS nurse visits (30 min) **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7
NAT	216.58 130.00 202.70	1 neurology visit 2 MS nurse visits (30 min) 2 MRI	160.76 130.00 145.34	1 neurology visit 2 MS nurse visits (30 min)	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance

	1.18 6.42 **767.18**	2 liver function tests 2 JCV tests **Total**	 1.18 6.42 **451.30** **596.64**	1 MRI (year 2), 4 MRIs (JCV+, 50% of pts, year 3+) 2 liver function tests 2 JCV tests **Total (year 2)** **Total (year 3+)**	Hospital based nurse band 7 RD03Z and RD03A. Magnetic Resonance Imaging Scan of one area, with pre and post contrast DAPS05, DAPS04, DAPS06
OCR	216.58 130.00 3.10 6.42 6.42 **365.62**	1 neurology visit 2 MS nurse visits (30 min) 2 full blood counts 1 HBV test 1 varicella zoster virus test **Total**	160.76 130.00 3.10 **296.96**	1 neurology visit 2 MS nurse visits (30 min) 2 full blood counts **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 DAPS05, DAPS04, DAPS06
TERI	216.58 130.00 3.10 1.18 6.42 **381.18**	1 neurology visit 2 MS nurse visits (30 min) 3 full blood counts 16 liver function tests 1 tuberculin skin test **Total**	160.76 130.00 3.10 1.18 **240.22**	1 neurology visit 1 MS nurse visits (30 min) 2 full blood counts 7 liver function tests **Total**	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance Hospital based nurse band 7 DAPS05, DAPS04, DAPS06

*Monitoring requirements continue for 4 years after treatment cessation

Source: (141, 142)

Table 49: Summary of drug acquisition, drug administration, and monitoring costs

Cost items (£)	ALEM	DAC	DMF	FINGO	GA	IFNB-1a (Avonex)	IFNB-1a (Rebif)	IFNB-1b	NAT	OCR	pegIFNB-1a	TERI
Drug acquisition, year 1	35225	19160	17898	19163	6681	8502	10572	7259	14690	19160 [redacted]	8502	13529
Drug acquisition, year 2+	21135*	19160	17898	19163	6681	8502	10572	7259	14690	19160 [redacted]	8502	13529
Drug administration, year 1	2497	172	130	494	172	172	172	172	6422	1501	172	0
Drug administration, year 2+	1509*	0	0	0	0	0	0	0	6422	1007	0	0
Monitoring cost, year 1	1093	374	574	663	347	368	370	368	767	366	368	381
Monitoring cost, year 2+	1024*	317	243	231	237	237	237	237	451 (year 2) 597 (year 3+)	297	237	240

Amounts are rounded up and drug costs are input at list price, except for ocrelizumab.
* Costs for years 3 and beyond are adjusted with proportion of patients requiring re-treatment.

B.3.5.2 Health-state unit costs and resource use

A SR was conducted to identify published evidence regarding the resource use and costs associated with the management and treatment of MS in the UK. Four studies were identified that reported resource use and costs by EDSS health states in line with the reference case for health and social care (NHS and PSS) (Table 41). Only one of these reported costs by the full EDSS spectrum 0–9 (125), and another reported costs by EDSS 0-8 only (116). The other two studies reported cost data for pooled EDSS health states, EDSS 0–3 (mild disability), EDSS 4–6 (moderate disability), and EDSS 7–9 (severe disability). One study reported costs by disease type (RRMS, SPMS, and PPMS) (125), the others were based on mixed patient populations with MS.

A clear trend was seen in the literature for increasing costs with increasing disability. In particular for patients with severe disability (EDSS 7–9) health and social care costs are high. The type of MS (RRMS or SPMS) also has an impact, with more progressive disease associated with higher costs.

The publication by Tyas et al 2007 is based on the MS Trust survey, and contains the most complete and robust data on resource use and costs of MS in the UK. In line with the majority of previous appraisals in RRMS this source has been used to derive health state costs for RRMS and SPMS (125).

The definition of what constitutes direct non-medical care, i.e. social care, was not consistent across studies or was unclear. What proportion of direct non-medical care in the MS survey falls under the NHS and PSS perspective has often been a point of discussion by previous Committees. The publication by Kobelt et al 2006 (137) is based on the MS survey like Tyas et al 2007, and provides more information on methodology and breakdown of items under direct non-medical costs. It indicates that around 25% of direct non-medical costs are services and investments likely borne by PSS and the rest are informal care costs (productivity loss by informal caregiver). In order to be consistent with the reference case, data from Tyas et al has been adjusted to include direct medical costs and 25% of direct non-medical costs in the base case economic model (inflated to 2016 using the PSSRU 2016 hospital & community health services inflation index). The impact of excluding direct non-medical costs altogether is explored in scenario analysis.

Further research was conducted to quantify the effect of disease severity (measured by EDSS) and type of MS (RRMS or SPMS) on the cost of MS care from a NHS and PSS perspective (BOUNDS-MS study). A retrospective cross-sectional database was utilised which collected data from neurologists, MS patients and their carers during the years 2010-

2016 (see Appendix M for more details about this research study). The main strength of the study was inclusion of resource use and cost data from recent years, hence it is expected to be reflective of today's management of MS in NHS/PSS. However, there were several key limitations of this study which precluded it from being applied in the base case. There was likely to be selection bias as only patients seen by a consulting neurologist were recruited into the study, as opposed to the general patient population reached through the national MS Survey. This resulted in small sample sizes and uncertain estimates at the higher end of the EDSS scale as these patients are generally no longer seen or treated by a neurologist. In addition, the number of resource use items and cost categories included in the study were more limited than the MS survey reported by Kobelt and Tyas, and this may have resulted in underestimation of the cost of management of MS. Due to these limitations this study is considered less robust than Tyas et al and its impact is explored in scenario analysis only.

The direct medical cost of a relapse reported in the literature varied widely depending on severity of relapse and study methodology. To ensure consistency with the source for cost of EDSS states and previous appraisals in RRMS, the study by Tyas et al was chosen to derive cost of relapse in the base case economic analysis (£1,623, before inflation to 2016 using the PPSRU 2016 hospital & community health services inflation index).

The impact of using a different source for cost of relapse is explored in scenario analysis, based on the average of costs reported by Hawton et al (£1,194).

Table 50: Summary of cost of relapse

Relapse type	Perspective	Cost (£)	Source
Relapse not treated with steroids	Health and social care	152	(116)
Relapse limiting everyday activities	Health and social care	328	
Relapse resulting in oral steroids	Health and social care	509	
Relapse resulting in IV steroids	Health and social care	1631	
Relapse resulting in hospital admission	Health and social care	3350	
Relapse requiring no steroid treatment or hospitalisation	Direct medical cost	1400*	(143)
Relapse requiring steroid treatment with/without hospitalisation	Direct medical cost	1800*	
Relapse	Direct medical cost, excl sick leave and informal care	561	(137)
Relapse	Direct medical cost	1623	(125)

* Read from graph using WebPlotDigitizer software

Table 51: Summary of annual EDSS health state costs

	0	1	2	3	4	5	6	7	8	9	Reference
Health and social care*	510 (931)	455 (789)	358 (582)	334 (485)	501 (706)	503 (699)	652 (1210)	658 (953)	1660 (1723)		(116)
Inpatient	70 (25-229)				54 (17-146)			1838 (758, 5191)			(143)
Outpatient	346 (200-754)				698 (435, 1103)			435 (106, 986)			
Consultations	578 (404, 838)				923 (745, 1192)			826 (334, 1609)			
Investigations	82 (56, 123)				74 (49, 109)			29 (0, 147)			
MS treatments	5369 (4494, 6270)				5499 (4682, 6351)			2098 (0, 10491)			
Prescribed & OTC medications	269 (205, 378)				851 (685, 1398)			832 (535, 1101)			
Total direct medical costs	6714 (5760, 7717)				8101 (7153, 9072)			6059 (2907, 10735)			
Investments/ modifications	48 (16, 226)				1457 (1127, 1761)			2989 (1168, 4433)			
Professional care	0				950 (6885, 11462)			16430 (16763, 54939)			
Informal care	1865 (789, 5321)				7893 (6115, 10237)			21824 (9957, 34697)			
Total direct non-medical costs	1913 (811, 5038)				10299 (8170, 12772)			41242 (17653, 59378)			
Direct healthcare costs**	5400				7000			7700			(137)
Services/ investments**	400				1200			9000			
Informal care**	1100				7000			25200			
Direct medical costs, RRMS	250 (-3623, 4123)	85 (-1678, 1849)	213 (-1489, 1915)	850 (-1575, 3275)	806 (-927, 2539)	1419 (-195, 3032)	2162 (492, 3832)	6583 (4632, 8534)	10761 (8665, 12857)	15121 (9912, 20330)	(125)
Direct medical costs, SPMS	530	365	493	1130	1086	1699	2442	6863	11041	15401	
Direct non-medical costs	2536 (-1745, 6817)	3462 (886, 6039)	4414 (1836, 6991)	6212 (3103, 9321)	4028 (1439, 6617)	6333 (3709, 8958)	6580 (3956, 9204)	10808 (7895, 13721)	15339 (12369, 18309)	10161 (4598, 15725)	

Amounts in table are in GBP (£).
* Costs reported on a 6-monthly basis not annual.
** Read from graph using WebPlotDigitizer software

B.3.5.3 Adverse reaction unit costs and resource use

Costs of treating AEs, consistent with annual risk of AEs, disutilities and durations of AEs, were mostly sourced from the recent daclizumab manufacturer submission to NICE (53). Resource use was based on a Delphi panel that the manufacturer conducted. Resource use and cost associated with treating infusion related reaction, insomnia, and sinusitis were derived from the alemtuzumab manufacturer submission. Costs were not inflated from the year these estimates were reported in the daclizumab and alemtuzumab submissions.

Table 52: Summary of AE management costs

	Non-serious		Serious		
AE	**Cost (£)**	**Resource use**	**Cost (£)**	**Resource use**	**Average cost***
Arthralgia	1.74	NSAIDs: 350 mg 3x daily for 6 days	424.00	1 MS specialist visit 1 rheumatologist visit (non-admitted face to face)	30.88
Back pain	0.00	None	666.00	1 MS specialist visit 12 physical therapy sessions	45.95
Bronchitis	131.19	2 GP consultations 1 course of amoxicillin	131.19	2 GP consultations 1 course of amoxicillin	131.19
Depression	820.86	4 GP consultations Citalopram: 20 mg per day for 6 months 12 psychotherapy sessions	2996.38	9 GP consultations Citalopram: 40 mg per day for 6 months 52 psychotherapy sessions	970.97
Fatigue	0.00	None	108.98	1 GP consultation Provigil 200 mg/day for 2 months	7.52
Headache	0.00	None	210.00	1 neurologist visit (non-admitted face to face)	14.49
Influenza-like illness	0.00	None	0.00	None	0.00
Infusion related reaction	0.00	None	0.00	None	0.00
Injection site pain	0.00	None	65.00	1 GP consultation	4.49
Insomnia	0.00	None	0.00	None	0.00
Nasopharyngitis	0.00	None	65.00	1 GP consultation	4.49
PML	12810.33	MRI Plasma exchange Lumbar puncture Hospitalisation (long stay) Excess day	12810.33	MRI Plasma exchange Lumbar puncture Hospitalisation (long stay) Excess day	12810.33
Sinusitis	0.00	None	0.00	None	0.00
Upper respiratory tract infection	65.00	1 GP consultation	65.00	1 GP consultation	65.00
Urinary tract infection	1.80	Ciprofloxacin: 100 mg twice daily for 3 days	907.06	1 hospital visit	64.26

Source: manufacturer submission for daclizumab and alemtuzumab (53, 55)
* It is assumed that for each type of AE 93.1% are non-serious and 6.9% are serious, based on average proportion of SAEs in OPERA studies.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The list of variables used in the economic model and the measurement of uncertainty around them is presented below. When standard errors are not reported in the literature a standard assumption of 20% of the mean is used.

Table 53: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Demographics			
Age	37 years	Scenario analysis	B.3.3
Gender (male)	34%		
Baseline EDSS distribution	Pooled analysis OPERA (ITT) (Table 26)	• Dirichlet • Scenario analysis	
Model structure			
Time horizon	50 years	Fixed	B.3.2
Cycle length	Yearly		
Discount rate for costs and outcomes	3.5%		
Half cycle correction	Yes		
Transition probabilities			
Relapse rate by EDSS	Values based on Patzold et al (Table 35)	• Log Normal • scenarios analysis	B.3.3
RRMS to RRMS matrix	Values based on British Columbia dataset (Table 28)	Dirichlet	
RRMS to SPMS	Values based on London Ontario dataset (Table 31)	Beta	
SPMS to SPMS matrix	Values based on British Columbia dataset (Table 28)	Dirichlet	
Mortality risk	Values based on Pokorski et al (Table 37)	Log Normal	
Treatment effect			
Relapse rate	Values derived from base case MTC (Appendix D.1.4)	• Log Normal for CIs taken from CODA • scenario analysis	B.3.3 and Appendix D.1.4
Disability progression	Values derived from base case MTC for CDP-12 (Appendix D.1.4)		
All-cause discontinuation	Values derived from base case MTC (Appendix D.1.4)	• Lognormal for CIs taken from MTC • Beta for ocrelizumab	
Utilities			
Patient utility by EDSS	Pooled analysis OPERA (ITT) (Table 43)	Cholesky covariance matrix	B.3.3 and Appendix D.1.4

SPMS disutility	-0.045	Beta	
Caregiver disutility	Values based on previous RRMS appraisals (Table 44)		
Relapse disutility (non-hospitalised)	-0.071		
Resource use and cost			
Relapse, requiring no hospitalisation	£ 2000.96	Gamma	
EDSS health states	Values derived from Tyas et al (Table 51)		
Drug acquisition	Drug-specific	Fixed	
Drug administration	Drug-specific	Log Normal	
Monitoring	Drug-specific	Log Normal	
AE management	Drug-specific	Fixed	

B.3.6.2 Assumptions

Assumptions made in the base case are summarised below with justifications.

Table 54: List of model assumptions

Assumption	Justification
The population in OPERA I and II is representative of UK population	The OPERA I and II studies included 9 UK trial sites across the country. The randomised control period of the OPERA studies ran from 2011 - 2015 and included a broad range of patients across relevant subgroups. It is therefore considered reflective of patients seen in clinical practice in the UK today.
Treatment is not assumed to have a direct impact on severity or duration of relapses.	The severity of relapses has implications for costs and disutilities, e.g. when hospitalization and treatment with IV steroids is required. However, due to lack of trial evidence of treatment effect on severity of relapses, average cost and disutility of relapses are applied in the base case. This may underestimate the clinical benefit of active treatment if high-efficacy therapies like ocrelizumab not only reduce the frequency of relapses but also their severity and duration.
Patients with RRMS and SPMS can progress or regress in EDSS	The understanding of disease course in MS has evolved over the last decade. At the time of analysis of the older London Ontario dataset it was assumed by clinical experts that improvements in EDSS were measurement errors. However, in recent years it has become generally accepted that some patients with RRMS and SPMS do experience improvements in EDSS and that real world data to derive transition probability matrices should not be smoothened to remove these. The British Columbia dataset which allows for progression and regression was therefore used in the base case, in line with recent Committee conclusions.
Treatments effect is applied to EDSS progression but not regression	Despite evidence of ocrelizumab increasing the probability of 12-week confirmed disability improvement compared with IFNB-1a (Table 11), a conservative assumption has been made that active treatment does not affect EDSS improvements. In line with previous appraisals, treatment effect is only applied to EDSS progression, i.e. active treatment slows disease progression. This may underestimate the clinical benefit of high-efficacy DMTs like ocrelizumab which have demonstrated the ability to reverse disability.
Transitioning from RRMS to SPMS is accompanied by a 1-point increase in EDSS	Previous NICE appraisals deemed the assumption of a 1-point increase in EDSS to be an appropriate reflection of increasing disability experienced upon progression to a SPMS disease course. This was applied when using the London Ontario natural history in the base case which has separate transition probabilities for RRMS and SPMS patients. The British Columbia

	dataset used to derive transition probabilities between EDSS states in the ITT analysis in the base case model included both RRMS and SPMS patients. An increase in disability may have been partially captured within the British Columbia dataset, however the proportion of SPMS patients at baseline is low (15.7%) and therefore the increase is still assumed to be valid. The natural history dataset for the HA and RES subgroups is based on trial data in RRMS patients (supplemented by British Columbia data for the higher EDSS states), and the 1-point increase in EDSS upon conversion to SPMS is appropriate in these subgroups, in line with previous appraisals.
Partial treatment effect on transition from RRMS to SPMS	Treatment with DMTs is not only assumed to influence progression to SPMS indirectly by slowing progression through EDSS in RRMS, but is also assumed to reduce the rate of conversion to SPMS directly. In line with the previous appraisal of natalizumab, 50% of the treatment effect on confirmed disability progression is applied to the probability to convert from RRMS to SPMS.
No direct treatment effect on mortality	Literature has demonstrated that the risk of death is primarily dependent on the level of disability (EDSS). The duration of clinical trials in MS is not long enough to detect a direct impact of treatment on mortality. Instead, treatment influences mortality indirectly by slowing of disability progression.
Constant rate of all-cause treatment withdrawal	Applying a constant rate of all-cause discontinuation is considered valid because 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). Furthermore, withdrawal due to lack of efficacy is suggested to show a similar dynamic, with early withdrawal occurring in non-responders and late withdrawal occurring after development of neutralizing antibodies / drug resistance. This assumption is in line with the approach taken in several previous appraisals (Table 25) and is supported by real world data on long-term adherence and persistence of DMTs collected as part of the 10-year UK Risk Sharing Scheme (53).
No treatment waning for ocrelizumab	Long-term waning of treatment effect with DMTs has not been definitively proven nor disproven, and remains an area of debate. Open label extension data of up to four years is available for ocrelizumab and demonstrates sustained treatment effect across ARR, CDP, and MRI outcomes (see Appendix D.1.4). Treatment waning is biologically implausible with ocrelizumab as it generates negligible neutralising antibodies, unlike other DMTs (Table 24). Furthermore, the range of treatment options available to patients with RRMS nowadays likely means that any perceived reduction in clinical benefit over time results in switching to a different therapy with a different mechanism of action. Waning is therefore not assumed in the base case but included in scenario analysis.
Patients with SPMS receive BSC	There are no licensed treatments for patients with SPMS. However, some DMTs are licensed for relapsing forms of SPMS (IFNB-1a, daclizumab, and ocrelizumab subject to licence indication). The extent to which patients with relapsing forms of SPMS are treated with active therapy is uncertain. The point at which a patient is considered to have progressed to SPMS can be difficult to define in routine practice, particularly if patients are still experiencing relapses. It is commonly defined in retrospect due to the unpredictable nature of the MS disease course. Patients are likely to experience a period of overlap between RRMS and relapsing SPMS and may continue to receive DMTs in line with the clinical guideline and NHS England Commissioning Policy. Once a patient progresses to non-relapsing SPMS active treatment is expected to cease in line with clinical guidance. The base case does not differentiate between relapsing and non-relapsing forms of SPMS and all SPMS patients are assumed to receive BSC only.
Only common AEs (≥5 %) observed in OPERA studies	Due to the complexity and number of comparators in the economic model, the set of AEs included in the base case were based on the safety profile of

were included in base case	ocrelizumab only. This could have underestimated the impact of AEs for comparators if these weren't common in the OPERA studies. An exception was made for the risk of PML as this is known to be associated with high costs and disutilities and is relatively common with natalizumab (≥2 %). Other high-efficacy DMTs like alemtuzumab are associated with rare but severe AEs like renal failure requiring dialysis or renal transplantation. These AEs are not included in the base case as they were assumed to have little impact on results due to their low frequency.
Constant rate of AEs	The safety profiles of DMTs are complex and have evolved over time as long-term usage increases. 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). It is therefore considered appropriate to assume constant rates of annual AEs over the lifetime horizon of the model, in line with the approach used in several previous appraisals (Table 25).

B.3.7 Base-case results

As the MTC in the ITT population is supported by a more robust evidence base compared with the subgroup MTC (see Section B.2.9.1), results of the ITT economic analysis are presented for a set of comparators broader than outlined in the decision problem (including fingolimod and natalizumab). Results are based on list prices for comparators, which do not reflect the real prices paid by the NHS due to patient access schemes or other commercial arrangements for the majority of DMTs.

The ABCR comparators were considered individual treatments in the MTCs as each is associated with a slightly different efficacy and safety profile. However, the range of QALYs gained and costs accrued for the ABCRs is relatively large for treatments that are generally considered by clinicians to be broadly equivalent (in line with Committee discussions for the ongoing MTA for beta-interferons and glatiramer acetate, ID809). As such the results of the economic analyses for the ABCRs were blended based on current NHS market share information to facilitate interpretation of the incremental analyses (Table 55).

Table 55: Blended deterministic results for ABCRs (based on list prices)

Technologies	Total cost (£)	Total LYG	Total QALYs	Market share (%)	Weighted total cost (£)	Weighted total LYG	Weighted total QALYs
Glatiramer acetate	200,295	20.07	8.21	37	74,109	7.43	3.04
IFNB-1a (Avonex)	205,822	20.06	8.15	23	47,339	4.61	1.88
IFNB-1a (Rebif)	209,026	20.10	8.47	23	48,076	4.62	1.95
pegIFNB-1a	196,648	20.09	8.45	11	21,631	2.21	0.93
IFNB-1b	205,534	20.07	8.20	6	12,332	1.20	0.49
Blended ABCRs	-		-	100	203,487	20.08	8.28

The incremental analysis indicates that alemtuzumab is the most efficacious DMTs with 10.09 QALYs gained, closely followed by ocrelizumab with 9.75 QALYs gained. Alemtuzumab is the only cost-effective DMT at £8,296 per QALY gained versus the blended ABCRs, all other DMTs are dominated (Table 56 and Table 57).

As maintenance therapies accrue drug-associated costs over a lifetime, it is not entirely unexpected that an induction therapy with a fixed treatment duration dominates maintenance therapies. However, the results need to be interpreted with caution as the difference in total QALYs between ocrelizumab and alemtuzumab is relatively small (0.34 over a lifetime) and the phase 3 studies evaluating alemtuzumab (CARE MS I and II) were of lower overall quality and associated with more risk of bias than OPERA I and II studies, particularly due to their open label design. In addition, there is considerable uncertainty about the extent of re-treatment required with alemtuzumab in routine practice and the long-term costs of alemtuzumab may be underestimated.

It is important to maintain treatment choice in RRMS as the different DMTs represent different trade-offs between efficacy, safety, convenience, resource use, and cost. Patient choice and preference is an important factor in clinician prescribing behaviour, and the long-term safety risk and monitoring requirements associated with alemtuzumab mean it is not suitable for every patient (as recognised by the Committee during the recent appraisal of daclizumab, (53)).

Given the importance of allowing patient choice, incremental analysis was also conducted excluding alemtuzumab. In this case ocrelizumab is the only DMT not dominated or extendedly dominated compared to the blended ABCRs with incremental ICERs of [redacted] and £26,435 respectively, based on list and PAS price (Table 58 and Table 59).

Table 56: Incremental analysis, base case ITT (based on list prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Outside of NICE scope for this population. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 57: Incremental analysis, base case ITT (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,296	8,296
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

* Outside of NICE scope for this population. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 58: Incremental analysis, ITT excluding alemtuzumab (based on list prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Outside of NICE scope for this population.

Table 59: Incremental analysis, ITT excluding alemtuzumab (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	176,885	Extendedly dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,435	26,435
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

* Outside of NICE scope for this population.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

All model variables that had a distribution assigned are presented in Table 53. Probabilistic sensitivity analysis was conducted with 1,000 iterations to determine the uncertainty surrounding the base-case ICERs.

The probabilistic results are broadly similar to the deterministic results, lending support to the overall conclusions.

Alemtuzumab dominates all other DMTs compared to the blended ABCRs in the incremental probabilistic analysis (Table 60 and Table 61). Cost-effectiveness acceptability curves (CEAC) and scatter plots for analyses including alemtuzumab are shown in Appendix J.1.3.

When excluding alemtuzumab from the analysis to allow patient choice for different treatment options to be considered, the probability of ocrelizumab with PAS being cost-effective at a £30k ICER threshold is broadly similar to the ABCRs (Figure 29).

The cost-effectiveness plane indicates that, compared to ocrelizumab, most other DMTs are situated in the south-west quadrant, meaning they are less efficacious and less costly (Figure 28 and Figure 30). The only exceptions are natalizumab which is of broadly similar effectiveness but costlier, and fingolimod which has broadly similar costs but is less effective.

Table 60: Probabilistic results, base case ITT (based on list prices)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Outside of NICE scope for this population.

Table 61: Probabilistic results, base case ITT (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	8,366	8,366
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

* Outside of NICE scope for this population.

Table 62: Probabilistic results, ITT excluding alemtuzumab (based on list prices)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Outside of NICE scope for this population.

Table 63: Probabilistic results, ITT excluding alemtuzumab (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Blended ABCRs	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	160,619	Extendedly dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	27,415	27,415
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

* Outside of NICE scope for this population.

Figure 27: Cost-effectiveness acceptability curve, ITT excluding alemtuzumab (based on list prices)

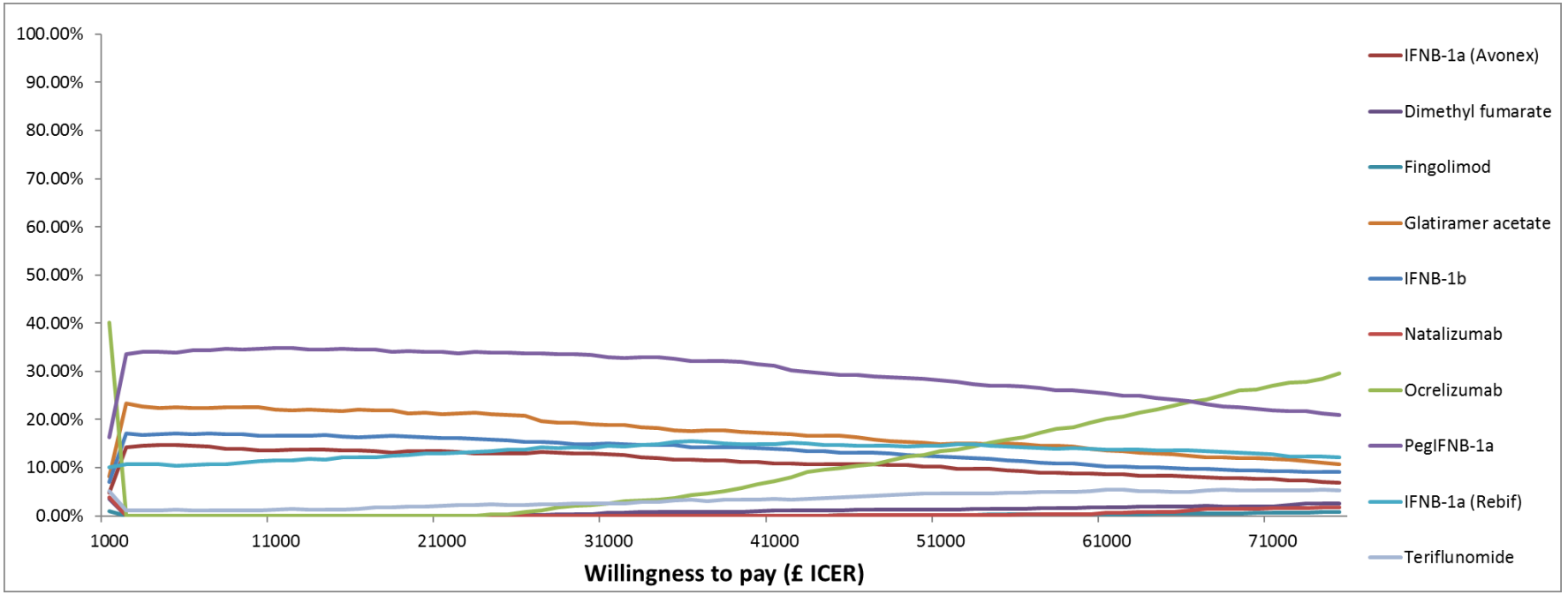


Figure 28: Cost-effectiveness plane for DMTs compared to ocrelizumab, ITT excluding alemtuzumab (based on list prices)

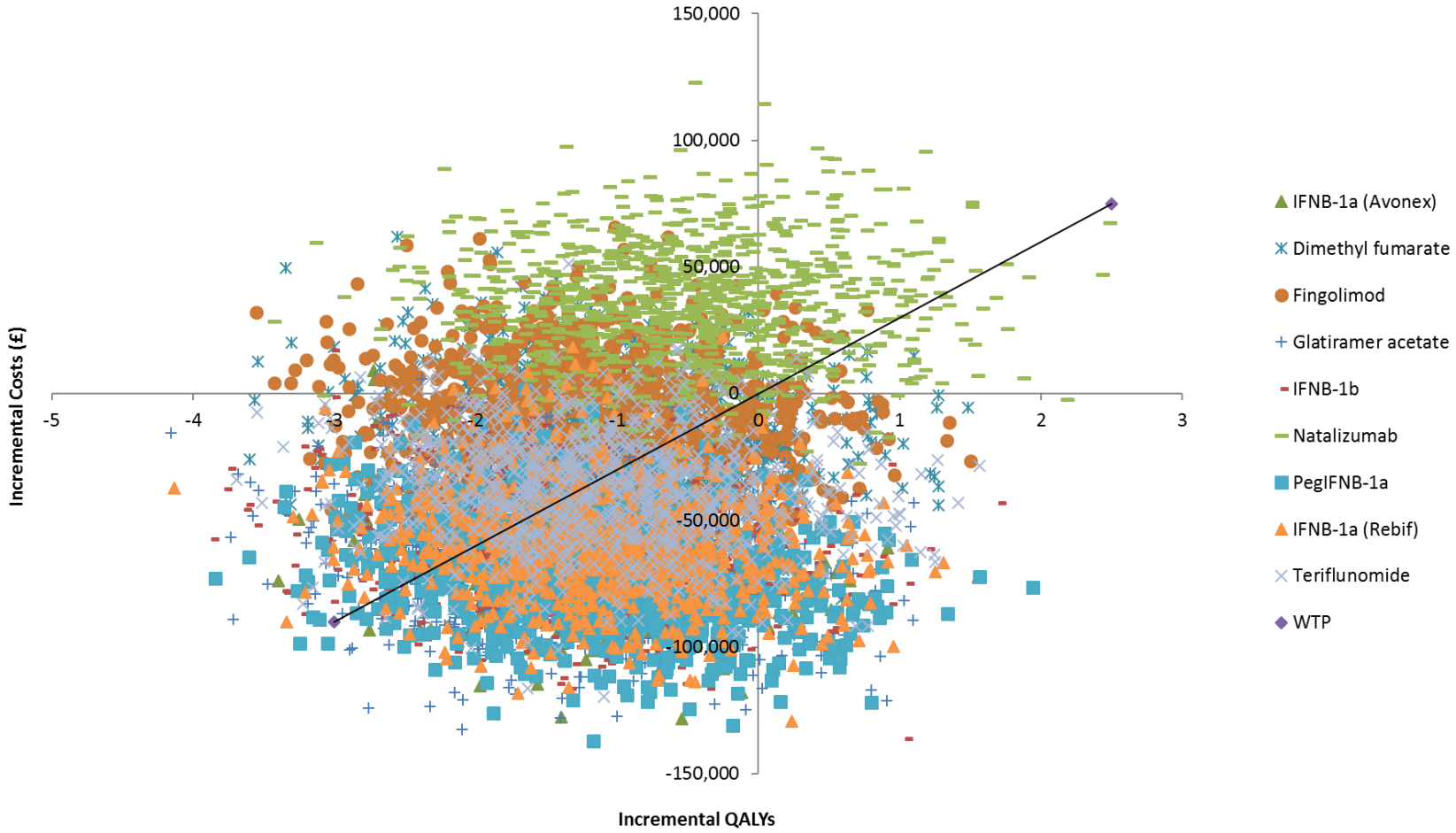


Figure 29: Cost-effectiveness acceptability curve, ITT excluding alemtuzumab (based on ocrelizumab PAS)

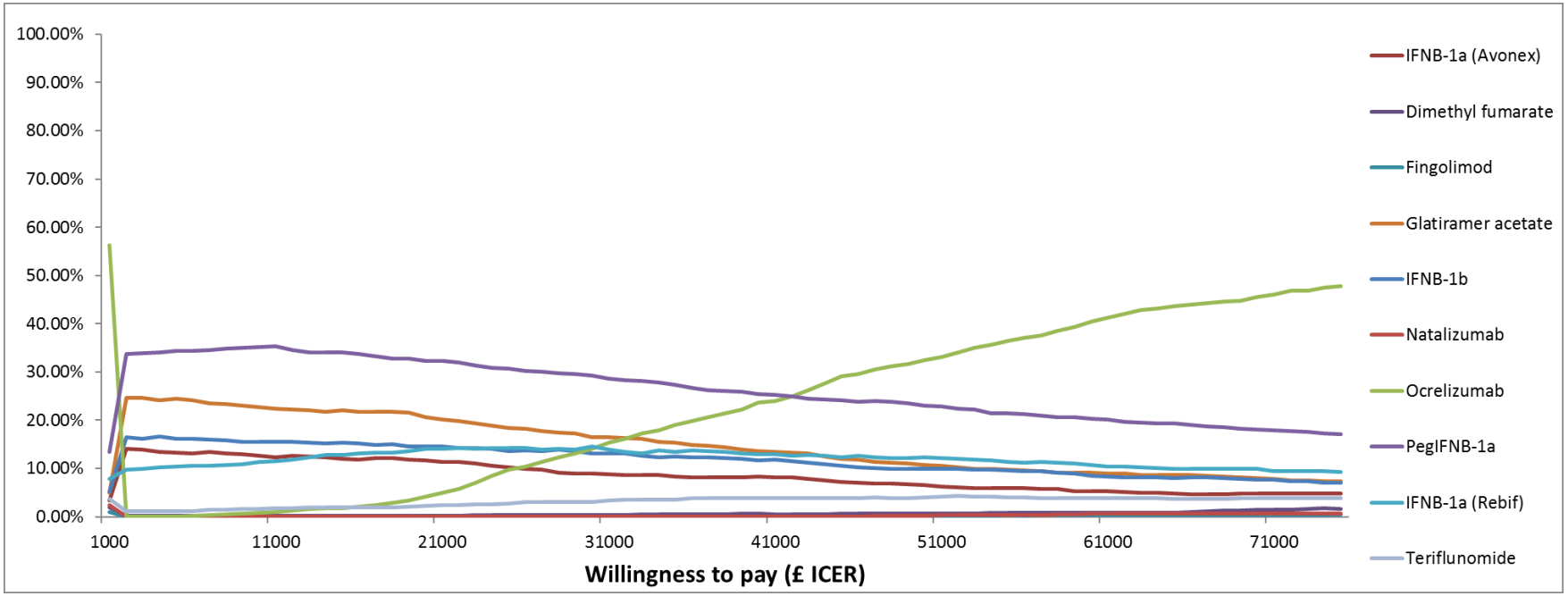
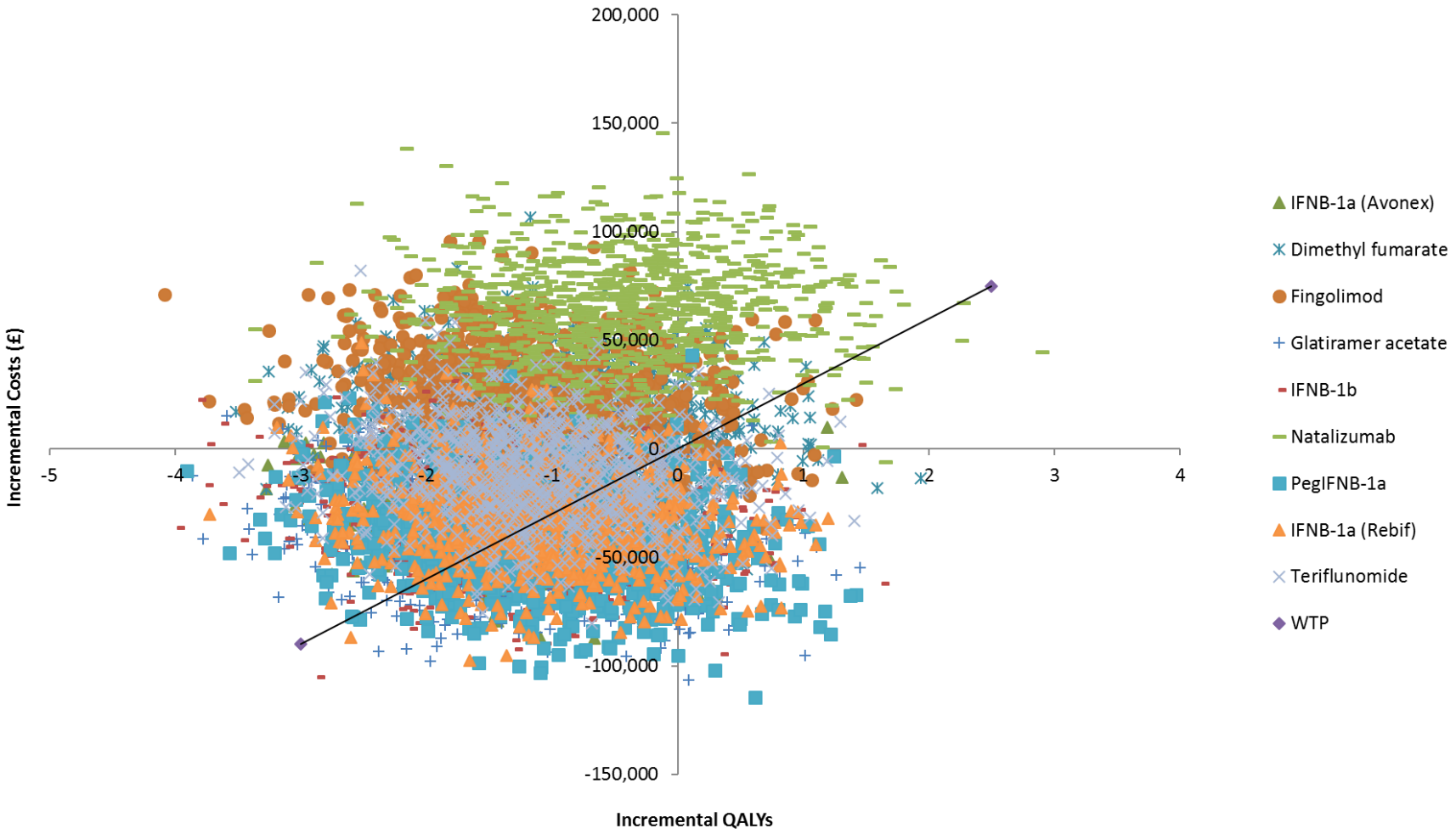


Figure 30: Cost-effectiveness plane for DMTs compared to ocrelizumab, ITT excluding alemtuzumab (based on ocrelizumab PAS)



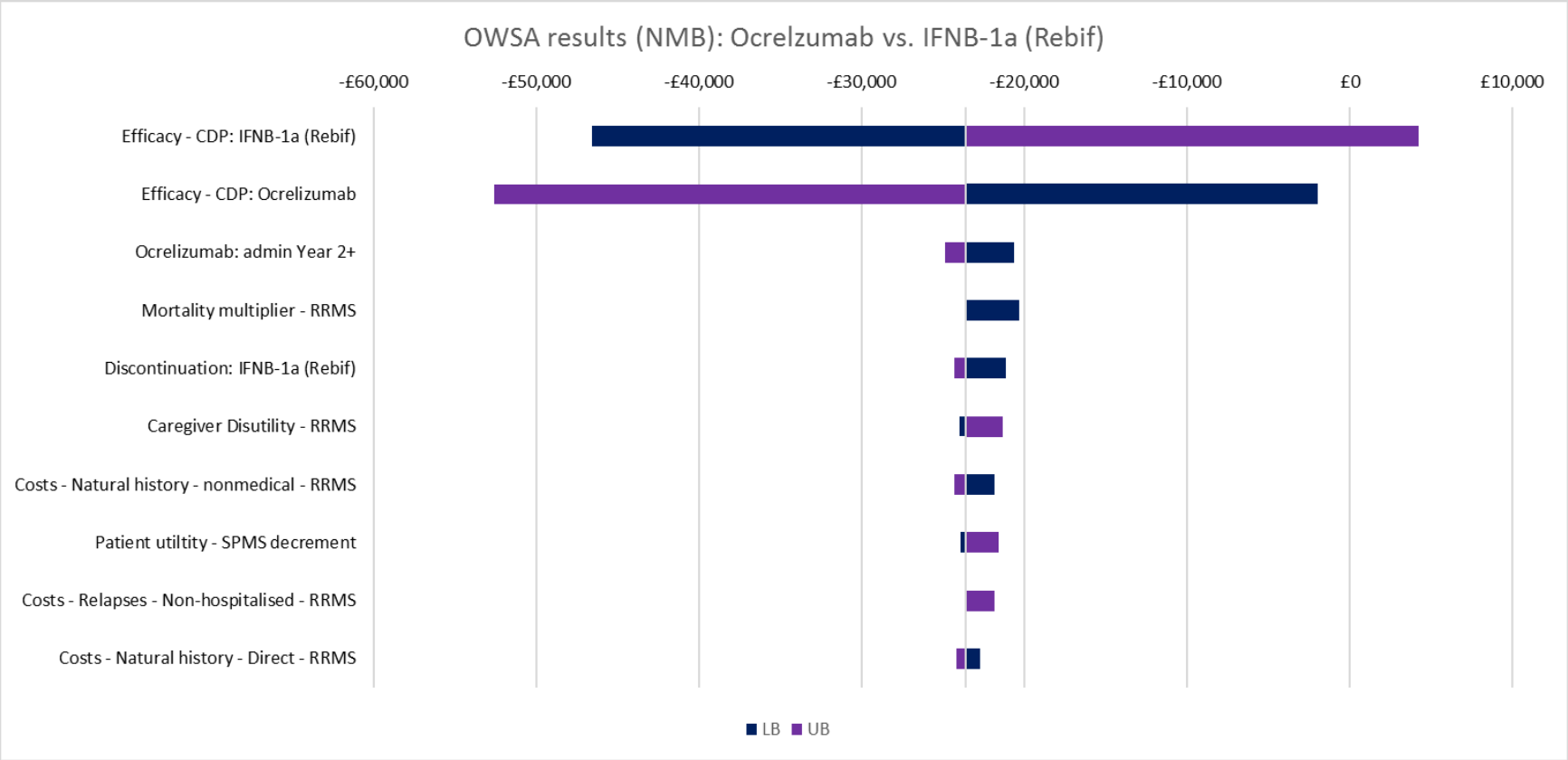
B.3.8.2 Deterministic sensitivity analysis

For one-way sensitivity analysis parameters were varied between the lower and upper boundary of the 95% confidence/credible interval or by 20% of the mean if a distribution was not available (values available in cost-effectiveness model). The ten parameters most sensitive to change were included in the tornado diagram. The results are presented as net monetary benefit for a willingness to pay threshold of £30,000 per QALY.

The results of the one-way sensitivity analyses are summarised below with a tornado diagram for the comparison ocrelizumab versus IFNB-1a (Rebif) based on list price. This comparison is considered representative for the other comparators as the model drivers are broadly similar between comparisons.

As can be expected, the results were most sensitive to treatment effect on CDP. All other parameters have only modest impact on the results, including administration costs, excess mortality risk, discontinuation, and caregiver disutility (Figure 31). Some exceptions are discontinuation rates for fingolimod, natalizumab, dimethyl fumarate, and teriflunomide, and administration costs for natalizumab which were also key model drivers (see Appendix J.1.3).

Figure 31: One-way sensitivity analysis for ocrelizumab compared to IFNB-1a (Rebif), based on list prices



B.3.8.3 Scenario analysis

Scenario analysis was performed to test the sensitivity of the economic model to different model assumptions or input sources. This included varying the natural history to the London Ontario dataset which does not allow EDSS improvements, and different sources for cost of relapse, disability progression, patient utilities, baseline demographics, and mortality multiplier. Key assumptions around long-term discontinuation and treatment waning were also varied to test the robustness of the base case.

In general, the results of the scenario analysis support the base case results and the cost-effectiveness of ocrelizumab compared to other DMTs does not vary a great deal. However, there are some exceptions. The ICER for ocrelizumab compared with other DMTs was most sensitive to changing the source of social care costs (substantially lower ICERs if using the BOUNDS-MS study (see Appendix M), and applying the same treatment waning assumption across all DMTs (substantially higher ICERs).

As explained in Section B.3.3, we do not believe treatment waning to be clinically plausible for ocrelizumab due to its limited immunogenicity and sustained treatment effect as demonstrated in the OLE study. In addition, we consider treatment waning as applied in economic modelling not to be reflective of today's clinical practice as patients would be expected to switch between treatment options with different mechanisms of action if a diminished treatment benefit is perceived.

The impact of applying treatment effect on disability progression as expressed by CDP-24 instead of CDP-12 varies across different comparators, some ICERs compared to ocrelizumab are increased and some are decreased. As explained in Section B.2.9, we believe that the evidence base for CDP-24 in the MTC is associated with considerable uncertainty and is less robust than CDP-12. CDP-24 is generally perceived to be clinically more meaningful than CDP-12 as it is assumed to be less sensitive to fluctuations in EDSS caused by relapses. However, this is not entirely consistent with the generally accepted assumption in previous RRMS appraisals that an average relapse lasts for 46 days.

Table 64: Results of scenario analysis, based on list prices

	ICER ocrelizumab versus comparator									
	Alemtuzumab	IFNB-1a (Avonex)	Dimethyl fumarate	Fingolimod	Glatiramer acetate	IFNB-1b	Natalizumab	pegIFNB-1a	IFNB-1 (Rebif)	Teriflunomide
Natural history for EDSS transitions in RRMS and SPMS and off treatment: London Ontario	[redacted]									
Efficacy: disability progression set to 24-week confirmation (CDP-24)	[redacted]									
ARR natural history: HA subgroup (natalizumab NICE submission)	[redacted]									
ARR natural history: RES subgroup (natalizumab NICE submission)	[redacted]									
ARR natural history: Held et al 2005 and UK MS Survey 2005 (alemtuzumab NICE submission)	[redacted]									
Relapse duration:1 month	[redacted]									
Relapse duration: 2 months	[redacted]									
Direct medical costs RRMS and SPMS: BOUNDS-MS study	[redacted]									
Direct nonmedical costs RRMS and SPMS: BOUNDS-MS study	[redacted]									
Relapse cost: average of Hawton et al 2016 (see B.3.5.2)	[redacted]									
Efficacy: MTC population HA subgroup	[redacted]									
Efficacy: MTC population RES subgroup	[redacted]									
Baseline demographics: UK Risk Sharing Scheme (Pickin et al 2009)	[redacted]									
Patient utilities: Orme et al 2007	[redacted]									

Treatment waning: 75% after 2 years and 50% after 5 years for all DMTs	[redacted]									
Treatment waning: 75% after 2 years and 50% after 5 years for comparators; 75% after 4 years and 50% after 7 years for ocrelizumab	[redacted]									
Mortality risk: Kingwell et al 2012	[redacted]									
All-cause discontinuation: 50% after year 2	[redacted]									
Relapse disutility from OPERA I and II regression analysis	[redacted]									

Highlighted cells are outside of NICE scope for particular population. NR, not reported. SW quadrant = less effective and less costly. Dominated, ocrelizumab dominated by comparator; dominant, ocrelizumab dominates comparator

Table 65: Results of scenario analysis, based on ocrelizumab PAS

	ICER ocrelizumab versus comparator									
	Alemtuzumab	IFNB-1a (Avonex)	Dimethyl fumarate	Fingolimod	Glatiramer acetate	IFNB-1b	Natalizumab	pegIFNB-1a	IFNB-1 (Rebif)	Teriflunomide
Natural history for EDSS transitions in RRMS and SPMS and off treatment: London Ontario	Dominated	22,781	Dominant	Dominant	27,822	23,885	Dominant	36,150	25,803	8,054
Efficacy: disability progression set to 24-week confirmation (CDP-24)	Dominated	37,805	Dominant	Dominant	37,113	25,663	SW quadrant	94,196	24,329	9,198
ARR natural history: HA subgroup (natalizumab NICE submission)	Dominated	22,843	Dominant	Dominant	27,304	23,712	Dominant	35,030	25,913	9,833
ARR natural history: RES subgroup (natalizumab NICE submission)	Dominated	20,695	Dominant	Dominant	25,869	22,254	Dominant	32,772	23,913	8,116
ARR natural history: Held et al 2005 and UK MS Survey 2005 (alemtuzumab NICE submission)	Dominated	21,309	Dominant	Dominant	25,985	22,408	Dominant	33,419	24,423	8,473
Relapse duration:1 month	Dominated	22,910	Dominant	Dominant	27,358	23,759	Dominant	35,134	25,983	9,857

Relapse duration: 2 months	Dominated	22,775	Dominant	Dominant	27,252	23,665	Dominant	34,927	25,843	9,808
Direct medical costs RRMS and SPMS: BOUNDS-MS study	Dominated	21,732	Dominant	Dominant	26,203	22,633	Dominant	33,854	24,756	8,687
Direct nonmedical costs RRMS and SPMS: BOUNDS-MS study	Dominated	13,296	Dominant	Dominant	17,698	14,221	Dominant	25,469	16,423	129
Relapse cost: average of Hawton et al 2016 (see B.3.5.2)	Dominated	23,644	Dominant	Dominant	27,828	24,252	Dominant	35,832	26,649	10,508
Efficacy: MTC population HA subgroup	NR	16,657	NR	Dominant	19,920	17,297	NR	NR	18,006	NR
Efficacy: MTC population RES subgroup	NR	25,071	NR	Dominant	29,036	25,613	SW quadrant	NR	28,792	NR
Baseline demographics: UK Risk Sharing Scheme (Pickin et al 2009)	Dominated	21,773	Dominant	Dominant	26,079	22,691	Dominant	33,717	24,670	9,225
Patient utilities: Orme et al 2007	Dominated	23,905	Dominant	Dominant	28,582	24,807	Dominant	36,605	27,070	10,288
Treatment waning: 75% after 2 years and 50% after 5 years for all DMTs	Dominated	34,704	Dominant	Dominant	40,986	35,193	Dominant	56,070	40,523	15,232
Treatment waning: 75% after 2 years and 50% after 5 years for comparators; 75% after 4 years and 50% after 7 years for ocrelizumab	241,081	28,487	Dominant	Dominant	33,524	28,836	Dominant	43,869	31,167	11,761
Mortality risk: Kingwell et al 2012	Dominated	21,987	Dominant	Dominant	26,690	22,941	Dominant	34,830	25,198	8,272
All-cause discontinuation: 50% after year 2	Dominated	24,546	Dominant	Dominant	29,322	25,987	Dominant	37,064	27,406	11,733
Relapse disutility from OPERA I and II regression analysis	Dominated	22,757	Dominant	Dominant	27,238	23,652	Dominant	34,898	25,823	9,801

Highlighted cells are outside of NICE scope for particular population. NR, not reported. SW quadrant = less effective and less costly. Dominated, ocrelizumab dominated by comparator; dominant, ocrelizumab dominates comparator

B.3.9 Subgroup analysis

As per the decision problem, subgroup analyses were performed in HA and RES subgroups. However, the subgroup results need to be interpreted with caution due to the considerable limitations of the subgroup MTCs (see Section B.2.9.1) and the sparsity of natural history data for subgroups. The natural history data for subgroups is either based on small sample sizes in clinical trials, or lacking altogether (e.g. no disability natural history available for HA subgroup). Nevertheless, subgroup results are presented here for completeness and transparency.

There are no subgroup MTC results available for alemtuzumab in the base case.

The HA subgroup results are broadly consistent with the pairwise ITT results. The results in the HA subgroup indicate that ocrelizumab is more effective than fingolimod with an incremental ICER of [redacted] at list price, and dominates fingolimod when incorporating the PAS for ocrelizumab (Table 66 and Table 67). The conclusions of the probabilistic analyses are similar to the deterministic analyses.

The results in the RES subgroup are not consistent with the ITT results where ocrelizumab was shown to dominate natalizumab. In the subgroup analysis, the results indicate that natalizumab is marginally more effective but considerably costlier than ocrelizumab, with an incremental ICER of [redacted] (Table 70). When incorporating the PAS for ocrelizumab this increases significantly, in other words ocrelizumab saves £1,065,854 per QALY lost compared with natalizumab (Table 71). The conclusions of the probabilistic analyses are similar to the deterministic analyses, but the ICER estimates are different. This is likely due to the wider confidence intervals in subgroups causing disparate results each time a simulation is run.

Table 66: Incremental deterministic analysis, base case HA subgroup (based on list prices)

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

Table 67: Incremental deterministic analysis, base case HA subgroup (based on ocrelizumab PAS)

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

Table 68: Incremental probabilistic analysis, base case HA subgroup (based on list prices)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 69: Incremental probabilistic analysis, base case HA subgroup (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Figure 32: Cost-effectiveness acceptability curve, base case HA subgroup (based on list prices)

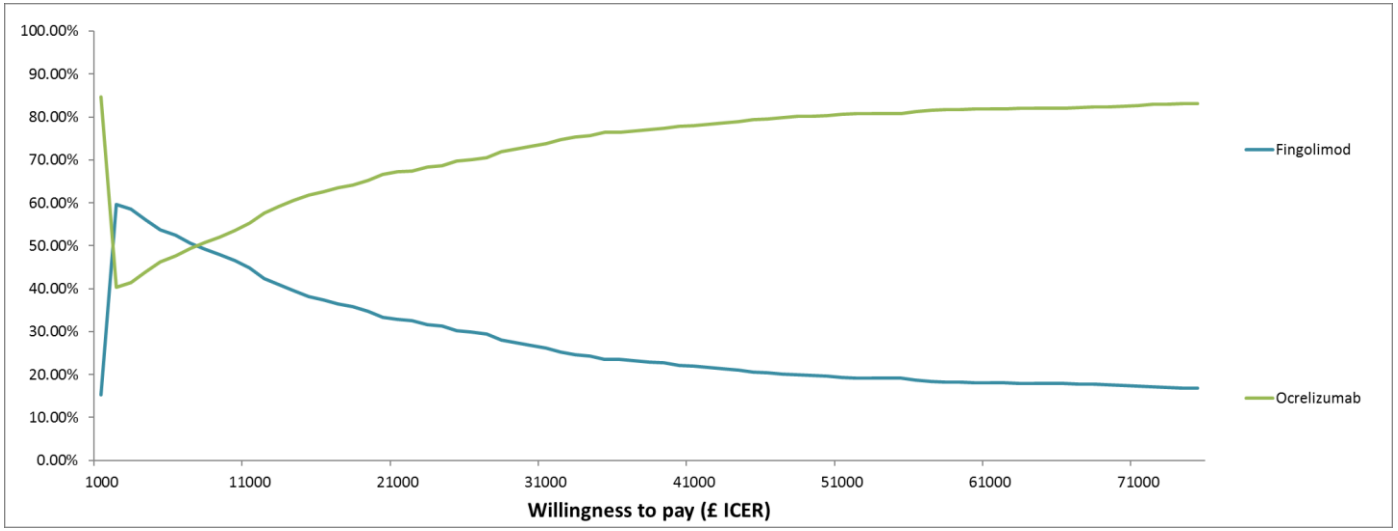


Figure 33: Cost-effectiveness acceptability curve, base case HA subgroup (based on ocrelizumab PAS)

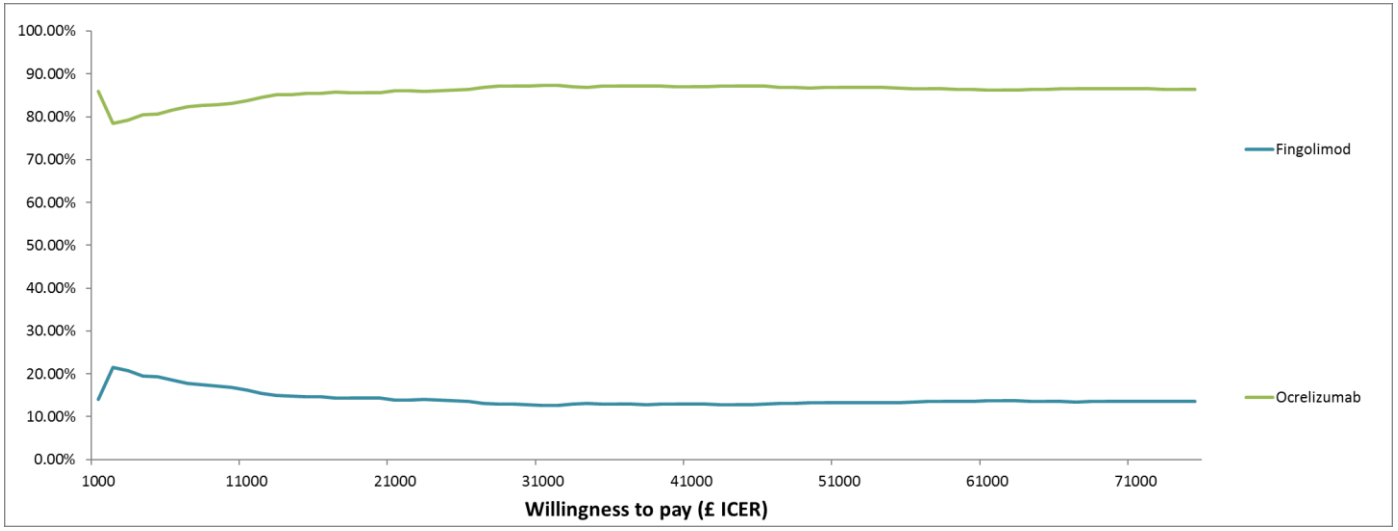


Table 70: Incremental deterministic analysis, base case RES subgroup (based on list prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 71: Incremental deterministic analysis, base case RES subgroup (based on ocrelizumab PAS)

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

Table 72: Incremental probabilistic analysis, base case RES subgroup (based on list prices)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 73: Incremental probabilistic analysis, base case RES subgroup (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	718,717	718,717

Figure 34: Cost-effectiveness acceptability curve, base case RES subgroup (based on list prices)

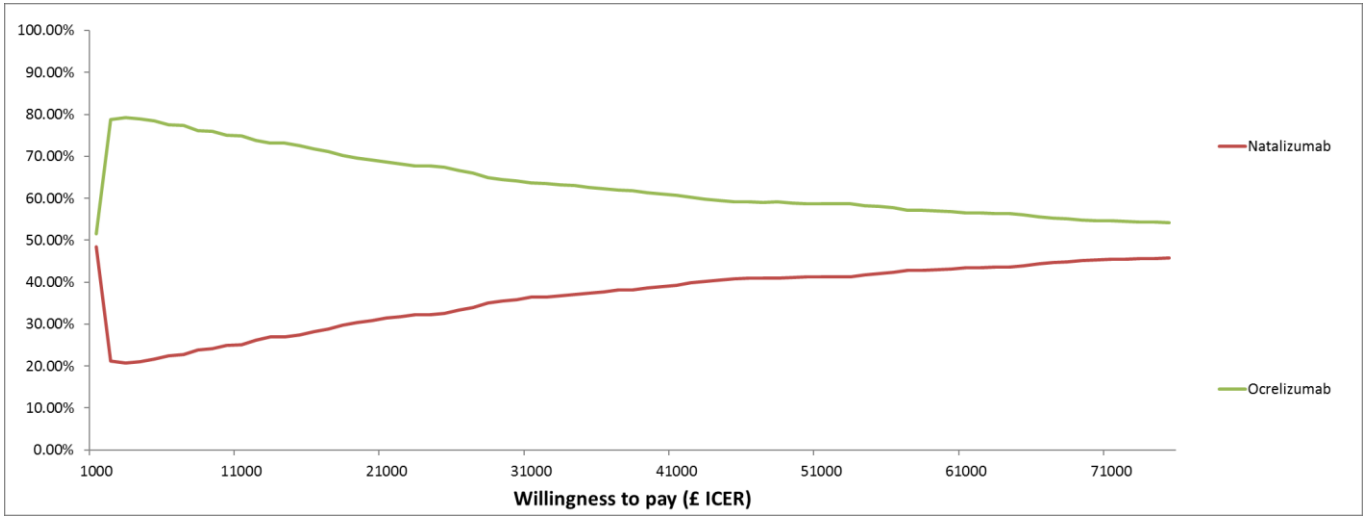
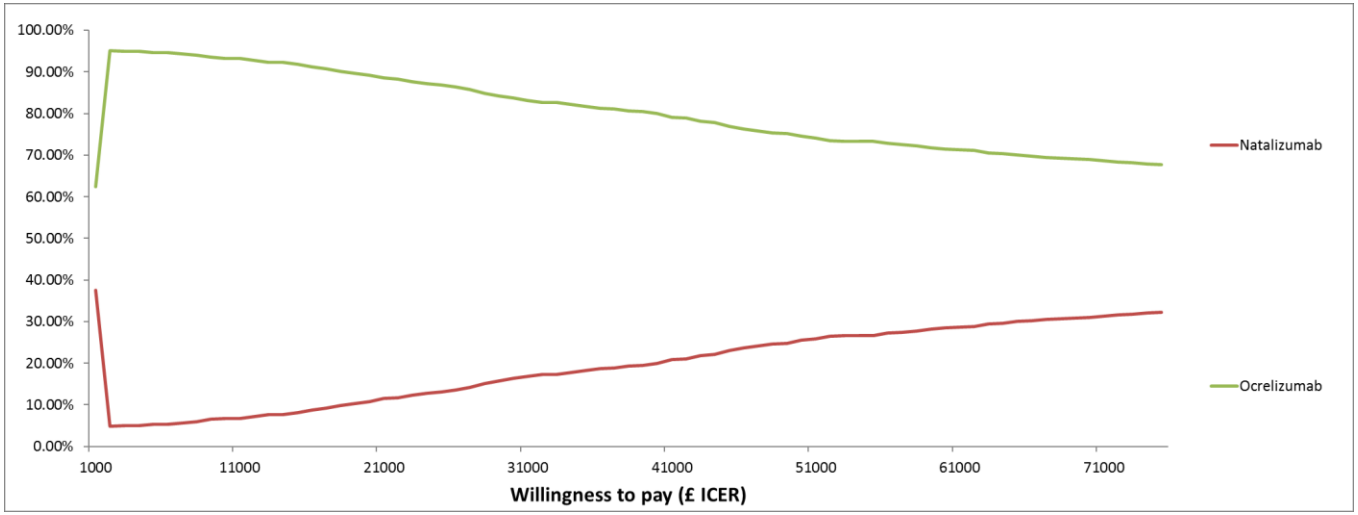


Figure 35: Cost-effectiveness acceptability curve, base case RES subgroup (based on ocrelizumab PAS)



B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Two separate quality checks of the economic model were performed by external agencies. This included review of the implementation of calculations and testing of extreme values. Any modelling errors identified were corrected before submission.

The face validity of the model structure, inputs, and results was tested at an advisory board with clinical and health economic experts from the UK who are familiar with MS. The experts confirmed the face validity of the economic analysis. Cross-comparison of economic results between NICE appraisals was complicated by the amount of redacted information in previous submissions. As the economic model inputs and features are largely in line with previous submissions the outputs are expected to be broadly similar.

The results of the base case MTC were compared with the MTC conducted by ICER (144). A summary is provided below (Table 74). MTC results for ARR were comparable but the CDP MTC results - the key driver of the economic model - varied between the two sources and methodologies. For some DMTs, the CDP-12 base case results were closer to the ICER report MTC results and in other cases the CDP-24 results were more aligned. These differences are likely explained by application of different MTC methodologies and assumptions.

Table 74: Cross-validation of MTC results between Roche model and ICER report

Technologies	Roche ARR	ICER report ARR	Roche CDP-24 Estimate and rank*		Roche CDP-12 Estimate and rank*		ICER report CDP-24/12 Estimate and rank^	
Ocrelizumab	[redacted]	0.35	[redacted]	2	[redacted]	1	0.47	2
Alemtuzumab	[redacted]	0.28	[redacted]	1	[redacted]	2	0.42	1
Natalizumab	[redacted]	0.31	[redacted]	4	[redacted]	3	0.56	3
PegIFNB-1a	[redacted]	0.63	[redacted]	3	[redacted]	4	0.63	5
IFNB-1a (Rebif)	[redacted]	0.64	[redacted]	9	[redacted]	5	0.73	9
Dimethyl fumarate	[redacted]	0.53	[redacted]	7	[redacted]	6	0.62	4
Teriflunomide	[redacted]	0.67	[redacted]	10	[redacted]	7	0.72	8
Fingolimod	[redacted]	0.46	[redacted]	5	[redacted]	8	0.68	7
IFNB-1 (Avonex)	[redacted]	0.83	[redacted]	6	[redacted]	9	0.79	11
Glatiramer acetate	[redacted]	0.63	[redacted]	8	[redacted]	10	0.74	10
IFNB-1b	[redacted]	0.65	[redacted]	-	[redacted]	11	0.66	6

ARR and CDP results are those compared to placebo. ^ = ICER report used CDP-24 values, or if these were not available for DMTs CDP-12 values. * = where the point estimates are equal, the lower bound of the credible interval is used for rank.

B.3.11 Interpretation and conclusions of economic evidence

A de novo economic analysis was performed to assess the cost-effectiveness of ocrelizumab compared to other DMTs. The design and features of the economic model followed precedents set by previous NICE appraisals in MS (Table 25), and SRs and MTCs were conducted to derive the best available evidence to populate the model. The robustness of the base case analysis was comprehensively tested in sensitivity analyses.

The treatment landscape in RRMS is becoming ever more complex with increasing segmentation of patient groups according to disease activity and lines of therapy. The results of the base case analysis indicate that ocrelizumab with the associated PAS is a cost-effective maintenance therapy option for all patients with RRMS, be it active RRMS, or HA and RES subgroups.

It is important to maintain treatment choice in RRMS as the different DMTs represent different trade-offs between efficacy, safety, convenience, and long-term certainty of outcomes and costs. The latter factor is especially pertinent for induction therapies like alemtuzumab which for a minority of patients in clinical practice can turn into maintenance therapies due to persistent treatment failure and breakthrough disease. The impact of re-treatment on costs has been accounted for in the model based on real world evidence on re-treatment rates. However, the detrimental impact that failure on induction therapy can have on patients' HRQoL has not been taken into account in the economic model and may have led to overestimation of the lifetime QALY gain with alemtuzumab.

The results of the analysis are generally consistent, but more conservative, compared with the only other cost-effectiveness analysis identified in the literature that included ocrelizumab, namely the report by ICER. In both sets of analyses alemtuzumab and ocrelizumab were ranked number 1 and 2 respectively of the most effective DMTs in terms of QALY gain over a lifetime. The ICER report suggested a QALY gain for alemtuzumab of 12.46 and 10.94 for ocrelizumab (144). In the base case analysis conducted here alemtuzumab gained 10.09 QALYs compared with 9.75 for ocrelizumab. The differences between the two studies can be explained by the application of different MTC methodologies (Table 74), different model structures (i.e. up to 3 lines of therapy modelled in ICER report), and different inputs (i.e. patient utilities valued from a US perspective).

A key strength of the economic analysis presented here was that, where possible, clinical data from the OPERA I and II studies were incorporated, such as the EQ-5D regression analysis. The MTC was comprehensive and included all licensed treatments in RRMS (manuscript is under peer-review). Another key strength was that analyses were conducted

in various populations as requested by the NICE scope. Subgroup data was sourced from the subgroup MTCs and natural history relevant for the subgroup was applied, where possible, to reflect faster progression/higher rate of relapses in more active disease. Finally, a comprehensive list of scenarios was tested including assumptions about treatment waning for completeness and cross-comparison to previous NICE appraisals.

A key limitation of the economic analysis was that despite best efforts, data for some comparisons in subgroups were limited or lacking altogether. As explained in Section B.1.1, some analyses requested in the NICE scope were not conducted due to a lack of clinical data available to inform them, such as modelling treatment in relapsing SPMS or in treatment-naïve versus treatment-experienced patients. The HA and RES subgroup analysis suffered from a lack of robustness and therefore additional analysis in the overall population of RRMS patients was presented for all comparators.

Finally, the model structure was designed to be in line with previous NICE appraisals for comparability. However, it may be argued that a treatment sequence or discrete event simulation model would have been more appropriate to reflect today's complexities in clinical practice and switching between therapeutic options in RRMS.

B.4 References

1. European Medicines Agency. Daclizumab PRAC recommendation, October 2017 2017. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Zinbryta/human_referral_prac_000067.jsp&mid=WC0b01ac05805c516f.
2. Genovese MC, Kaine JL, Lowenstein MB, Del Giudice J, Baldassare A, Schechtman J, et al. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008;58(9):2652–61.
3. Klein C, Lammens A, Schafer W, Georges G, Schwaiger M, Mossner E, et al. Response to: monoclonal antibodies targeting CD20. MAbs. 2013;5(3):337-8.
4. Lehmann-Horn K, Kinzel S, Weber MS. Deciphering the Role of B Cells in Multiple Sclerosis-Towards Specific Targeting of Pathogenic Function. Int J Mol Sci. 2017;18(10).
5. F. Hoffmann-La Roche Ltd. Summary of Product Characteristics - ocrelizumab (DRAFT). 2017.
6. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372(9648):1502–17.
7. Nylander A, Hafler DA. Multiple sclerosis. J Clin Invest. 2012;122(4):1180–8.
8. Ahlgren C, Oden A, Lycke J. High nationwide prevalence of multiple sclerosis in Sweden. Mult Scler. 2011;17(8):901-8.
9. Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359(9313):1221-31.
10. Orton S-M, Ramagopalan SV, Brocklebank D, Herrera BM, Dyment DA, Yee IM, et al. Effect of immigration on multiple sclerosis sex ratio in Canada: the Canadian Collaborative Study. Journal of Neurology, Neurosurgery & Psychiatry. 2010;81(1):31-6.
11. Wallin MT, Culpepper WJ, Coffman P, Pulaski S, Maloni H, Mahan CM, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. Brain. 2012;135(Pt 6):1778-85.
12. Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain. 2004;127(Pt 4):844–50.
13. Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry. 2012;83(1):61–6.
14. Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, Ebers GC. Mortality in patients with multiple sclerosis. Neurology. 2013;81(2):184–92.
15. Bar-Or A, Fawaz L, Fan B, Darlington PJ, Rieger A, Ghorayeb C, et al. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? Ann Neurol. 2010;67(4):452–61.
16. Magliozzi R, Howell OW, Reeves C, Roncaroli F, Nicholas R, Serafini B, et al. A Gradient of neuronal loss and meningeal inflammation in multiple sclerosis. Ann Neurol. 2010;68(4):477-93.
17. Weber MS, Hemmer B, Cepok S. The role of antibodies in multiple sclerosis. Biochim Biophys Acta. 2011;1812(2):239-45.
18. Weiner HL. A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis. J Neurol. 2008;255 Suppl 1:3-11.
19. Rasmussen S, Wang Y, Kivisakk P, Bronson RT, Meyer M, Imitola J, et al. Persistent activation of microglia is associated with neuronal dysfunction of callosal projecting pathways and multiple sclerosis-like lesions in relapsing--remitting experimental autoimmune encephalomyelitis. Brain. 2007;130(Pt 11):2816-29.
20. Fazekas F, Soelberg-Sorensen P, Comi G, Filippi M. MRI to monitor treatment efficacy in multiple sclerosis. J Neuroimaging. 2007;17 Suppl 1:50S-5S.

21. National Multiple Sclerosis Society. Magnetic Resonance Imaging (MRI) [Accessed August 2017]. Available from: http://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools/MRI.

22. Sailer M, Losseff NA, Wang L, Gawne-Cain ML, Thompson AJ, Miller DH. T1 lesion load and cerebral atrophy as a marker for clinical progression in patients with multiple sclerosis. A prospective 18 months follow-up study. Eur J Neurol. 2001;8(1):37-42.

23. Lee MA, Smith S, Palace J, Matthews PM. Defining multiple sclerosis disease activity using MRI T2-weighted difference imaging. Brain. 1998;121 (Pt 11):2095-102.

24. Stevenson VL, Ingle GT, Miller DH, Thompson AJ. Magnetic resonance imaging predictors of disability in primary progressive multiple sclerosis: a 5-year study. Mult Scler. 2004;10(4):398-401.

25. Kantarci OH. Genetics and Natural History of Multiple Sclerosis. Semin Neurol. 2008;28(01):007-16.

26. Vollmer T. The natural history of relapses in multiple sclerosis. J Neurol Sci. 2007;256 Suppl 1:S5-13.

27. Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ. 2006;332(7540):525–7.

28. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003;61(11):1528-32.

29. Coles A. Multiple sclerosis. THE BARE ESSENTIALS. 2009;9(2):118-26.

30. Coles AJ, Cox A, Le Page E, Jones J, Trip SA, Deans J, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol. 2006;253(1):98-108.

31. Gold R, Wolinsky JS, Amato MP, Comi G. Evolving expectations around early management of multiple sclerosis. Therapeutic Advances in Neurological Disorders. 2010;3(6):351-67.

32. Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol. 2014;72 Suppl 1:1–5.

33. Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain. 2010;133(Pt 7):1914–29.

34. National Multiple Sclerosis Society. Secondary progressive MS (SPMS) [Accessed November 2017]. Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS.

35. Ahrweiller K, Rousseau, Leray E, LePage E, Bajeux, Edan G, et al., editors. Relapses in patients with secondary progressive MS: a matter of disease duration or age? ECTRIMS; 2017.

36. Ontaneda D, Fox RJ. Progressive multiple sclerosis. Curr Opin Neurol. 2015;28(3):237-43.

37. Lamers I, Feys P. Assessing upper limb function in multiple sclerosis. Mult Scler. 2014;20(7):775-84.

38. 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 & Psychiatry. 2014;85(1):76-84.

39. Multiple Sclerosis Society UK. MS in the UK 2016 [cited 2017 27th March]. Available from: https://www.mssociety.org.uk/sites/default/files/MS%20in%20the%20UK%20January%202016_0.pdf.

40. Fox CM, Bensa S, Bray I, Zajicek JP. The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria. J Neurol Neurosurg Psychiatry. 2004;75(1):56-60.

41. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Epidemiology of multiple sclerosis: results from a large observational study in the UK. Journal of Neurology. 2015;262:2033-41.

42. Multiple Sclerosis Society UK. Disease modifying therapies 2017 [cited 2017 27th March]. Available from: https://www.mssociety.org.uk/dmts.

43. National Institute for Health and Care Excellence (NICE). Managing multiple sclerosis. Available from: http://pathways.nice.org.uk/pathways/multiple-sclerosis. (Accessed October 2017). 2017.

44. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13(7):657–65.

45. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819–28.

46. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.

47. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899–910.

48. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):911–23.

49. Ziemssen T, De Stefano N, Pia Sormani M, Van Wijmeersch B, Wiendl H, Kieseier BC. Optimizing therapy early in multiple sclerosis: An evidence-based view. Mult Scler Relat Disord. 2015;4(5):460–9.

50. Morris K, Yiannikas C. Treatment update in multiple sclerosis. Curr Allergy Asthma Rep. 2012;12(3):246-54.

51. Oh J, O'Connor PW. Established disease-modifying treatments in relapsing-remitting multiple sclerosis. Curr Opin Neurol. 2015;28(3):220-9.

52. Wilson LS, Loucks A, Gipson G, Zhong L, Bui C, Miller E, et al. Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis. Int J MS Care. 2015;17(2):74-82.

53. National Institute for Health and Care Excellence. Daclizumab for treating relapsing–remitting multiple sclerosis 2017 [cited 2017 27th March]. Available from: https://www.nice.org.uk/guidance/gid-ta10013/documents/final-appraisal-determination-document.

54. Pardo G, Jones DE. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. J Neurol. 2017.

55. National Institute for Health and Care Excellence. Alemtuzumab for treating relapsing‐remitting multiple sclerosis 2014 [cited 2017 24th March]. Available from: https://www.nice.org.uk/guidance/ta312?unlid=9383831612016229111.

56. 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. Pract Neurol. 2015;15(4):273–9.

57. National Institute for Health and Care Excellence. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis 2007 [cited 2017 24th March]. Available from: https://www.nice.org.uk/Guidance/TA127.

58. NHS England Clinical Reference Group for Neurosciences. Clinical Commissioning Policy: Disease modifying therapies for patients with multiple sclerosis (MS) 2014 [cited 2017 27th March]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf.

59. European Medicines Agency. Tysabri Summary of Prodcut Characteristics [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf.

60. European Medicines Agency. Plegridy Summary of Product Characteristics 2014 [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002827/WC500170302.pdf.

61. European Medicines Agency. Copaxone SmPC 2017 [November 2017]. Available from: https://www.medicines.org.uk/emc/medicine/17516.

62. European Medicines Agency. Tecfidera Summary of Product Characteristics 2014 [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002601/WC500162069.pdf.

63. European Medicines Agency. Aubagio Summary of Product Characteristics [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002514/WC500148682.pdf.

64. European Medicines Agency. Gilenya Summary of Product Characteristics [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf.

65. European Medicines Agency. Zinbryta Summary of Product Characteristics [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003862/WC500210598.pdf.

66. European Medicines Agency. Lemtrada Summary of Product Characteristics [November 2017]. Available from: https://www.medicines.org.uk/emc/medicine/28917.

67. Mehr SR, Zimmerman MP. Reviewing the Unmet Needs of Patients with Multiple Sclerosis. American Health & Drug Benefits. 2015;8(8):426-31.

68. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(3):247–56.

69. National Institute of Health and Care Excellence. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis 2014 [cited 2017 24th March]. Available from: https://www.nice.org.uk/guidance/ta320.

70. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293–303.

71. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545–56.

72. Kappos L, Selmaj K, Arnold D, Havrdova E, Boyko A, Kaufman M, et al. Primary results of DECIDE: a randomized, double-blind, double-dummy, active-controlled trial of daclizumab HYP vs. Interferon β-1a in RRMS patients. Abstract presented at the 2014 joint ACTRIMS-ECTRIMS Meeting, 10–13 September 2014, Boston, MA, USA. 2014.

73. Coles AJ, Cohen JA, Fox EJ, Giovannoni G, Hartung HP, Havrdova E, et al. Alemtuzumab CARE-MS II 5-year follow-up: Efficacy and safety findings. Neurology. 2017;89(11):1117-26.

74. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1829–39.

75. Havrdova E, Arnold DL, Cohen JA, Hartung HP, 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.

76. Kappos L, Li D, Calabresi PA, 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(9805):1779–87.

77. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221-34.

78. F. Hoffmann-La Roche Ltd. Primary Clinical Study Report – Protocol WA21093 (OPERA II) – A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif ®) in patients with relapsing multiple sclerosis. 2016.

79. F. Hoffmann-La Roche Ltd. Primary Clinical Study Report – Protocol WA21092 (OPERA I) – A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif ®) in patients with relapsing multiple sclerosis. 2016.

80. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50(1):121–7.

81. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402–15.

82. Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol. 2014;261(4):773–83.

83. F. Hoffmann-La Roche Ltd. Pooled Analysis Report – OPERA I, WA21092 and OPERA II, WA21093 – Randomized, double-blind, double-dummy, parallel-group studies to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis. 2016.

84. 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(9316):1453–60.

85. 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(1):105–18.

86. 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.

87. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8(10):889–97.

88. Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med. 1987;317(7):408–14.

89. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012;18(4):418–24.

90. CAMMS Trial Investigators, Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359(17):1786–801.

91. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sorensen P, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416-26.

92. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. Ann Neurol. 2013;73(3):327–40.

93. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087–97.

94. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of

a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268–76.

95. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367(12):1098–107.

96. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand. 2006;113(5):283–7.

97. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002;59(10):1496–506.

98. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, Group GS. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013;73(6):705-13.

99. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43(4):655-61.

100. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996;39(3):285–94.

101. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet. 1998;352(9139):1498–504.

102. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7(10):903–14.

103. Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet. 2013;381(9884):2167–75.

104. Stepien A, Chalimoniuk M, Lubina-Dabrowska N, Chrapusta SJ, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study. Neuroimmunomodulation. 2013;20(4):213–22.

105. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20(6):705–16.

106. Clinicaltrials.gov. A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis 2016 [cited 2017 1st June]. Available from: https://clinicaltrials.gov/ct2/show/NCT01412333.

107. Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. Ther Adv Neurol Disord. 2016;9(1):44–52.

108. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376(3):209-20.

109. Multiple Sclerosis Trust. Evidence for MS Specialists: findings from GEMSS. 2015.

110. Anthony DC, Dickens AM, Seneca N, Couch Y, Campbell S, Checa B, et al. Anti-CD20 inhibits T cell-mediated pathology and microgliosis in the rat brain. Ann Clin Transl Neurol. 2014;1(9):659-69.

111. Fujihara K, Nakashima I. Secondary progression and innate immunity in NMO: A possible link to alemtuzumab therapy? Neurol Neuroimmunol Neuroinflamm. 2014;1(3):e38.

112. Fox RJ, Cree BA, De Seze J, Gold R, Hartung HP, Jeffery D, et al. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. Neurology. 2014;82(17):1491-8.

113. Hatcher SE, Waubant E, Nourbakhsh B, Crabtree-Hartman E, Graves JS. Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment. JAMA Neurol. 2016;73(7):790-4.

114. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health: time matters in multiple sclerosis. Multiple Sclerosis and Related Disorders. 2016;9, Supplement 1:S5-S48.

115. European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. 26 March 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf. (Accessed 8 April 2015).

116. Hawton A, Green C. Health Utilities for Multiple Sclerosis. Value Health. 2016;19(4):460-8.

117. Maurer M, Comi G, Freedman MS, Kappos L, Olsson TP, Wolinsky JS, et al. Multiple sclerosis relapses are associated with increased fatigue and reduced health-related quality of life - A post hoc analysis of the TEMSO and TOWER studies. Mult Scler Relat Disord. 2016;7:33-40.

118. Pugliatti M. Multiple sclerosis: Preventing progression and disability in MS[mdash]when to treat? Nat Rev Neurol. 2013;9(3):129-30.

119. Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer. 2006;118(4):979-84.

120. European Medicines Agency. Avonex Summary of Product Characteristics [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000102/WC500029425.pdf.

121. European Medicines Agency. Rebif Summary of Product Characteristics [November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000136/WC500048681.pdf.

122. Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Mult Scler. 2012;18(2 Suppl):7–15.

123. 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 Health. 2007;10(1):54–60.

124. Phillips G, Guo S, Bender R, Havrdova E, Proskorovsky I, Vollmer T. Assessing the impact of multiple sclerosis disease activity and daclizumab HYP treatment on patient-reported outcomes: Results from the SELECT trial. Mult Scler Relat Disord. 2016;6:66-72.

125. 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(5):386–9.

126. Institute for Clinical and Economic Review. Disease-Modifying Therapies for RelapsingRemitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. 2017.

127. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444–52.

128. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol. 2014;14:58.

129. Gudesblatt M, Wissemann K, Zarif M, Bumstead B, Fafard L, Blitz K, et al. Multiple sclerosis, EDSS, and objective cognitive function: a walking scale with no apparent brains and limited thought. Mult Scler J. 2016;22:144-5.

130. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand. 1982;65(4):248-66.

131. National Institute for Health and Care Excellence. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis 2002 [cited 2017 24th March]. Available from: https://www.nice.org.uk/Guidance/ta32.

132. Office for National Statistics. National life tables, UK: 2013 – 2015 [Accessed August 2017]. Available from:

https://www.ons.gov.uk/releases/nationallifeexpectancytablesuk2013to2015.

133. Sadovnick AD, Ebers GC, Wilson RW, Paty DW. Life expectancy in patients attending multiple sclerosis clinics. Neurology. 1992;42(5):991-4.

134. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med. 1997;29(2):101-6.

135. National Institute for Health and Care Excellence. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis 2012 [cited 2017 24th March]. Available from: https://www.nice.org.uk/Guidance/ta254.

136. Dolan P, Gudex C, Kind P, A W. A Social Tariff for EuroQoL: Results from a UK General Population Survey. University of York, Discussion Paper 138. 1995.

137. Kobelt G, Berg J, Lindgren P, Kerrigan J, Russell N, Nixon R. Costs and quality of life of multiple sclerosis in the United Kingdom. Eur J Health Econ. 2006;7 Suppl 2:S96-104.

138. Fogarty E, Walsh C, Adams R, McGuigan C, Barry M, Tubridy N. Relating health-related Quality of Life to disability progression in multiple sclerosis, using the 5-level EQ-5D. Mult Scler. 2013;19(9):1190-6.

139. 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. J Neurol Neurosurg Psychiatry. 2015;86(2):208-15.

140. Willis MD, Harding KE, Pickersgill TP, Wardle M, Pearson OR, Scolding NJ, et al. Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort. Mult Scler. 2016;22(9):1215-23.

141. Curtis L, Burns A. PSSRU Unit Costs of Health and Social Care 2016. University of Kent, Canterbury, Unit PSSR; 2016.

142. Department of Health. NHS reference costs 2016 [cited 2017 September]. Available from: https://www.gov.uk/government/collections/nhs-reference-costs.

143. Karampampa K, Gustavsson A, Miltenburger C, Tyas D. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. Mult Scler. 2012;18(2 Suppl):41–5.

144. Institute for Clinical and Economic Review. Institute for Clinical and Economic Review Releases Evidence Report on Disease-Modifying Therapies for Multiple Sclerosis, including Daclizumab and Ocrelizumab 2017 [Accessed September 2017]. Available from: https://icer-review.org/announcements/ms-evidence-report/.

B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: OPERA I and OPERA II open-label extension data

Appendix M: Research study into healthcare and social care costs in MS

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Single technology appraisal

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Dear [redacted]

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 27th November from Roche. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **8 January 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [https://accounts.nice.org.uk/signin?wa=wsignin1.0&wtrealm=https%3a%2f%2fappraisals.nice.org.uk&wctx=rm%3d0%26id%3dpassive%26ru%3dhttps%253a%252f%252fappraisals.nice.org.uk%252f&wct=2014-06-06T11%3a16%3a46Z].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to [redacted] Project Manager [redacted]

Yours sincerely

[redacted]

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Associate Director – Appraisals
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Encl. checklist for confidential information

Not applicable – no confidential information in this document.

Section A: Clarification on effectiveness data

Literature searching and screening

A1. Please explain the methods used for eligibility screening in each of the systematic reviews conducted (clinical effectiveness, cost effectiveness, HRQoL, resource use): how many reviewers checked titles, abstracts and full-text records and how were any disagreements between reviewers resolved?

A2. Who is the client referred to in Table 4, Appendix D.1.1 and what were the four papers supplied by the client?

A3. What were the additional sources for the 987 references in Figure 1, Appendix D.1.1?

A4. As the PICO criteria for the searches were broader than the NICE decision problem, did this remain the same for the screening of the full papers or was it refined (if refined, please provide details)?

Missing references

A5. **Priority question:** company submission Appendix Tables 5-6 list the 184 references for the 46 studies that are included in the systematic review of clinical effectiveness. However, copies of only 38 of these references were provided with the submission.

(a) Please provide copies of all the references listed in company submission Appendix Tables 5-6, together with any supplementary appendices they contain. Please provide as a priority the references listed in the following table (these relate to non-open-access studies for which no references were provided in the submission and therefore the ERG cannot currently appraise these studies):

References for which full text plus any supplementary appendices is required:
Cohen J, Belova A, Selmaj K. Equivalence of generic glatiramer acetate in multiple sclerosis. A randomized clinical trial. JAMA Neurol. 2015;72:1433-41.

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Kappos L, Selmaj K, Arnold D, Havrdova E, Boyko A, Kaufman M, et al. Primary results of DECIDE: a randomized, double-blind,double-dummy active controlled trial of daclizumab HYP vs. interferon β-1a in RRMS patients. 2014 Joint ACTRIMS-ECTRIMS Meeting, 10-13 September 2014; Boston, MA, USA2014.
Koch-Henriksen N, Sorensen P, Christensen T, Frederiksen J, Ravnborg M, Jensen K, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006;66:1056-60.
Knobler R, Greenstein J, Johnson K, Lublin F, Panitch H, Conway K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. J Interferon Res. 1993;13:333-40.
The primary reference for Saida et al. 2016 study (unclear what this is in the submission)
References for which the supplementary appendix only is required:
Calabresi P, Radue E, Goodin D, Jeffery D, Rammohan K, Reder A, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:545-56.
Calabresi P, Kieseier B, Arnold D, Balcer L, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13:657-65.
O'Connor P, Filippi M, Amason B, Comi G, Cook S, Goodin D, et al. 250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8:889-97.
Cohen J, Coles A, Arnold D, Confavreux C, Fox E, Hartung H-P, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380:1819-28.

(b) Please indicate which is the primary reference for each study (company submission Appendix page 23 states these are highlighted in bold, but no references are highlighted).

(c) Figure 1 in the Appendix indicates searches identified 184 documents but the total number of documents listed in Tables 6 and 7 of the Appendix is 183. Please explain the discrepancy.

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A6. Please provide a copy of the ocrelizumab EPAR. Appendix C1.2 states that the EPAR was to be provided with the submission but it is not included in the reference pack.

Ocrelizumab studies

A7. **Priority question:** The phase II ocrelizumab study includes a placebo arm and an IFN B-1a arm and therefore meets the NICE scope. The lack of a placebo arm in the OPERA studies is stated as being a limitation in several places in the submission (pages 25, 93, 97). We appreciate that the OPERA studies had longer duration than the phase II study but the phase II study could provide relevant information on early adverse events and early disease activity, as well as adding general support for the clinical evidence provided by the phase III studies.

(a) Please provide the clinical study report and protocol for the phase II study of ocrelizumab.

(b) Please provide a summary of the phase II study methods, results and conclusions for all outcomes assessed in the phase II study, including safety.

(c) The IFN B-1a and placebo comparators in the phase II study may have enabled different networks to have been formed for MTC analyses, or extension of existing MTC networks. For example, effects of ocrelizumab on early disease activity (which is prognostic of disability progression) might be compared across studies using MRI outcomes (e.g. changes in lesion activity as defined on MRI T1 and T2 weighted images, and changes in brain volume) which were widely reported. Although such outcomes do not directly inform the economic analysis they provide additional clinical information and may aid interpretation of clinical effectiveness. Please consider whether these analyses can be provided, or explain why analyses of early disease activity were not considered relevant for the current appraisal.

A8. EQ-5D was measured in the OPERA studies and also used for estimation of utilities in the economic analysis. However, the EQ-5D values provided in the submission were pooled across OPERA studies and categorised by EDSS score. Please provide the EQ-5D results for all available time points in the studies including: the mean (SE) EQ-5D values by trial arm and time point, and a p-value for the between-arm difference. Please also clarify whether there were any missing EQ-5D data and how these were taken into account when estimating utilities.

A9. **Priority question:** For the OPERA study subgroup analyses of HA and RES patients reported in section B.2.7 Tables 13-15 of the submission:

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(a) Please provide an additional row in each of Tables 13-15 for the residual subgroup of patients, i.e. those patients from the ITT population who are not in the HA and RES subgroups.

(b) Please provide data in a similar format as in Table 13-15 for the all-cause discontinuation outcome, for the HA, RES and residual subgroups.

(c) please provide baseline characteristics of the patients in each subgroup so that they can be compared with the baseline characteristics of the ITT population (i.e. presented in the same format as Table 8 section B.2.3 in the submission).

A10. Appendix E states that a greater reduction of CDP12 and CDP24 was observed for ocrelizumab than with IFNB-1a across all subgroups. Patients with baseline weight <75 kg showed a greater reduction in CDP12 and CDP24 in the OCR versus IFN groups compared with patient with baseline weight ≥ 75 kg. Please provide empirical evidence to support these statements (e.g. tables and/or forest plots).

A11. Please explain the rationale for stratifying analyses by USA versus rest of the world groups and for stratifying analyses by baseline EDSS values of <4.0 versus ≥4.0 (submission Table 10).

A12. Please explain why the analysed population for the NEDA outcome was restricted to patients with an EDSS score of ≥2 at baseline.

MTC analyses

A13. Please provide the programming code for each MTC analysis.

A14. **Priority question.** Page 104 of the Appendix states that 13 studies were excluded from the MTC but Table 9 in the Appendix appears to suggest that up to 19 studies were excluded. However, Table 9 in the Appendix does not provide any reference citation numbers so it is not fully clear which studies are being referenced. Furthermore, 23 separate MTCs were conducted rather than just one and it is not clear which of the 46 studies included in the systematic review were excluded from each specific MTC and why.

(a) For each of the MTCs conducted please provide a table listing the studies that were excluded and the reason(s) why.

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(b) The statement in the bottom-left cell of Table 9 of the Appendix appears to imply that the statistical power of studies was related to study duration. Please explain this. The calculations for ARR, CDP12, CDP24 and all-cause discontinuation specified on pages 133-135 of the Appendix appear to be independent of the statistical power of primary studies, so why is this relevant?

(c) Please explain why a cut-off of 48 weeks was considered appropriate for excluding studies rather than, say, 36 weeks or 96 weeks. Was this a pragmatic decision to maximise data availability for MTCs or based on clinical reasons? Was sensitivity analysis conducted to ascertain the impact of the time cut-off on MTC results?

(d) Please explain the "feasibility" assessment referred to on page 42 of the submission and on pages 104 and 106 of the Appendix. This appears to be a post-hoc determination and application of eligibility criteria. Why were the eligibility criteria not pre-specified, as is normally considered good practice in evidence synthesis?

A15. **Priority question:** company submission Appendix pages 133-134 briefly describe the general methods used to estimate the risk ratios for ARR, the hazard ratios for CDP12 and CDP24, and the odds ratios for all-cause discontinuation that were calculated in MTC analyses. However, the data extracted from the studies to enable these calculations are not reported in the submission. For each MTC analysis please provide the specific input data for the analysis, so that it is clear how these data were obtained from the data given in each study report (e.g. the numbers at risk at each time point, number of events, etc).

A16. **Priority question:** company submission Appendix page 133 describes the methods of analysing adjusted and unadjusted annualised relapse rates but the methods are stated as being identical.

(a) Please confirm whether the description of the analyses is correct.

(b) Please explain how the inclusion of adjusted and unadjusted relapse rates in MTC analyses influences interpretation of the results. Was sensitivity analysis conducted to clarify the impact of (lack of) adjustment?

(c) Where adjusted relapse rates were used please provide details of the variables that were adjusted for and comment on the significance of any differences in the adjustments between the studies.

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(d) The definition of annualised relapse rate differed among the included studies (e.g. any relapses, confirmed relapses, protocol-defined relapses, qualifying relapses) and some studies conducted sensitivity analyses on the different definitions (e.g. CombiRx, CONFIRM, DEFINE, REGARD, TENERE). Please explain how variation in the definitions would influence interpretation of the MTC results. Where studies reported more than one definition of the annualised relapse rate please explain which definition was used in the MTC analyses.

A17. **Priority question:** In section B.2.9.1 (page 69) an assumption is made that hazards are proportional for CDP outcomes. Please provide a justification for this assumption.

A18. **Priority question:** company submission Appendix pages 133-134 describe the methods of analysing CDP12 and CDP24 outcomes in the MTCs but the definition of the event (CDP) is not explicitly considered. According to the study publications there appear to be differences between studies in the EDSS cut-off values used to determine disability progression.

(a) Please provide details of any differences between studies in the definitions of CDP and comment on the significance of these for interpretation of the MTC results.

(b) On page 134 of the Appendix it is stated that the appropriateness of the method for analyzing CDP12 and CDP24 outcomes was assessed by reviewing the studies that reported both HRs and count data. Generally the observed and derived hazard ratios are similar. Please provide the data from these studies comparing HRs and counts to justify this assertion.

A19. **Priority question:** Meta-regression on study duration was employed in MTC analyses. Although network diagrams are given for these analyses, few other details of these analyses are provided in the submission.

(a) Please explain the rationale for these analyses.

(b) Please describe the method employed for fitting the meta-regression model for each outcome.

(c) Please present the results of each meta-regression analysis in such a way that they can be compared against the results of the meta-analyses (e.g. tables and/or forest plots comparable to those currently given in the submission for the MTC results). Please provide the estimates of model fit for the meta-regression and the corresponding meta-analysis of each outcome.

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A20. **Priority question:** company submission Appendix D presents results of heterogeneity assessments in the MTC, with forest plots provided for the direct pairwise meta-analysis comparisons where moderate to high heterogeneity had been identified (I^2 50%-75%).

> (a) Please would you provide the forest plots for all of the remaining pairwise direct comparisons as indicated in Appendix Table 27, with heterogeneity statistics included. This will enable us to check the consistency of these point estimates with those from the MTC.
>
> (b) Please would you supply the forest plots for all the direct pairwise meta-analysis comparisons for the sub-group MTCs (i.e. for the HA and RES subgroups).
>
> (c) Please explain what you mean by the "inconsistency model". Does this assess the consistency of direct and indirect evidence where there are closed loops in a network, or some other aspect of consistency? Please provide an explicit definition of the consistency assumption as employed in the MTC models. Please explain how the MTC models were altered to remove the consistency assumption.

A21. Please supply the full citation for Turner et al.2015, as cited in Appendix D (page 135).

A22. According to Appendix Table 12, the majority of studies considered for MTC analyses were on treatment-experienced patients with relatively few being treatment-naïve. Please justify the rationale for including both groups in the same analysis. Was sensitivity analysis conducted on these groups? Please comment on how the results from the MTC analysis apply to the anticipated use of ocrelizumab in clinical practice in treatment-experienced and treatment-naïve patients.

A23. **Priority question:** According to pages 102-104 in the current ocrelizumab submission, the daclizumab company submission to NICE conducted a MTC for adverse events and these data were used to source the annual risk of adverse events for the comparators. As IFNB-1a (Rebif) is common between the OPERA studies and the daclizumab MTC, the ocrelizumab adverse event rates were adjusted using an adverse event rate ratio estimated from adverse event rates for IFNB-1a (Rebif) from the daclizumab submission and pooled analysis of OPERA I and II.

The source of the data given in Table 40 of the current ocrelizumab submission appears to be Table 79 (page 214) in the daclizumab company submission. However, these data are not referred to in the daclizumab submission as having been derived from an MTC.

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(a) Please confirm whether a MTC of adverse events was indeed conducted in the daclizumab appraisal. If so, please provide a list of the studies included. Please explain why that existing MTC was not updated to include the OPERA studies.

(b) Please comment on the reliability of the adverse event rate estimates for ocrelizumab given that they were estimated by a post-hoc adjustment using external data rather than by including the OPERA studies in an MTC.

A24. In the BRAVO trial the placebo was matched to laquinimod (oral capsule once daily) whereas the active comparator of interest (interferon beta-1a) was administered intra-muscularly once per week. There was no placebo matched to interferon beta-1a in BRAVO. Please explain why BRAVO was included in the MTC and how the lack of a matched placebo affects interpretation of the MTC results.

A25. In company submission Appendix Table 10 the MSCRG trial (Jacobs et al 1996, reference 100 in the submission) is stated as having a natalizumab arm containing 47 patients. However, the Jacobs et al. reference does not mention a natalizumab arm. Please explain this discrepancy.

A26. At what time point in the OPERA I trial were the baseline and post-baseline anti-drug antibody assays carried out (section B.2.10, page 76, Table 22)?

A27. Please provide annual rates of discontinuation from the OPERA and OLE studies.

A28. The submission section B.2.10 and Appendix L do not report any adverse events in the OPERA OLE study.

(a) Please provide information on all adverse events that have occurred in the OPERA OLE study.

(b) The adverse events data as summarised in Table 40 of the submission do not appear to capture any events observed in the OLE study for ocrelizumab or (where conducted) the extension studies for the comparators. As such, the full available data on adverse events does not appear to have been utilised. Please explain this omission.

Section B: Clarification on cost-effectiveness data

B1. The results of the economic analysis are presented using a ‘blended ABCR’ comparator, with costs and QALYs weighted according to market share (company submission Table 55,

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page 125). In previous appraisals, sensitivity analysis has been used to investigate the robustness of cost-effectiveness results to uncertainty over market share. Please explain how the market share estimates in Table 55 were derived, the extent of uncertainty over them, and the sensitivity of results to this uncertainty.

B2. Treatments contained in a blended comparator must be mutually exclusive, it must be reasonable that they could be collectively displaced by ocrelizumab. Please provide details of how this assumption was validated for 'blended ABCR', give details of any clinical expert opinion that was sought.

B4. Please provide economic analyses comparing ocrelizumab with glatiramer acetate alone and ocrelizumab compared with one interferon beta alone.

Section C: Textual clarifications and additional points

C1. What does N/A mean for the outcomes in Table 6 of the company submission? The ocrelizumab phase II study did report outcomes relevant to the decision problem, so this may appear misleading.

ID937 Ocrelizumab in RRMS

Roche Response to ERG Clarification Questions

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Section A: Clarification on effectiveness data

Literature searching and screening

A1. Please explain the methods used for eligibility screening in each of the systematic reviews conducted (clinical effectiveness, cost effectiveness, HRQoL, resource use): how many reviewers checked titles, abstracts and full-text records and how were any disagreements between reviewers resolved?

Response: For each of the systematic reviews (clinical effectiveness, cost effectiveness, HRQoL, resource use), two reviewers independently checked titles, abstracts and full-text records, and any disagreements were resolved by a third reviewer.

A2. Who is the client referred to in Table 4, Appendix D.1.1 and what were the four papers supplied by the client?

Response: The 'client' meant 'Roche'. Apologies for this oversight. The four documents referred to were:

- 2 CSRs for the OPERA trials
- A power point presentation from a conference: Hauser SL, Comi CC, Hartung HP, Selmaj K, Traboulsee A, Bar-Or A, et al. Efficacy and safety of ocrelizumab in relapsing multiple sclerosis – results of the phase iii double-blind, interferon beta-1a-controlled opera i and ii studies [Powerpoint presentation]. ECTRIMS 2015. Presentation 190.
- A poster from a conference: Newsome S, Balcer L, Boyko A, Pelletier J, Arnold D, Liu S, et al. Efficacy and safety of peginterferon beta-1a in relapsing-remitting multiple sclerosis: 2-year data from the ADVANCE study [poster]. In: Joint Meeting of the CMSC and ACTRIMS, Dallas, TX; 2014. DX57

A3. What were the additional sources for the 987 references in Figure 1, Appendix D.1.1?

Response: These additional records were identified through systematic hand searching of specific conferences and regulatory websites, as opposed to systematic database searching.

The conference and regulatory websites searched are described in the NICE submission Appendix D1.1, page 9-10.

A4. As the PICO criteria for the searches were broader than the NICE decision problem, did this remain the same for the screening of the full papers or was it refined (if refined, please provide details)?

Response: The PICO criteria applied and remained the same throughout the systematic literature review stages of a) title and abstract screening, and b) full text review.

The specific treatments and doses approved by the European Medicines Agency were identified at the feasibility assessment stage. The scope was then narrowed down accordingly.

Sensitivity analyses in light of the NICE decision problem were run for restricted networks and results provided in the NICE submission Appendix D1.4.

Missing references

*A5. **Priority question:** company submission Appendix Tables 5-6 list the 184 references for the 46 studies that are included in the systematic review of clinical effectiveness. However, copies of only 38 of these references were provided with the submission.*

(a) Please provide copies of all the references listed in company submission Appendix Tables 5-6, together with any supplementary appendices they contain. Please provide as a priority the references listed in the following table (these relate to non-open-access studies for which no references were provided in the submission and therefore the ERG cannot currently appraise these studies):

References for which full text plus any supplementary appendices is required:

Cohen J, Belova A, Selmaj K. Equivalence of generic glatiramer acetate in multiple sclerosis. A randomized clinical trial. JAMA Neurol. 2015;72:1433-41.

Kappos L, Selmaj K, Arnold D, Havrdova E, Boyko A, Kaufman M, et al. Primary results of DECIDE: a randomized, double-blind,double-dummy active controlled trial of daclizumab HYP vs. interferon β-1a in RRMS patients. 2014 Joint ACTRIMS-ECTRIMS Meeting, 10-13 September 2014; Boston, MA, USA2014.

Koch-Henriksen N, Sorensen P, Christensen T, Frederiksen J, Ravnborg M, Jensen K, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006;66:1056-60.

Knobler R, Greenstein J, Johnson K, Lublin F, Panitch H, Conway K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. J Interferon Res. 1993;13:333-40.

The primary reference for Saida et al. 2016 study (unclear what this is in the submission)

References for which the supplementary appendix only is required:

Calabresi P, Radue E, Goodin D, Jeffery D, Rammohan K, Reder A, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:545-56.

Calabresi P, Kieseier B, Arnold D, Balcer L, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13:657-65.

O'Connor P, Filippi M, Amason B, Comi G, Cook S, Goodin D, et al. 250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8:889-97.

Cohen J, Coles A, Arnold D, Confavreux C, Fox E, Hartung H-P, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380:1819-28.

Response: Apologies for the omission, these references have now been uploaded to NICE Docs.

(b) Please indicate which is the primary reference for each study (company submission Appendix page 23 states these are highlighted in bold, but no references are highlighted).

Response: Apologies for the formatting error, the two tables have been recreated in the Appendix below with primary studies highlighted in bold (Table 25 and Table 26).

(c) Figure 1 in the Appendix indicates searches identified 184 documents but the total number of documents listed in Tables 6 and 7 of the Appendix is 183. Please explain the discrepancy.

Response: Apologies for the oversight, the number of documents identified was 183.

A6. Please provide a copy of the ocrelizumab EPAR. Appendix C1.2 states that the EPAR was to be provided with the submission but it is not included in the reference pack.

Response: We do not yet have a copy of the EPAR. The EPAR is expected to become available on the EMA website upon marketing authorization in mid-January. A copy will be uploaded to NICE Docs once available.

Ocrelizumab studies

*A7. **Priority question:** The phase II ocrelizumab study includes a placebo arm and an IFN B-1a arm and therefore meets the NICE scope. The lack of a placebo arm in the OPERA studies is stated as being a limitation in several places in the submission (pages 25, 93, 97). We appreciate that the OPERA studies had longer duration than the phase II study but the phase II study could provide relevant information on early adverse events and early disease activity, as well as adding general support for the clinical evidence provided by the phase III studies.*

Response: Having a placebo-controlled trial would have facilitated a MTC with fewer node jumps, this is what the limitation refers to. However, we would like to clarify that we do not consider the lack of a placebo arm in the two OPERA studies a limitation in study design. On the contrary, the fact that the OPERA studies were uniquely designed as head-to-head studies with a blinded active control arm to avoid the potential influence of differential use of comparator therapy represents a key strength of the ocrelizumab clinical trial program.

The purpose of the Phase II study was to estimate the potential effect of ocrelizumab and to determine the appropriate dose to be tested in Phase III.

(a) Please provide the clinical study report and protocol for the phase II study of ocrelizumab.

Response: Two CSRs for the phase II study (WA21092), one for the core phase of the trial and another for Treatment-Free Period (TFP) and Open-label Extension (OLE) phase, and the corresponding protocol are included in the updated reference pack uploaded to NICE Docs.

(b) Please provide a summary of the phase II study methods, results and conclusions for all outcomes assessed in the phase II study, including safety.

Response:

Methods

Study WA21092 was a supportive proof-of-concept and dose-finding Phase II study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS. The Phase II trial was a parallel-group, double-blind, placebo-controlled study. The design of the study is summarised in Table 1 and comprised of low-dose ocrelizumab (600 mg given in two 300 mg doses on days 1 and 15) and high-dose ocrelizumab (2000 mg; given as two 1000 mg doses on days 1 and 15), versus placebo, with an open-label active comparator group (IFNB-1a [Avonex.], given as 30 µg once per week). At week 24 all patients switched over to receive ocrelizumab. At week 24 and 48, patients in the initial placebo group, 600 mg ocrelizumab group and IFNβ-1a groups received ocrelizumab 600 mg, and the ocrelizumab 2000 mg group received 1000 mg ocrelizumab. At week 72 all patients received 600 mg ocrelizumab.

Table 1 Design of the ocrelizumab Phase 2 trial

Screening	**Randomization**	**Treatment Period (96 week)**					
		Placebo-controlled period (24 weeks)		**OCR Treatment Period (doses separated by 24 weeks)**			
		Dose 1		**Dose 2**		**Dose 3**	**Dose 4**
4 weeks	Group	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1
	A (1000 mg regime)	OCR 1000	OCR 1000	OCR 1000	Placebo	OCR 1000	OCR 600
	B (600 mg regime)	OCR 300	OCR 300	OCR 600	Placebo	OCR 600	OCR 600
	C	Placebo	Placebo	OCR 300	OCR 300	OCR 600	OCR 600
	D	IFNB-1a (Avonex) 30 ug IM qwk		OCR 300	OCR 300	OCR 600	OCR 600

The primary objective was to investigate the effect of ocrelizumab on the total number of gadolinium-enhancing T1 lesions observed on brain MRI scans for weeks 12, 16, 20, and 24 versus placebo. A fourth study group with interferon beta-1a was included as an active, open label, rater-masked control. Key secondary endpoints included: the annualised protocol-defined relapse rate; proportion of relapse-free patients; total

number of gadolinium-enhancing T1 lesions (all data points from 4–24 weeks); total number of new gadolinium-enhancing T1 lesions; change in total volume of T2 lesions from baseline to week 24; safety and tolerability of two dose regimens of ocrelizumab versus placebo and interferon beta-1a at week 24; and safety of ocrelizumab therapy up to 96 weeks of follow-up.

A total of 220 patients were enrolled in the phase II trial: 54 patients in the placebo group; 56 in the ocrelizumab 600 mg group; 55 in the ocrelizumab 1000 mg group; 55 in the IFNB-1a group. One patient in the low-dose ocrelizumab group and one in the IFNB-1a group were not treated and were excluded from the ITT and safety populations. At week 48, a total of 196 patients completed the trial (placebo, n = 52; 600 mg ocrelizumab, n = 49; 1000 mg ocrelizumab, n = 46; IFNB-1a, n = 49).

Baseline demographics and disease characteristics were mostly similar across the treatment groups, with slight numerical differences for duration of MS and Gd-T1 lesions. The majority of patients were female (59-69% across treatment groups) and baseline EDSS scores were 3.1–3.5. Duration since MS symptom onset ranged from 4.8 years in the placebo group to 7.7 years in the ocrelizumab 1000 mg group.

Results

Primary endpoint

The primary endpoint of the study was met, with the total number of Gd-enhancing T1 lesions reduced for the ocrelizumab 600 mg and 2000 mg groups compared with placebo (Table 2; both p < 0.0001). No clear separation in the primary endpoint was observed between the OCR 600 mg group and the OCR 1000 mg groups.

Table 2 Results for primary endpoint of ocrelizumab phase II study: number of Gd-enhancing T1 lesions

Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
WEEK 12, 16, 20 and 24				
n	54	51	52	52
Mean (SD)	5.6 (12.53)	0.6 (1.52)	0.2 (0.65)	6.9 (16.01)
SE	1.71	0.21	0.09	2.22
Median	1.7	0.0	0.0	1.0
95% CI of Median	(0.4,3.0)	(0.0,0.0)	(0.0,0.0)	(0.0,2.0)
Range	0-79	0-7	0-3	0-78
Van Elteren Test (stratified) p-value		<0.0001	<0.0001	0.7496
Van Elteren Test (stratified*) p-value		<0.0001	<0.0001	0.3457
Wilcoxon-Mann-Whitney Rank Sum Test p-value		<0.0001	<0.0001	0.3721

Van Elteren test is stratified by region and presence of baseline gadolinium-enhancing lesions (absent or present).
* Van Elteren test is stratified by region only.
Average Method Imputation only occurs from Weeks 0-24; No Imputation at Weeks 96 and 144
For the calculation of Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain at a specific week before week 24, the missing value at a time point is imputed using the average of available observations at the other time points before week 24.
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.
Source: page 552

Secondary endpoints

Over weeks 4 to 24, the total number of new and persisting Gd-enhancing lesions was lower in both ocrelizumab groups compared to placebo (both $p < 0.0001$). The change in total volume of T2 lesions did not differ significantly between groups at week 24.

Treatment with ocrelizumab was associated with a significant reduction in ARR over 24 weeks compared with placebo. Although results numerically favoured ocrelizumab, the proportion of patients relapse-free at week 24 were not significantly different between groups.

No clear separation in the secondary endpoints was observed between the OCR 600 mg group and the OCR 1000 mg groups.

All efficacy endpoints were generally consistent with what was later observed in the larger Phase III trials, OPERA I and OPERA II.

Table 3 Overview of clinical results from ocrelizumab phase II study

Endpoint p-value vs Placebo	Placebo	OCR 600 mg Arm	OCR 1000 mg Arm	Avonex
Total No. of Gd T1 lesions (Week 12 to 24) Mean (SD)	5.6 (12.53)	0.6 (1.52) <0.0001	0.2 (0.65) <0.0001	6.9 (16.01) 0.3457
Adjusted ARR [a] (95% CI)	0.557 (0.370,0.839)	0.127 (0.054,0.299) 0.0019	0.213 (0.110,0.414) 0.0136	0.364 (0.220,0.602) 0.1814
Proportion of relapse-free patients (95% CI)	75.9% (64.5%,87.3%)	85.5% (76.1%,94.8%) 0.1978	87.3% (78.5%,96.1%) 0.1310	77.8% (66.7%,88.9%) 0.8206
Total No. of Gd T1 lesions (Week 4 to 24) Mean (SD)	8.7 (17.54)	2.5 (5.10) <0.0001	1.8 (5.26) <0.0001	10.3 (22.15) 0.2725
Total No. of new Gd T1 lesions (Week 4 to 24) Mean (SD)	5.1 (11.99)	0.8 (1.95) <0.0001	0.8 (2.16) <0.0001	6.2 (13.79) 0.4985
Total T2 volume (change from BL to Week 24) Median (95% CI)	23.7 (-121.2,192.3)	-76.3 (-297.6,-34.2) 0.1391	-163.4 (-679.5,60.5) 0.1596	2.6 (-121.2,555.8) 0.4740

Gd = gadolinium, BL = baseline

[a] adjusted for geographic region

Safety

The overall proportion of patients with AEs was similar between treatment groups (Table 4). During the placebo-controlled 24-week period, the number of AEs was similar between the placebo (117 events) and the OCR 600 mg group (116 events) and higher in the OCR 1000 mg group (142 events). The percentage of patients with at least one AE was similar across all 4 treatment groups. The higher number of AEs in the OCR 1000 group was driven mainly by higher number of IRRs reported during the first and the second infusions of 1000 mg.

Following the initial placebo-controlled period, the AE profile of OCR during the open label treatment period up to Week 96 was consistent with observations during the first 24 weeks.

Table 4 Overview of adverse events from placebo-controlled period and treatment period*

	Group C: Placebo	Group A: Ocrelizumab 600 mg regime	Group B: Ocrelizumab 1000 mg regime	Group D: Avonex
Baseline to Week 24, Cycle 1				
	N=54	N=55	N=55	N=54
Nr of patients with AEs	38 (70.4%)	35 (63.6%)	36 (65.5%)	32 (59.3%)
Nr of AEs	117	116	142	91
Nr of patients with SAEs	2 (3.7%)	1 (1.8%)	2 (3.6%)	2 (3.7%)
Week 24 to 48, Cycle 2				
	N=53	N=50	N=47	N=50
Nr of patients with AEs	38 (71.7%)	27 (54.0%)	24 (51.1%)	30 (60.0%)
Nr of AEs	88	74	61	66
Nr of patients with SAEs	1 (1.9%)	1 (2.0%)	2 (4.3%)	3 (6.0%)
Week 48 to 72, Cycle 3				
	N=50	N=49	N=46	N=49
Nr of patients with AEs	25 (50.0%)	24 (49.0%)	27 (58.7%)	19 (38.8%)
Nr of AEs	43	53	40	46
Nr of patients with SAEs	1 (2.0%)	3 (6.1%	2 (4.3%)	4 (8.2%)
Week 72 to 96, Cycle 4				
	N=49	N=46	N=44	N=46
Nr of patients with AEs	24 (49.0%)	21 (45.7%)	21 (47.7)	16 (34.8)
Nr of AEs	42	34	42	28
Nr of patients with SAEs	-	-	1 (2.3%)	2 (4.3%)

*All patients were scheduled to undergo 96 weeks of study treatment, representing four 24-week treatment cycles

Additional Safety Follow-up

The Phase II study consisted of a 24-week placebo-controlled period and a 96-week treatment period. Thereafter the study was followed by a Treatment-Free period (TFP) of variable duration (minimum 48 weeks). This period included at least 3 visits at Week 108, Week 120, and Week 144. Patients who completed both the main (96-week) treatment period and the TFP were invited to participate in the open label extension (OLE) study. During the OLE patients received ocrelizumab 600 mg every 24 weeks.

A total of 196 patients entered the TFP, and over 90% of them completed safety follow-up. 131 patients completed the TFP. Thereafter, 103 patients entered the OLE period. The population enrolled into the OLE was representative of the overall population of patients enrolled in the main study. However, due to the low number of patients and the fact that selection bias cannot be excluded, data should be interpreted with caution.

No new safety findings were identified during the TFP or the OLE period. No increase in the rate or incidence of infections or serious infections was observed during the TFP or the OLE period compared with the main 96-week treatment period. The IRR

profile observed during the OLE was consistent with the main 96-week treatment period in terms of severity and nature of symptoms.

(c) The IFN B-1a and placebo comparators in the phase II study may have enabled different networks to have been formed for MTC analyses, or extension of existing MTC networks. For example, effects of ocrelizumab on early disease activity (which is prognostic of disability progression) might be compared across studies using MRI outcomes (e.g. changes in lesion activity as defined on MRI T1 and T2 weighted images, and changes in brain volume) which were widely reported. Although such outcomes do not directly inform the economic analysis they provide additional clinical information and may aid interpretation of clinical effectiveness. Please consider whether these analyses can be provided, or explain why analyses of early disease activity were not considered relevant for the current appraisal.

Response: The two Phase III trials, OPERA I and OPERA, demonstrated near-complete suppression of both Gd-T1 and new or enlarging T2 lesions. Patients in the Phase II trial underwent more frequent MRIs, as scans were performed every 4 weeks in the controlled period of the phase II trial as opposed to after 6, 12 and 18 months in the OPERA trials. The results from the Phase II study confirmed that suppression of brain lesions occurred soon after initiation of ocrelizumab.

The rationale for not including results from the ocrelizumab Phase II trial in the MTC, and majority of Phase II results from other treatments, is that the short duration of these trials preclude meaningful results on clinical outcomes (see response to question A14.c). Phase II studies are typically proof of concept studies in the target patient population with surrogate marker primary endpoints (typically MRI endpoints in MS) and are not powered for meaningful comparisons of clinical endpoints.

Although early disease activity as measured by the more frequent MRIs in Phase II trials is important (details of MRI outcomes from the ocrelizumab Phase II trial have been provided in response to question A7.b), comparing MRI outcomes across clinical trials is especially difficult as the quality and sensitivity of MRI measurements has evolved considerably over time. Thus, a MTC of MRI outcomes was not conducted.

However, in response to the question and to contextualize the MRI results of ocrelizumab, a *simplified and exploratory* indirect comparison was performed versus alemtuzumab. The rationale for selecting alemtuzumab that it is another high efficacy DMT and the pivotal studies had a common comparator, IFNB-1a (Rebif). Furthermore, the ocrelizumab and alemtuzumab pivotal studies were conducted in a similar era and as such it was reasonable to assume that MRI techniques were comparable. The alemtuzumab Phase II trial, although having IFNB-1a (Rebif) as comparator and having similar duration to the Phase III trials, did not report standard lesion outcomes and as such was not included in the *exploratory* indirect comparison.

<u>Aim</u>

The purpose of this *exploratory* analysis was to perform an indirect treatment comparison (ITC) between ocrelizumab 600mg (OCR) and alemtuzumab. There were two types of lesions considered in the analysis: Gadolinium (Gd)-enhancing T1 lesions and new or enlarging T2 lesions. The endpoints analysed were as follows:

- proportion of patients with one or more Gd-T1 lesions
- proportion of patients with one or more T2 lesions
- Gd-T1 lesion mean count
- T2 lesions mean count.

Data

The following trials were included in the ITC: OPERA 1, OPERA 2, CARE-MS I and CARE-MS II. Two sets of analyses were performed:

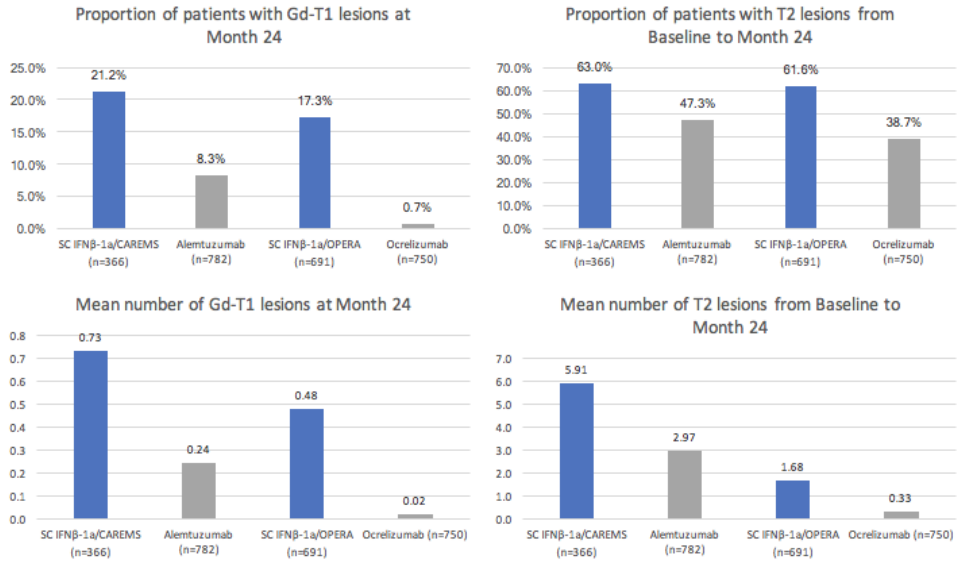
Base case analysis - Observed Cases

The observed case analysis consisted of all patients with available data (as presented in each publication) for the time period being analysed. Therefore, missing data was not considered in these analyses.

Sensitivity analysis - Randomised/Treated

The randomised/treated analysis included imputation for patients with missing data on each of the two dichotomous endpoints (proportion of patients with one or more lesions). It was considered inappropriate to assume that these data were missing at random, as patients with missing MRI assessments might have been too ill to attend the scheduled visits. Therefore, these patients were assumed to have one or more lesions.

Figure 1 MRI outcomes in CARE-MS and OPERA trials



Methods

A fixed effects logistic regression model was used to model the proportion of patients with one or more lesions. The model adjusted for study and treatment and assumed a binomial distribution and logit link function and it was applied using PROC GLIMMIX in SAS®. The difference in least squares means of OCR 600mg compared to each comparator treatment in the given network was presented along with its

corresponding standard error. The odds ratio, associated 95% CI and p-value were also provided for each treatment comparison of interest.

A random effects analysis of the proportion of patients with one or more lesions was carried out within a Bayesian framework using PROC MCMC in SAS® (using an arm-parameterization, (1). A logistic regression model was applied with study and treatment as fixed effects and study-by-treatment as normally distributed random effect. The prior for the standard deviation was a uniform distribution between 0 and 5. The priors for the fixed effects were all uninformative with mean 0. The mean differences on the log-scale between OCR 600mg and each other treatment in the given network was calculated from the posterior distribution and presented along with the standard error. The odds ratio and their associated 95% credible intervals (2.5% to 97.5% percentiles) were also provided for each treatment comparison. Validation of these Bayesian analyses was undertaken in OpenBUGS. The posterior densities were checked for convergence and lack of auto-correlation after a suitable burn-in and thinning scheme were applied.

Given the highly skewed nature of the lesion counts (variances typically exceeding the mean), we determined that a typical MTC modelling approach whereby the data was assumed to be normally distributed was not appropriate. Indeed, most recent analyses of lesions counts in MS trials employ negative binomial or zero-inflated Poisson regression methodology. Accordingly, we chose to simulate individual patient lesion count data from the summary-level means and SDs, such that the summary statistics of the resulting individual patient count data matched the published 'target' means and SDs. The lesion count outcomes within the individual patient data were modelled using a negative binomial regression model adjusting for treatment and study as fixed effects (PROC GENMOD in SAS®). The logarithm of planned time on study was used as an offset (the actual time on study was not simulated at patient level). The difference in least square means of OCR 600mg compared to each treatment was presented along with the corresponding standard error. The rate ratio, associated 95% CI and p-value were also provided for each treatment comparison of interest.

Results

The indirect comparison demonstrates that ocrelizumab has significantly lower rate of both Gd-T1 enhancing and new or enlarging T2 lesions (Table 5). With respect to proportions of patients with lesions, base-case and sensitivity analyses show numerical results favoring ocrelizumab.

Table 5 Comparison of MRI outcomes of ocrelizumab and alemtuzumab

	CARE-MS trials Pooled		**OPERA trials Pooled**		**Basecase analyses - Observed cases**		**Sensitivity - Randomized/ Treated[a]**	
Outcome	**ALEM** N=802	**IFN** N=389	**OCR** N=827	**IFN** N=829	**OR/RR (95% CI)[b]**	**p-value**	**OR/RR (95% CI)[b]**	**p-value**
Proportion of patients with Gd-T1 lesions at	8.3%	21.2%	0.7%	17.3%	0.10 (0.04,	<0.001	0.78 (0.53,	0.232

Month 24					0.26)		1.17)	
Mean number of Gd-T1 lesions at Month 24	0.24	0.73	0.02	0.48	0.09 (0.05, 0.15)	<0.001	-	-
Proportion of patients with T2 lesions from Baseline to Month 24	47.3%	63.0%	38.7%	61.6%	0.75 (0.54, 1.03)	0.076	0.77 (0.56, 1.06)	0.107
Mean number of T2 lesions from Baseline to Month 24	2.97	5.91	0.33	1.68	0.35 (0.25, 0.49)	<0.001	-	-

[a] Patients with no MRI assessment are considered as having 1+ lesions
[b] Proportion outcomes were analyzed with a fixed-effects logistic regression model, adjusting for treatment and study. Count outcomes were analyzed with a negative binomial regression model, adjusting for treatment and study as fixed effects and logarithm of study duration as an offset.
ALEM: alemtuzumab, OCR: ocrelizumab

Discussion

There are some limitations to these analyses which should be considered when interpreting the results. Firstly, the network is small. Another point for consideration is that most comparisons are indirect and for the treatment comparisons of interest there are no direct comparisons to assess the assumption of consistency.

It has been presumed that the studies chosen met the assumption of similarity, therefore this was not explored further in these analyses. Patients were assumed to have been from similar demographic backgrounds, have similar disease severity and exposure to prior therapies.

The definition of patient populations varied across studies, observed case analysis was taken as subjects with available data from the publications. For the randomised/treated analyses missing data was assumed to be due to a relapse or progression in disease severity and imputed as if at least one lesion was present (for the dichotomous endpoint analyses). The amount of missing data did vary across the studies and endpoints. Finally, it was often unclear from the publications if imputations or other missing data assumptions had already been applied.

In addition to demonstrating near-complete suppression of brain lesions, and superiority of IFNB-1a (Rebif), in the OPERA trials, this exploratory indirect treatment comparison suggests that ocrelizumab also has significantly greater reduction in brain lesions compared to alemtuzumab.

A8. EQ-5D was measured in the OPERA studies and also used for estimation of utilities in the economic analysis. However, the EQ-5D values provided in the submission were pooled across OPERA studies and categorised by EDSS score. Please provide the EQ-5D results for all available time points in the studies including: the mean (SE) EQ-5D values by trial arm and time point, and a p-value for the between-arm difference. Please also clarify whether there were any missing EQ-5D data and how these were taken into account when estimating utilities.

Response: The OPERA I and II study protocol specified that EQ-5D was collected for the purpose of deriving health state utility values for economic modelling. No pre-specified analysis was planned to assess EQ-5D between treatment arms or time points as no significant differences are expected over the trial duration.

Post hoc analysis to derive mean EQ-5D values by trial arm and time point are illustrated below (Table 6). Mean utility values for patients on study treatment are fairly similar over time and between treatments arms, and the main reduction in utility occurs at the point of withdrawal from treatment.

Given the structure of the economic model with health states defined by EDSS, only EQ-5D measurements recorded on the same day as an EDSS assessment could be used for modelling. In total 87% of the EQ-5D measurements were applicable to modelling. No imputation for missing EDSS or EQ-5D was performed for the regression analysis of utility by EDSS state. However, in general the mean utility for all observations and for those used for modelling were similar and the impact of missing data is assumed to be minimal. The low amount of data used for modelling from OLE week 46 visit is due to the protocol scheduled assessment of EDSS occurring at the later OLE week 48 visit.

The regression model used to estimate health state utility values was adjusted for EDSS state, sex, region, and relapse (see NICE submission Appendix H). Extending it to include randomized treatment did not improve the model fit (p=0.9047).

Table 6 EQ-5D values by trial arm and time point in OPERA I, II and OLE study

	IFNB-1a (Rebif)					**Ocrelizumab**				
	All		**Used for modelling**			**All**		**Used for modelling**		
Visit	**n with EQ-5D**	**Mean Utility**	**n used**	**%**	**Mean Utility**	**N with EQ-5D**	**Mean Utility**	**n used**	**%**	**Mean Utility**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Week 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Week 46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal from treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	
Visits with < 10 patients										
Screening	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2						[redacted]	[redacted]			
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 24						[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]								
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					
Week 84						[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Week 12						[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Week 94						[redacted]				
Total	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	

* EDSS measurement available on the same day

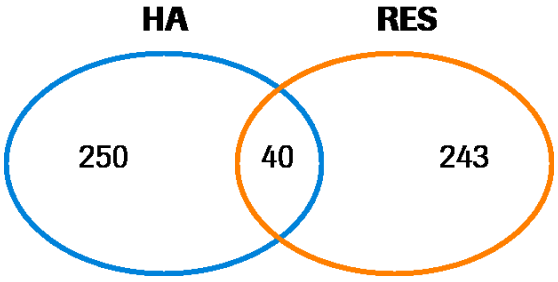
*A9. **Priority question:** For the OPERA study subgroup analyses of HA and RES patients reported in section B.2.7 Tables 13-15 of the submission:*

(a) Please provide an additional row in each of Tables 13-15 for the residual subgroup of patients, i.e. those patients from the ITT population who are not in the HA and RES subgroups.

Response: The definitions for the HA and RES subgroups both relate to disease activity as measured by relapses or MRI activity, and are not mutually exclusive. The key difference in the definitions of HA and RES subgroups is in the specification of line of therapy. HA disease occurs in pre-treated patients only whilst the definition of 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 as shown in the Venn diagram below (Figure 2). In the OPERA studies 14% of HA or RES patients could be defined as having both HA and RES RRMS.

The results for the residual subgroup of patients who have neither HA nor RES disease are provided in the tables below (Table 7, Table 8, and Table 9).

Figure 2 Venn diagram of overlap between HA and RES subgroups



(b) Please provide data in a similar format as in Table 13-15 for the all-cause discontinuation outcome, for the HA, RES and residual subgroups.

Response: A table for all-cause discontinuation in the subgroups is provided below (Table 10).

(c) please provide baseline characteristics of the patients in each subgroup so that they can be compared with the baseline characteristics of the ITT population (i.e. presented in the same format as Table 8 section B.2.3 in the submission).

Response: Tables with baseline characteristics for the subgroups can be found in the appendix below (Table 27, Table 28, and Table 29).

Table 7 ARR in HA, RES, and non-HA/RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Rate ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	ARR	N (patients)	n (event)	ARR				
ITT	829	334	0.291	827	194	0.156	0.535	0.435–0.659	<0.0001	-
HA	140	64	0.313	143	23	0.099	0.317	0.181–0.556	<0.0001	0.0346
RES	140	78	0.394	150	40	0.151	0.384	0.243–0.607	<0.0001	0.0811
non-HA/RES	567	189	0.250	556	137	0.173	0.691	0.538–0.888	0.0038	-

ARR: annualised relapse rate; CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

Table 8 CDP-12 in HA, RES, and non-HA/RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Hazard ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	% (event)	N (patients)	n (event)	% (event)				
ITT	829	113	13.6	827	75	9.1	0.60	0.45–0.81	0.0006	-
HA	140	22	15.7	143	12	8.4	0.47	0.23–0.95	0.0311	0.5109
RES	140	20	14.3	150	15	10.0	0.65	0.33–1.29	0.2163	0.8490
non-HA/RES	567	74	13.1	556	49	8.8	0.61	0.42–0.87	0.0065	-

CDP: confirmed disability progression; CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

Table 9 CDP-24 in HA, RES, and non-HA/RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Hazard ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	% (event)	N (patients)	n (event)	% (event)				
ITT	829	87	10.5	827	57	6.9	0.60	0.43–0.84	0.0025	-
HA	140	17	12.1	143	10	7.0	0.50	0.23–1.09	0.0763	0.6898
RES	140	20	14.3	150	14	9.3	0.61	0.31–1.22	0.1566	0.9853
non-HA/RES	567	53	9.3	556	34	6.1	0.60	0.39–0.92	0.0169	-

CDP: confirmed disability progression; CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

Table 10 All-cause discontinuation in HA, RES, and non-HA/RES subgroups (OPERA I and II pooled analysis)

	IFNB-1a			OCR			Odds ratio	95% CI	P value	Interaction test
	N (patients)	n (event)	% (event)	N (patients)	n (event)	% (event)				
ITT	829	169	20.4	827	101	12.2	0.54	0.41-0.71	<.0001	-
HA	140	28	20.0	143	18	12.6	0.58	0.30-1.11	0.1000	0.8508
RES	140	26	18.6	150	17	11.3	0.56	0.29-1.10	0.0913	0.8989
non-HA/RES	567	117	20.6	556	69	12.4	0.54	0.39-0.75	0.0003	-

CI: confidence interval; HA, highly active inadequate responders; IFNB-1a: interferon beta-1a; ITT, Intention-to-treat; OCR: ocrelizumab; RES, rapidly evolving severe.

A10. Appendix E states that a greater reduction of CDP12 and CDP24 was observed for ocrelizumab than with IFNB-1a across all subgroups. Patients with baseline weight <75 kg showed a greater reduction in CDP12 and CDP24 in the OCR versus IFN groups compared with patient with baseline weight ≥ 75 kg. Please provide empirical evidence to support these statements (e.g. tables and/or forest plots).

Response: The forest plots for subgroup analysis based on baseline characteristics are provided in the submission to NICE, Appendix E Figures 34-35.

A11. Please explain the rationale for stratifying analyses by USA versus rest of the world groups and for stratifying analyses by baseline EDSS values of <4.0 versus ≥4.0 (submission Table 10).

In randomized controlled trials it is generally of value to stratify randomized treatment allocation by important prognostic factors (e.g. severity of disease) in order to promote balanced allocation within strata (2). Since baseline EDSS>=4 is known to be a strong prognostic factor for future disability progression in RMS patients (3) it was included as a stratification factor for the WA21092 and WA21093 studies.

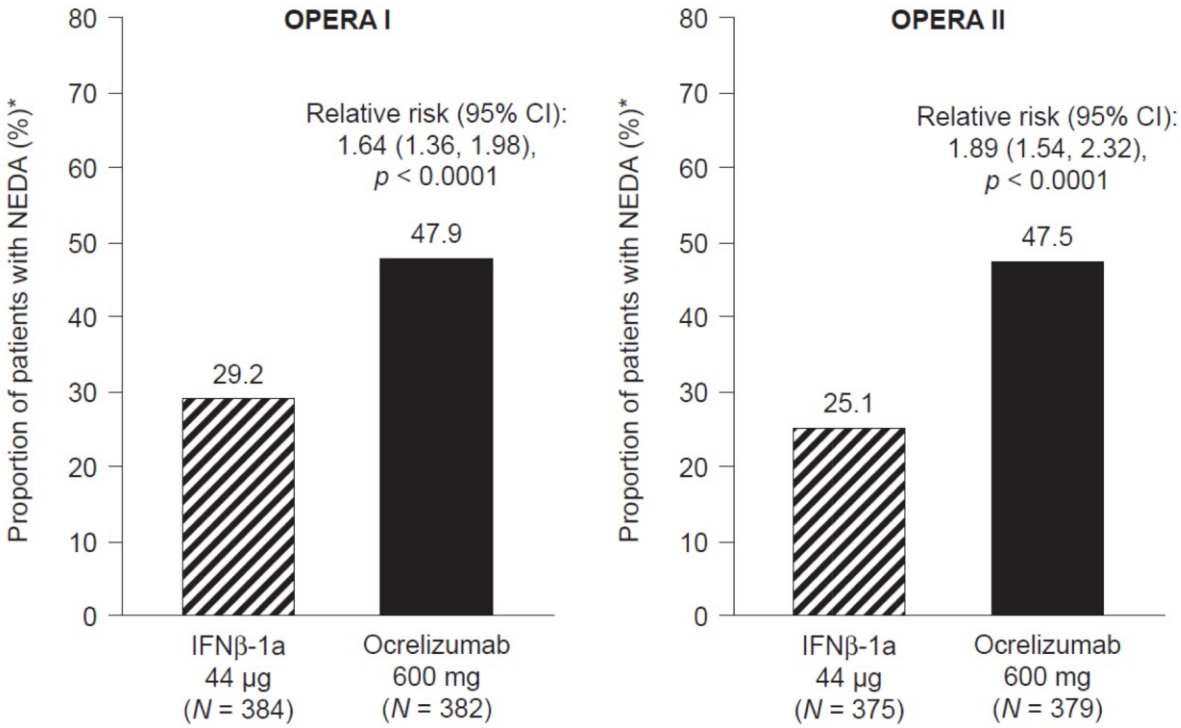
For multicentre trials that cannot be stratified for centre due to small number of patients within many centres, randomisation should be stratified by country or region (4). Since many centers in the WA21092 and WA21093 studies were expected to have only very few patients, randomization was stratified by region (US as largest single country vs. rest of the world).

A12. Please explain why the analysed population for the NEDA outcome was restricted to patients with an EDSS score of ≥2 at baseline.

Response: No Evidence of Disease Activity (NEDA) was a pre-specified secondary endpoint analysed only in the subgroup of patients with a baseline EDSS score ≥ 2. The NEDA ITT analysis was not pre-specified as each individual disease activity component (relapses, confirmed disability progression, Gd-T1 lesions, and new or enlarging T2 lesions) had already been assessed in other pre-specified ITT analyses.

For completeness, NEDA in the ITT population was also tested in a post-hoc exploratory analysis. The post hoc analysis including all patients in the ITT population showed that ocrelizumab significantly increased the likelihood of achieving NEDA status compared with IFNB-1a.

Figure 3 NEDA results in OPERA I and II (ITT population, post hoc analysis)



*Compared using the Cochran–Mantel–Haenszel test stratified by geographic region (US vs rest of world) and baseline EDSS score (< 4.0 vs ≥ 4.0).

CI, confidence interval; EDSS, Expanded Disability Status Scale; IFNB-1a, interferon beta-1a; ITT, intention-to-treat; NEDA, no evidence of disease activity.

MTC analyses

A13. Please provide the programming code for each MTC analysis.

Response: The JAGS programming codes can be found in the Appendix below.

*A14. **Priority question.** Page 104 of the Appendix states that 13 studies were excluded from the MTC but Table 9 in the Appendix appears to suggest that up to 19 studies were excluded. However, Table 9 in the Appendix does not provide any reference citation numbers so it is not fully clear which studies are being referenced. Furthermore, 23 separate MTCs were conducted rather than just one and it is not clear which of the 46 studies included in the systematic review were excluded from each specific MTC and why.*

Response: Thirteen studies were excluded for all MTCs. Table 9 mentions an additional six studies for which treatment arms were excluded due to unlicensed treatment regimens.

The specific treatment regimens that were unlicensed and not considered suitable for inclusion in the network are as follows;

- ALEM 24mg: All studies including this treatment (CAMMS223 and CARE MS-II) also reported data for other relevant treatments so only the ALEM 24mg arm has been excluded for these trials;
- DAC 300mg, Q4W: The only trial including this treatment arm (SELECT) also reported data for other relevant treatments so only the DAC 300mg, Q4W arm has been excluded for this trial;
- OCR 2000mg: The only trial including this treatment arm (Kappos 2011) also reported data for other relevant treatments so only the OCR 2000mg arm has been excluded for this trial;
- PEG-INFB-1A, 125mcg, Q4W: The only trial including this treatment arm (ADVANCE) also reported data for other relevant treatments so only the PEG-INFB-1A, 125mcg, Q4W arm has been excluded for this trial;
- SC IFNB-1b 500mcg, EOD: The only trial including this treatment arm (Knobler (1993)) also reported data for other relevant treatments so only the SC IFNB-1b 500mcg, EOD arm has been excluded for this trial.

(a) For each of the MTCs conducted please provide a table listing the studies that were excluded and the reason(s) why.

Response: Thirty-three studies were eligible for inclusion in the MTCs. However, not all of these studies reported outcomes of interest for the individual MTCs. A table listing the included studies per outcome is provided below and reasons for exclusion of studies are described.

Table 11 Summary of included studies per outcome in MTCs

Study Reference/ID	ARR	CDP-12	CDP-24	All cause Discontinuations
ADVANCE	√	√	√	√
AFFIRM	√	√	√	√
BEYOND	√	√		√
Bornstein 1987		√		
BRAVO	√	√	√	
Calabrese et al, 2012	√			
CAMMS223	√	√(1)	√	√
CARE-MS I	√	√(1)	√	√
CARE-MS II	√	√(1)	√	√
CLARITY	√	√	√	√

CombiRx	√		√	
CONFIRM	√	√	√	√
Copolymer 1 MS trial	√	√		√
DECIDE	√	√	√	√
DEFINE	√	√	√	√
Etemadifar 2006				
EVIDENCE	√	√	√	√
FREEDOMS	√	√	√	√
FREEDOMS II	√	√	√	√
GALA	√			
IFNB MS	√	√		√
INCOMIN	√		(2)	√
MSCRG	√		√	√
OPERA I	√	√	√	√
OPERA II	√	√	√	√
PRISMS		√		√
REGARD	√		√	√
SELECT	√	√	√	√
Stepien et al, 2013	√			
TEMSO	√	√	√	√
TENERE	√			√
TOWER	√	√	√	√
TRANSFORMS	√	√		√
Total number of data inputs included	**30**	**22**	**21**	**26**

(1) CDP-12 includes HAS MTC input based on CAMMS223, CARE-MS I, and CARE-MS II

(2) base-case CDP-24 NMA excludes INCOMIN. Sensitivity analysis including INCOMIN is provided in NICE submission Appendix (Figure 19).

ARR:

Thirty-one studies reported data on this outcome. However, Etemadifar (2006) reported the mean number of relapses rather than the ARR and there are a number of inconsistencies within the paper itself. For these reasons this trial is excluded from the MTC for this outcome.

CDP-12:

Twenty-one studies reporting data for CDP-12 or 'sustained disability for 12 weeks' were included in the MTC for this outcome. Results of the pooled meta-analysis of CAMMS223, CARE MS I and CARE MS II published in the HAS report were also included as the 22nd data input.

CDP-24:

Twenty-two studies reporting data for CDP-24 or 'sustained disability for 24 weeks' were included in the MTC for this outcome. However, the INCOMIN trial was excluded from the base-case network. The INCOMIN study is an outlier and widely regarded as such by the clinical community (see NICE submission page 42). (For completeness, sensitivity analysis of CDP-24 including the INCOMIN trial is presented in NICE submission Appendix Figure 19)

All-cause discontinuation: Twenty-six studies reported data on this outcome.

(b) The statement in the bottom-left cell of Table 9 of the Appendix appears to imply that the statistical power of studies was related to study duration. Please explain this. The calculations for ARR, CDP12, CDP24 and all-cause discontinuation specified on pages 133-135 of the Appendix appear to be independent of the statistical power of primary studies, so why is this relevant?

Response: The statement in the bottom-left cell of Table 9 of the Appendix states the following: "Studies with a controlled treatment duration of less than 48 weeks were not considered suitable for inclusion because they were not powered for clinical outcomes".

What is meant here is not that the statistical power of these studies was related to study duration. But rather that in trials with a controlled treatment duration of less than 48 weeks the statistical power was calculated to meet primary outcomes that are not clinical in nature. Indeed, these studies were all powered on primary outcomes related to MRI activity or frequency of adverse events (Table 12). This is relevant because these short trials are therefore unlikely to be powered to produce evidence on the clinical endpoints that are of interest in our MTC analyses – if such outcomes were even collected as secondary outcomes. This is why these trials were excluded from our MTC analyses.

(c) Please explain why a cut-off of 48 weeks was considered appropriate for excluding studies rather than, say, 36 weeks or 96 weeks. Was this a pragmatic decision to maximise data availability for MTCs or based on clinical reasons? Was

sensitivity analysis conducted to ascertain the impact of the time cut-off on MTC results?

Response: This was a clinical decision, whereby at least 48 weeks (~1 year) was judged to be the shortest time period to meaningfully measure clinical outcomes. This is supported by trials which are shorter than 48 weeks that do not report clinical outcomes such as disease progression.

The impact of different follow-up times was assessed in sensitivity analysis by way of meta-regression on trial duration (see response to question A19).

(d) Please explain the "feasibility" assessment referred to on page 42 of the submission and on pages 104 and 106 of the Appendix. This appears to be a post-hoc determination and application of eligibility criteria. Why were the eligibility criteria not pre-specified, as is normally considered good practice in evidence synthesis?

Response: In this field some decisions can only be made post-hoc, i.e. after the systematic literature review (SLR) was conducted. One example concerns outcomes: it is not usually known which trials report a given outcome before the SLR is completed in full, therefore it is not possible to know or pre-specify what the network will look like ahead of time or even whether it will be connected. Hence the need for a feasibility assessment step, after the SLR is conducted.

One possible outcome of the careful consideration and comparison of the trials that were picked up in the SLR, can be exclusion of trials due to lack of similarity. Back to the example of outcomes, if outcome definitions differ too much between trials, it is only after a thorough feasibility assessment of all outcome definitions reported by the trials picked up in a SLR that a determination can be made as to the appropriateness of their synthesis in an MTC.

The same judgment had to be made with respect to trial duration. Once we observed the large variation in length of trials picked up in the SLR (patient follow-up varied from 12 to 240 weeks across the studies), we estimated based on the arguments stated in response to question A14.b and after consulting with our medical colleagues that trials under 48 weeks in duration were too different in objective and design from the other trials and therefore were not appropriate for inclusion in our MTC analyses. These trials were therefore excluded at that point in the process: after completing the SLR but before running our MTC analyses.

Table 12 Summary of study designs of 11 excluded studies

Trial ID	Treatment	Follow up duration (weeks)	Primary outcome measures	Secondary outcome measures
Kappos 2011	Placebo IM IFNB-1a 30 µg, QW OCR 600 mg OCR 2000 mg	96	Total number of Gd enhancing T1 lesions observed on brain MRI scans for weeks 12, 16, 20, and 24 versus placebo	**Annualized protocol-defined relapse rate** (defined as the occurrence of new or worsening neurological symptoms attributable to MS, and immediately preceded by a stable or improving neurological state of at least 30 days); proportion of relapse-free patients; total number of Gd-enhancing T1 lesions (all data points from 4–24 weeks); total number of new Gd enhancing T1 lesions; change in total volume of T2 lesions from baseline to week 24; safety and tolerability of two dose regimens of OCR versus placebo and IFNB-1a at week 24 and safety of OCR.
European/Canadian Glatiramer Acetate trial	Placebo GA 20 mg, QD	36* (open label)	The total number of enhancing lesions	The total volume of enhancing lesions, proportion of patients with enhancing lesions, number of new enhancing lesions, number of new lesions on T2-weighted images, percent change of lesion volume on T2-weighted images and change in the volume of hypointense lesions on T1-weighted images
GATE	Placebo Generic GA 20mg, QD Brand GA 20mg, QD	60* week OLE optional	The total number of Gd-enhancing lesions (ie, the cumulative number of new and persisting Gd-enhancing lesions) during months 7 through 9	**ARR, EDSS score change from baseline to month 9**, cumulative combined unique active lesions during months 7 through 9, change in T2-weighted hyperintense lesion number and volume from baseline to month 9, change in nonenhancing T1-weighted hypointense lesion volume from baseline to month 9, percentage change in normalized brain volume from baseline to month 9, and proportion of participants who were free of disease activity at month 9.
IMPROVE	Placebo SC IFNB-1a 44 µg, TIW	24	The number of combined unique active MRI brain lesions at week 16	The number of combined unique active lesions /patient/scan during the double blind phase
Knobler 1993	Placebo (human serum albumin)	312*	Not reported	**Number of exacerbations and changes from baseline in EDSS** and NRS **values**

	SC IFNB-1b 250 µg, EOD			
	SC IFNB-1b 500 µg, EOD			
REFORMS	SC IFNB-1a 44 µg, TIW	112	Mean change in subject-reported injection-site pain	The mean difference in injection-site pain from pre-injection to immediately post-injection and to 10 min post-injection, the proportion of pain-free patients, number and severity of relapses, assessments of the treatment of side effects, patient-rated treatment satisfaction, and rater-blinded assessment of injection-site redness.
	SC IFNB-1b 250 µg, EOD			
Saida 2012	Placebo	24*	Percentage of patients free from Gd enhanced lesions at 3 and 6 months	Percentage of patients free from relapse over six months and safety measures.
	FINGO 0.5 mg, QD			
Saida 2016	Placebo	Not reported	Total number of new Gd+ lesions from week 12 to 24	Total number of new Gd+ lesions from baseline to week 24, new/newly enlarging T2 lesions from baseline to week 24
	DMF 240 mg, BID	Not reported		
Saida 2017	NAT 300mg, Q4W	32	Rate of development of new active lesions over 24 weeks	Cumulative number of new active lesions, **adjusted ARR** (the frequency of clinical exacerbations over 24 weeks was assessed using an annualized relapse rate that was calculated for each treatment group as the total number of relapses experienced in the group over the 24 weeks of treatment, divided by the total number of subject-years followed in the study. Obtained from a Poisson regression model, adjusted for the baseline relapse rate), cumulative number of Gd+ lesions, cumulative number of new or newly enlarging, non-enhancing T2-hyperintense lesions, number of participants relapse free, change from baseline to Weeks 12 and 24 in the Global Assessment of Well-Being as assessed by participants using a VAS, concentration of natalizumab in serum, number of participants with AEs
	Placebo			

Teriflunomide MS Trial	Placebo	36	Number of combined unique active (new and persisting) lesions per MRI scan during the 36-week double blind treatment phase	Number of T1 enhancing lesions; number of T2 active lesions; number of patients with combined unique active T1 enhancing and T2 active lesions; percentage change from baseline to endpoint in the burden of disease (T2 lesion volume); **number of patients experiencing an MS relapse; ARR**; number of relapse patients requiring a course of steroids
	TERI 7 mg, QD			
	TERI 14 mg, QD			
Wroe 2005	Placebo (Slow)	12*	Frequency of adverse events	**Exacerbations**
	Placebo (Rapid)			
	SC IFNB-1b (Slow) 250 µg, EOD			
	SC IFNB-1b (Rapid) 250 µg, EOD			

This table is a subset of Table 10 as included in the NICE submission Appendix.
QD: Once daily, BID: Twice daily, EOD: Every other day, QW: Once weekly, Q2W: Twice weekly, TIW: Three times weekly, Q4W: Once every four weeks, µg: Microgram, mg: milligram, ALEM: alemtuzumab, DAC: daclizumab HYP, DMF: dimethyl fumarate, FINGO: fingolimod, GA: glatiramer acetate, IM IFNβ-1A: Avonex (intramuscular interferon beta-1a), NAT: natalizumab, OCR: ocrelizumab, PEG-IFNβ-1A: peginterferon beta-1a, SC IFNβ-1A: Rebif (subcutaneous interferon beta-1a), SC IFNβ-1B: subcutaneous interferon beta-1b, TERI: teriflunomide. * date reported by study authors in months or years; **in bold, clinical secondary outcomes**

*A15. **Priority question:** company submission Appendix pages 133-134 briefly describe the general methods used to estimate the risk ratios for ARR, the hazard ratios for CDP12 and CDP24, and the odds ratios for all-cause discontinuation that were calculated in MTC analyses. However, the data extracted from the studies to enable these calculations are not reported in the submission. For each MTC analysis please provide the specific input data for the analysis, so that it is clear how these data were obtained from the data given in each study report (e.g. the numbers at risk at each time point, number of events, etc).*

Response: The input tables for the MTCs are provided in the appendix below (Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36, Table 37, Table 38, and Table 39).

*A16. **Priority question:** company submission Appendix page 133 describes the methods of analysing adjusted and unadjusted annualised relapse rates but the methods are stated as being identical.*

(a) Please confirm whether the description of the analyses is correct.

Response: This is correct. The same approach was taken in MTC whether the input was taken from a reported adjusted or unadjusted analysis. In case both unadjusted and adjusted results were provided in a publication then the adjusted results were to be preferred. In the review only 3 studies reported both adjusted and unadjusted ARR.

(b) Please explain how the inclusion of adjusted and unadjusted relapse rates in MTC analyses influences interpretation of the results. Was sensitivity analysis conducted to clarify the impact of (lack of) adjustment?

Response: This was primarily a pragmatic decision with a preference to include as many studies as possible. 10 studies reported unadjusted ARR only, 17 studies reported adjusted ARR only and 3 studies, AFFIRM; OPERA 1 & OPERA 2, reported both. Additionally, for a sensitivity analysis with an alternative definition of ARR TENERE reported an adjusted and unadjusted ARR. The few studies that reported both are shown below and do not show a large difference between the adjusted and unadjusted results in terms of the estimated rate ratio which is the basis of the MTC analysis.

Table 13 Comparison of adjusted and unadjusted ARR

Trial	Intervention	Reported Adjusted ARR	Estimated Adjusted Rate Ratio	Reported Unadjusted ARR	Estimated Unadjusted Rate Ratio
AFFIRM	Placebo	0.73	n/a	0.64	n/a
	NAT 300 mg, Q4W	0.23	**0.32**	0.22	**0.34**
OPERA 1	SC IFNB-1a 44 mcg, TIW	0.292	n/a	0.245	n/a
	OCR 600 mg	0.156	**0.53**	0.136	**0.56**

OPERA 2	SC IFNB-1a 44 mcg, TIW	0.290	n/a	0.254	n/a
	OCR 600 mg	0.155	**0.53**	0.138	**0.54**
TENERE*	Placebo	0.23	n/a	0.23	n/a
	TERI 7 mg, QD	0.44	**1.91**	0.43	**1.87**
	TERI 14 mg, QD	0.27	**1.17**	0.27	**1.17**
* For TENERE these results are provided for a sensitivity analysis of ARR only so these results were not used for the MTC. For the primary analysis of ARR included in the MTC only an adjusted ARR is reported.					

In general, as the MTC analysis were based on the log of the rate ratio as a treatment effect estimate, the use of adjusted and unadjusted ARR estimates where both are reported would only translate into differences between adjusted and unadjusted rate ratios in the case of an imbalance through randomization or through an imbalance in missing data between randomized arms. Assuming well conducted clinical trials we assume minimal differences between the use of adjusted and unadjusted estimates in the context of an MTC.

(c) Where adjusted relapse rates were used please provide details of the variables that were adjusted for and comment on the significance of any differences in the adjustments between the studies.

Response: For the 20 studies that reported an adjusted ARR the covariates adjusted for are shown below. The most common covariate to adjust for was baseline EDSS followed by region.

Table 14 Summary of covariates adjusted in studies

	Covariates included in estimate of adjusted ARR				
Trial ID (n = 20)	**Baseline EDSS (n = 15)**	**Region (n=14)**	**Prior Relapses (n=11)**	**Age (n=5)**	**Other (n=2)**
ADVANCE	Yes: <4.0 vs. >=4.0		Yes: in last 3 years	Yes: <40 vs. ≥40	
AFFIRM			Yes: in last 1 year		
BRAVO	Yes	Yes	Yes: in last 2 years		
CARE-MS I		Yes			
CARE-MS II		Yes			
CLARITY		Yes			
CONFIRM	Yes: ≤2.0 vs.>2.0		Yes: in last 1 year	Yes: <40 vs. ≥40	
DECIDE	Yes: ≤2.5 vs.>2.5		Yes	Yes: ≤35 vs. >35	Prior Interferon Beta Use: Yes vs. No

DEFINE	Yes		Yes	Yes	
EVIDENCE		Yes: Center			
FREEDOMS	Yes	Yes	Yes: in last 2 years		
FREEDOMS II	Yes	Yes	Yes: in last 2 years		
GALA	Yes	Yes	Yes: in last 2 years		Presence of T1 lesions, Volume of T2 lesions
OPERA I	Yes: <4.0 vs. >=4.0	Yes: US vs. ROW			
OPERA II	Yes: <4.0 vs. >=4.0	Yes: US vs. ROW			
SELECT	Yes: ≤2.5 vs.>2.5		Yes: in last 1 year	Yes: ≤35 vs. >35	
TEMSO	Yes	Yes			
TENERE	Yes	Yes			
TOWER	Yes	Yes			
TRANSFORMS	Yes	Yes	Yes: in last 2 years		

(d) The definition of annualised relapse rate differed among the included studies (e.g. any relapses, confirmed relapses, protocol-defined relapses, qualifying relapses) and some studies conducted sensitivity analyses on the different definitions (e.g. CombiRx, CONFIRM, DEFINE, REGARD, TENERE). Please explain how variation in the definitions would influence interpretation of the MTC results. Where studies reported more than one definition of the annualised relapse rate please explain which definition was used in the MTC analyses.

Response: The definition of relapse used in the primary (or if relapse was not primary then first secondary) endpoint was taken in each case for the MTC. A summary table with ARR and relapse definitions for each study included in the MTC is found in the appendix below (Table 40).

In general, the different definitions of relapse used appear to affect the absolute levels of ARR but have a limited impact on the estimated rate ratio. The results below for CombiRx and Opera illustrate this (Table 15). Based on these data we expect a negligible impact on the MTC.

Table 15 Comparison of protocol defined relapses and all relapses

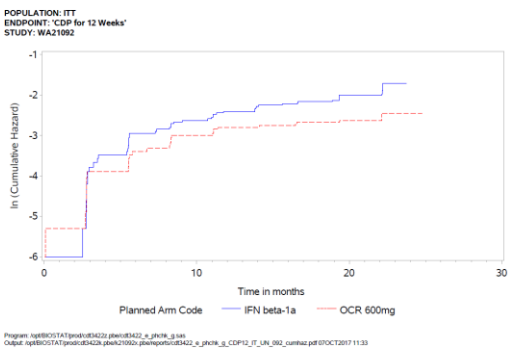
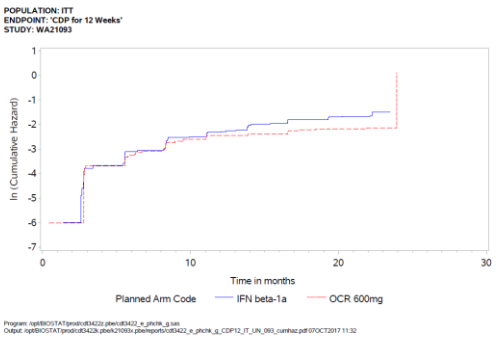
		Protocol Defined Relapses (PDR)		All relapses (PDR+NPDR)	
Trial	Intervention	Reported ARR	Estimated Rate Ratio	Reported ARR	Estimated Rate Ratio
CombiRX	IM IFNB-1a 30 mcg, QW	0.16	n/a	0.32	n/a

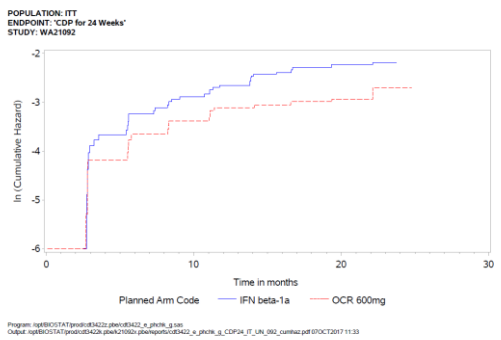
	GA 20 mg, QD	0.11	**0.69**	0.23	*0.72*
OPERA 1	SC IFNB-1a 44 mcg, TIW	0.292	n/a	0.381	n/a
	OCR 600 mg	0.156	**0.53**	0.222	**0.58**
OPERA 2	SC IFNB-1a 44 mcg, TIW	0.290	n/a	0.380	n/a
	OCR 600 mg	0.155	**0.53**	0.217	**0.57**

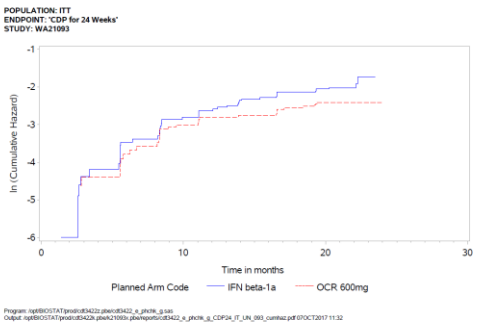
A17. ***Priority question:*** *In section B.2.9.1 (page 69) an assumption is made that hazards are proportional for CDP outcomes. Please provide a justification for this assumption.*

Response: The assumption of proportional hazards for CDP outcomes was made based upon examination of the Opera I and Opera II data. Plots of log(-cumulative hazard) for CDP-12 and CDP-24 show that the lines are reasonably parallel from around 3 months onwards. While we cannot assess such data for trials by other manufacturers we believe based on this evidence that it is reasonable to assume that the proportional hazards assumption will also hold in the other trials included in the MTC.

Figure 4 Overview of log(-cumulative hazard) plots in OPERA I and II

Opera I: CDP-12	**Opera II: CDP-12**
	
Opera I: CDP-24	**Opera II: CDP-24**





*A18. **Priority question:** company submission Appendix pages 133-134 describe the methods of analysing CDP12 and CDP24 outcomes in the MTCs but the definition of the event (CDP) is not explicitly considered. According to the study publications there appear to be differences between studies in the EDSS cut-off values used to determine disability progression.*

(a) Please provide details of any differences between studies in the definitions of CDP and comment on the significance of these for interpretation of the MTC results.

Response: A full list of CDP-12 and CDP-24 definitions used in each trial are presented in Table 41 and

Table 42 in the appendix below. There were two key definitions of CDP used by the majority of studies:

1) An increase of at least 1.5 points on the EDSS score from a baseline score of 0 or an increase of 1 point or more from a baseline score of 1
2) A 1 point change in EDSS score

A sensitivity analysis was performed whereby the more stringent criteria (definition #1 above) were applied to the OPERA studies. The results presented below indicate that there is limited impact on results and we are confident in the MTC results using different definitions.

Table 16 Comparison of different CDP definitions in OPERA I and II

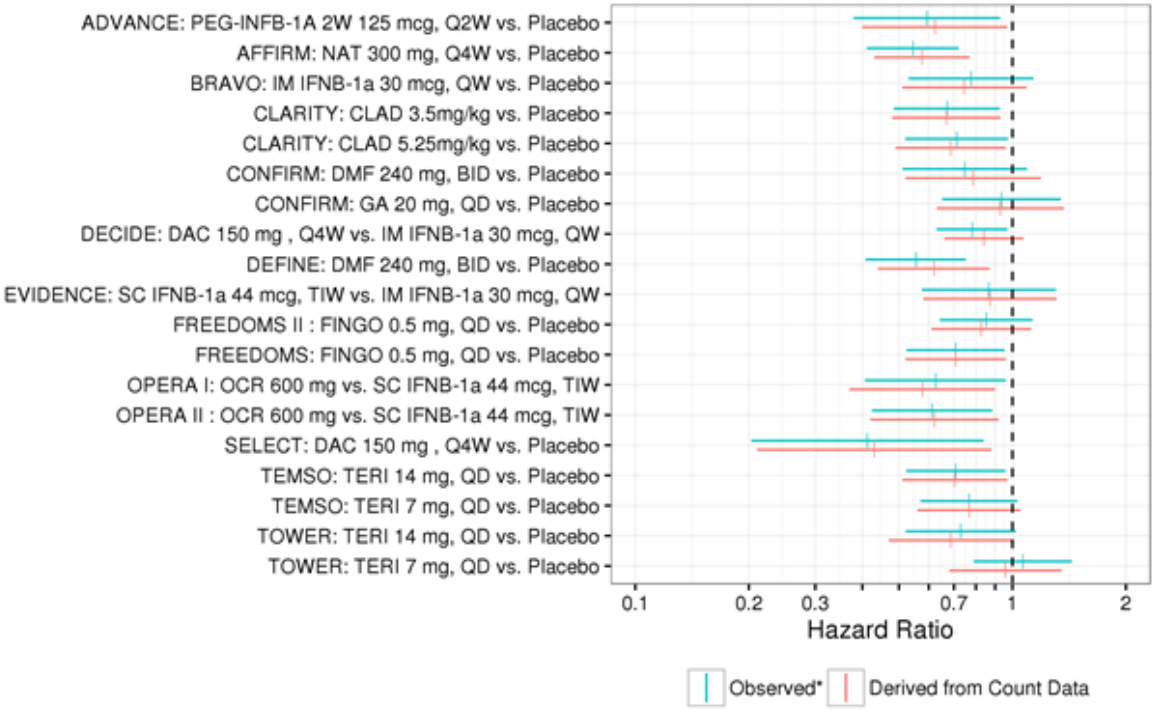
	IFNB-1a (Rebif) (N=829)		OCR (N=827)		Stratified analysis		
	Patients with event		Patients with event		Log rank	Hazard ratio	
	n	%	n	%	p value	Hazard ratio	95% CI

OPERA definition CDP-12	113	13.6	75	9.1	0.0006	0.60	0.45-0.81
More stringent CDP-12	109	13.1	69	8.3	0.0003	0.57	0.42-0.78
OPERA definition CDP-24	87	10.5	57	6.9	0.0025	0.60	0.43-0.84
More stringent CDP-24	84	10.1	51	6.2	0.0008	0.56	0.39-0.79

(b) On page 134 of the Appendix it is stated that the appropriateness of the method for analyzing CDP12 and CDP24 outcomes was assessed by reviewing the studies that reported both HRs and count data. Generally the observed and derived hazard ratios are similar. Please provide the data from these studies comparing HRs and counts to justify this assertion.

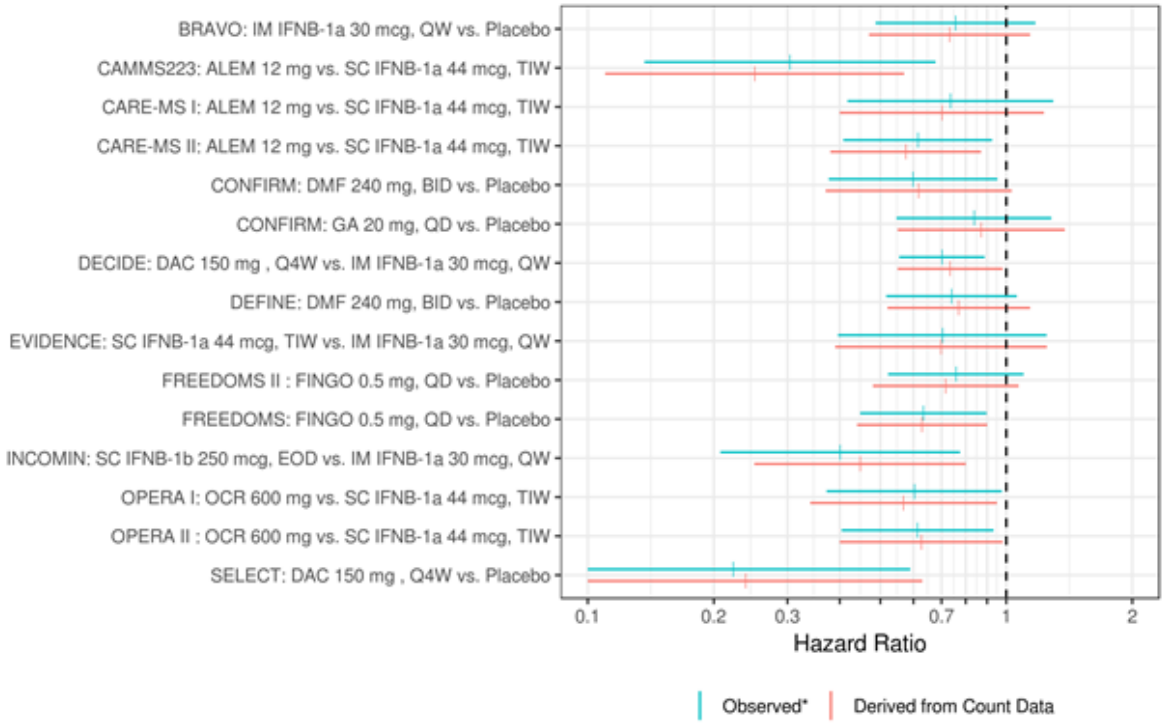
Response: The forest plots below indicate the similarity between observed and derived HRs from count data and support our method for analysing CDP-12 and CDP-24.

Figure 5 Forest plot of observed and derived HRs for studies reporting both HRs and count data for CDP-12



* Derived from estimated log HR and estimated SE (log HR)

Figure 6 Observed and derived HRs for studies reporting both HRs and count data for CDP-24



* Derived from estimated log HR and estimated SE (log HR)

*A19. **Priority question:** Meta-regression on study duration was employed in MTC analyses. Although network diagrams are given for these analyses, few other details of these analyses are provided in the submission.*

(a) Please explain the rationale for these analyses.

Response: The base-case analysis includes data from studies with a duration between 48 weeks to 240 weeks. It assumes that treatment effects are constant over this period. The meta-regression on study duration was conducted to explore whether the time at which the outcome was observed (follow-up time) influenced the relative treatment effects.

(b) Please describe the method employed for fitting the meta-regression model for each outcome.

Response: For each outcome, the appropriate MTC model was extended by incorporating follow-up time as a continuous covariate in a meta-regression. As advised by NICE DSU TSD3 (5) the regression covariate was centered on the mean trial duration. The model used for the analysis was "The same interaction effect for all treatments" model as defined in TSD3 with placebo chosen as the reference treatment. We acknowledge this requires more assumptions to be made on the form of the treatment and study duration interaction but this was a pragmatic decision based on the data available to perform the meta-regression.

(c) Please present the results of each meta-regression analysis in such a way that they can be compared against the results of the meta-analyses (e.g. tables and/or forest plots comparable to those currently given in the submission for the MTC results). Please provide the estimates of model fit for the meta-regression and the corresponding meta-analysis of each outcome.

Response: Forest plots of each meta-regression analysis compared with the base case MTC are provided below. The estimates of model fit for the meta-regression are provided in the NICE submission Appendix D Tables 16, 19, 22, and 25.

The forest plots and estimates of model fit indicated that differences in study duration had negligible impact on results and supported the base case analysis.

Figure 7 Forest plot for ARR meta-regression on study duration

Figure 8 Forest plot for CDP-12 meta-regression on study duration

Figure 9 Forest plot for CDP-24 meta-regression on study duration

Figure 10 Forest plot for all-cause discontinuation meta-regression on study duration

A20. ***Priority question:*** *company submission Appendix D presents results of heterogeneity assessments in the MTC, with forest plots provided for the direct pairwise meta-analysis comparisons where moderate to high heterogeneity had been identified (I^2 50%-75%).*

(a) Please would you provide the forest plots for all of the remaining pairwise direct comparisons as indicated in Appendix Table 27, with heterogeneity statistics included. This will enable us to check the consistency of these point estimates with those from the MTC.

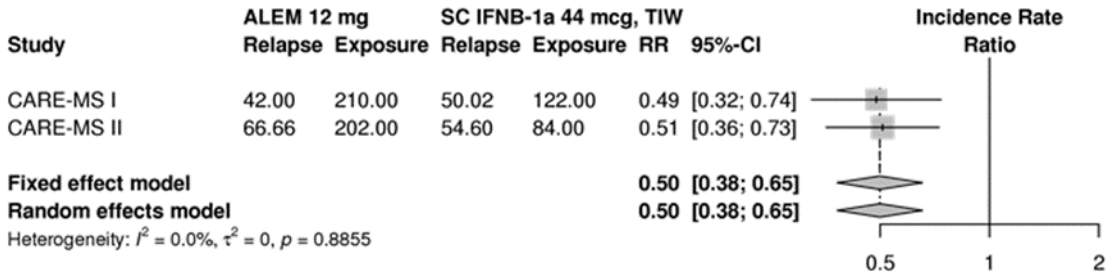
Response: The forest plots for all pairwise direct comparisons are provided in the appendix below.

(b) Please would you supply the forest plots for all the direct pairwise meta-analysis comparisons for the sub-group MTCs (i.e. for the HA and RES subgroups).

Response: Most inputs into the subgroup MTCs were extracted as pooled estimates as no individual study data were available (see Table 17 in the NICE submission). Only 1 link in all of the subgroup MTCs was informed by individual estimates reported in two studies. The pairwise meta-analysis for this link is shown below and indicated low heterogeneity (Figure 11).

The lack of direct pairwise meta-analysis comparisons in HA or RES subgroups highlights the general limitations of the subgroup MTCs as summarised in the NICE submission (see Section B.2.9.1); i.e. (i) potential publication bias due to post hoc nature of subgroup analyses (favourable subgroup results are more likely to be reported while unfavourable results are more likely to be withheld); (ii) subgroups break randomization in MTCs as trials were not stratified by these subgroups at the outset; and (iii) subgroup data are not reported by many of the trials, resulting in disconnected networks.

Figure 11 Heterogeneity assessment for ARR in RES subgroup: alemtuzumab vs IFNB-1a (Rebif)



Subgroup analyses were pre-specified as pooled analyses in OPERA I and II due to the small sample size of the subgroups in individual studies. However, in response to this question post hoc analyses were conducted to assess the heterogeneity in HA and RES subgroups in OPERA I and II (Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, and Figure 17).

Most pairwise meta-analysis comparisons in OPERA I and II indicated low heterogeneity, except for ARR in the HA subgroup. Conclusions based on these comparisons should be drawn with caution due to the small sample size of subgroups in individual studies and general limitations of subgroup MTCs as summarised above.

Figure 12 Heterogeneity assessment for ARR in HA subgroup: ocrelizumab vs IFNB-1a (Rebif)

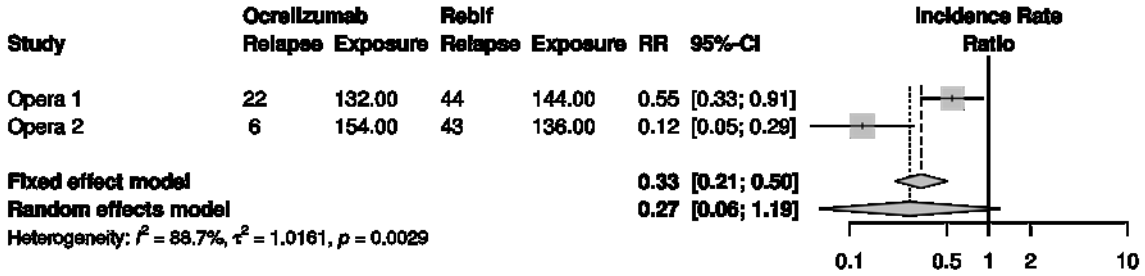


Figure 13 Heterogeneity assessment for CDP-12 in HA subgroup: ocrelizumab vs IFNB-1a (Rebif)

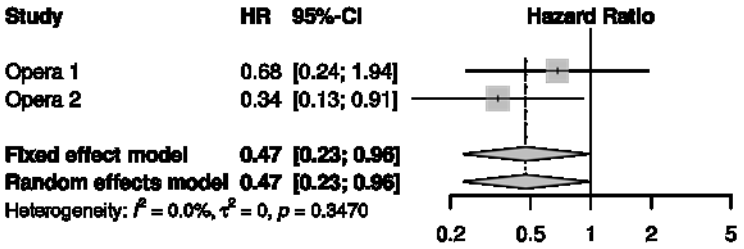


Figure 14 Heterogeneity assessment for CDP-24 in HA subgroup: ocrelizumab vs IFNB-1a (Rebif)

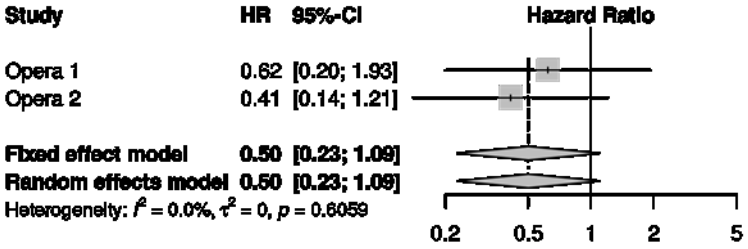


Figure 15 Heterogeneity assessment for ARR in RES subgroup: ocrelizumab vs IFNB-1a (Rebif)

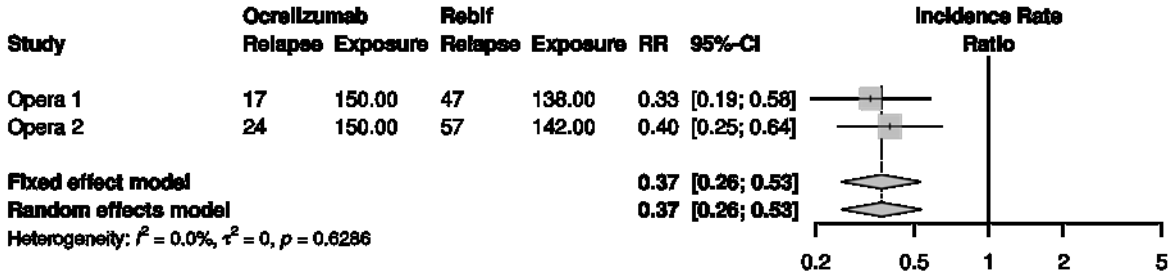


Figure 16 Heterogeneity assessment for CDP-12 in RES subgroup: ocrelizumab vs IFNB-1a (Rebif)

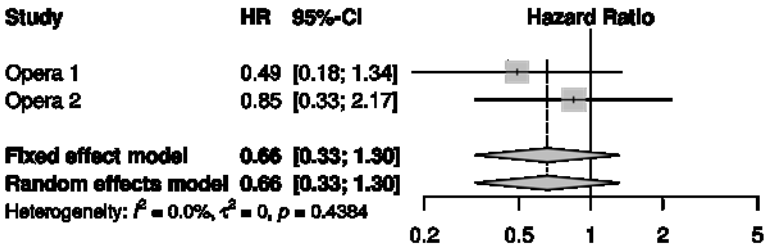
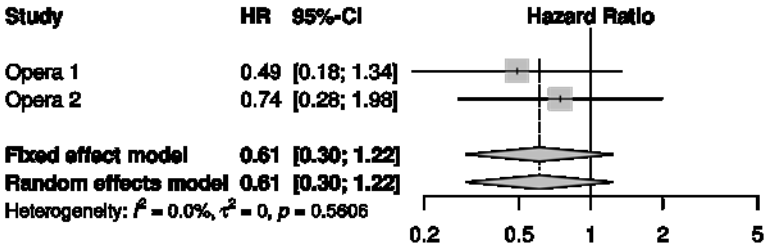


Figure 17 Heterogeneity assessment for CDP-24 in RES subgroup: ocrelizumab vs IFNB-1a (Rebif)



(c) Please explain what you mean by the "inconsistency model". Does this assess the consistency of direct and indirect evidence where there are closed loops in a network, or some other aspect of consistency? Please provide an explicit definition of the consistency assumption as employed in the MTC models. Please explain how the MTC models were altered to remove the consistency assumption.

Response: The consistency of direct and indirect evidence where there are closed loops in a network was evaluated by comparing the standard MTC model to an inconsistency model, as recommended in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 4 (6).

For each outcome, the MTC model was re-run without the assumption of consistency. The purpose of this 'inconsistency model' is to provide a comparison with the standard MTC model, and hence allow evaluation of whether the consistency assumption is valid or not. Dropping the consistency assumption means that the results are equivalent to a series of meta-analyses (one meta-analysis for each comparison where data is available). The inconsistency model does not allow for the estimation of treatment effects where no data is available (since we are not assuming that the unknown treatment effect is consistent with the available treatment effects).

A21. Please supply the full citation for Turner et al.2015, as cited in Appendix D (page 135).

Response: Turner RM, Jackson D, Wei Y, Thompson SG, Higgins J. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine. 2015;34:984-98.

A22. According to Appendix Table 12, the majority of studies considered for MTC analyses were on treatment-experienced patients with relatively few being treatment-

naïve. Please justify the rationale for including both groups in the same analysis. Was sensitivity analysis conducted on these groups? Please comment on how the results from the MTC analysis apply to the anticipated use of ocrelizumab in clinical practice in treatment-experienced and treatment-naïve patients.

Response: Most included studies were in fact of a mixed population of both treatment-naive and treatment-experienced, like the OPERA studies. This may not be immediately clear from Table 12 as it only specifies whether studies were purely treatment-naive or not. The proportion of pre-treated patients in studies, where reported, is listed in Table 43 in the appendix below. Most studies did not report subgroup analysis for treatment-naive and treatment-experienced patients and it was therefore not feasible to do sensitivity analysis.

Subgroup analysis of the OPERA studies in treatment-naive and treatment-experienced patients is provided in the NICE submission Appendix E. It demonstrated that the treatment effect of ocrelizumab compared with IFNB-1a was observed in both treatment-naïve and treatment-experienced subgroups across ARR, CDP12 and CDP24, consistent with the findings in the ITT population.

The anticipated licence for ocrelizumab is for adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features. The indication is therefore broad and reflects the trial evidence which included both treatment-naive and treatment-experienced patients. The MTC results in mostly mixed populations therefore reflect the anticipated use of ocrelizumab in clinical practice in the broadest set of patient subtypes with RRMS.

*A23. **Priority question:** According to pages 102-104 in the current ocrelizumab submission, the daclizumab company submission to NICE conducted a MTC for adverse events and these data were used to source the annual risk of adverse events for the comparators. As IFNB-1a (Rebif) is common between the OPERA studies and the daclizumab MTC, the ocrelizumab adverse event rates were adjusted using an adverse event rate ratio estimated from adverse event rates for IFNB-1a (Rebif) from the daclizumab submission and pooled analysis of OPERA I and II.*

The source of the data given in Table 40 of the current ocrelizumab submission appears to be Table 79 (page 214) in the daclizumab company submission. However, these data are not referred to in the daclizumab submission as having been derived from an MTC.

(a) Please confirm whether a MTC of adverse events was indeed conducted in the daclizumab appraisal. If so, please provide a list of the studies included. Please explain why that existing MTC was not updated to include the OPERA studies.

Response: This was incorrectly interpreted on our part. In the recently accepted overview of AEs of comparator DMTs presented in the daclizumab appraisal, it was stated in the Chapter 5 summary that a MTC for AEs had been conducted. However, it was clarified further on in the chapter that an MTC could not be performed as heterogeneity in AE reporting did not allow pooling of data. Annualised risks were said to have been taken from trials but no further information is provided in the

daclizumab appraisal about which studies and datacuts were used to derived the AE data.

(b) Please comment on the reliability of the adverse event rate estimates for ocrelizumab given that they were estimated by a post-hoc adjustment using external data rather than by including the OPERA studies in an MTC.

Response: As clarified above, no MTC was conducted for AEs in the daclizumab appraisal. Due to differences in the annualised risk of AEs with IFNB-1a (Rebif) as reported in the daclizumab appraisal (table 79, page 214) and as observed in the OPERA studies, we considered it appropriate to apply an adjustment to the annualised risks derived from the OPERA studies in order to compare appropriately with the external source.

This is a conservative assumption, as when no adjustment is applied and annualised risks for ocrelizumab and IFNB-1a (Rebif) are derived from the OPERA studies whilst annualised risks for other comparators are derived from the daclizumab appraisal, the ICERs for ocrelizumab versus comparators decrease marginally by 1-3%.

A24. In the BRAVO trial the placebo was matched to laquinimod (oral capsule once daily) whereas the active comparator of interest (interferon beta-1a) was administered intra-muscularly once per week. There was no placebo matched to interferon beta-1a in BRAVO. Please explain why BRAVO was included in the MTC and how the lack of a matched placebo affects interpretation of the MTC results.

Response: Although the open-label design of the IFNB-1a arm in the BRAVO trial is a limitation we do not believe that the BRAVO trial should be excluded in its entirety from the MTC. Although not providing the same robustness as a double-dummy design (such as done in the OPERA trials), the treatment arms were randomized and all outcomes were assessed by neurologists that were blinded to all treatments. All patients, including those receiving oral treatment, wore clothing and/or a robe that ensured coverage of all potential IM injection sites during examination and were instructed not to discuss adverse events (AEs), routes of administration, or treatment assignments with the examining neurologist.

We agree with the reviewers that limitations in trials should be discussed when assessing a treatment's benefit-risk profile. However, the BRAVO trial is not the only study that has an open-label comparator arm as a limitation, for example the CONFIRM trial included glatiramer acetate as an open-label reference arm and all alemtuzumab (intravenous administration) trials included IFNB-1a (Rebif, subcutaneous administration) as an open-label comparator. Whereas the BRAVO and CONFIRM trials demonstrated no apparent evidence that the open-label design impacted outcomes, the CARE-MS II trial showed evidence that bias could be present. The drop-out rate following randomization and prior to receiving study treatment was substantially higher in the control arm (12.6% in the IFNB-1a group compared to 2.3% in the alemtuzumab 12mg group). According to FDA documents the sponsor of the trials attributed this difference in dropout rates to subjects who had previously failed IFNB treatment refusing further treatment with the same drug.

In conclusion, rather than excluding trials from the MTC altogether based on an open-label design we think it is more appropriate that limitations in trial quality are taken into consideration when assessing the totality of evidence and benefits that treatments provide. As we highlighted in our submission, we believe that the OPERA trials are unique in being the first pivotal trial program to include two head-to-head trials versus an active comparator with double-dummy design. Importantly, ocrelizumab is the first treatment to replicate in two trials high efficacy in reducing clinical and subclinical outcomes compared to an active comparator.

A25. In company submission Appendix Table 10 the MSCRG trial (Jacobs et al 1996, reference 100 in the submission) is stated as having a natalizumab arm containing 47 patients. However, the Jacobs et al. reference does not mention a natalizumab arm. Please explain this discrepancy.

Response: This is an error, apologies for the oversight.

A26. At what time point in the OPERA I trial were the baseline and post-baseline anti-drug antibody assays carried out (section B.2.10, page 76, Table 22)?

Response: ADA assays were carried out in the OPERA I and II studies at baseline and at every 6-monthly treatment visit during the controlled trial period. Table 22 in the NICE submission refers to pooled analysis from OPERA I and II.

A27. Please provide annual rates of discontinuation from the OPERA and OLE studies.

Response: Annual rates of discontinuation from the OPERA and OLE studies are shown below (Figure 18 and Table 17). The rates of discontinuation for patients treated with ocrelizumab remain constant throughout the period of the OPERA and OLE studies, supporting the extrapolation method of discontinuation rates in the economic analysis. After patients switch from IFNB-1a (Rebif) to ocrelizumab in the OLE study the number of patients withdrawing from treatment each year is consistent with patients treated with ocrelizumab since the start of the OPERA studies, and remains constant up until the latest data point in year 5.

The rate of discontinuation for IFNB-1a (Rebif) appears to decrease in the second year but no data beyond 2 years are available in the OPERA studies to determine the long-term trajectory of treatment withdrawal on IFNB-1a (Rebif). However, the results of the 10-year UK Risk Sharing Scheme for the IFNBs and glatiramer acetate indicated that discontinuation rates remain constant in the long-term (7), further supporting the assumption used in the economic model for ocrelizumab and comparators.

Figure 18 Annual all-cause discontinuation in OPERA I, II and OLE study

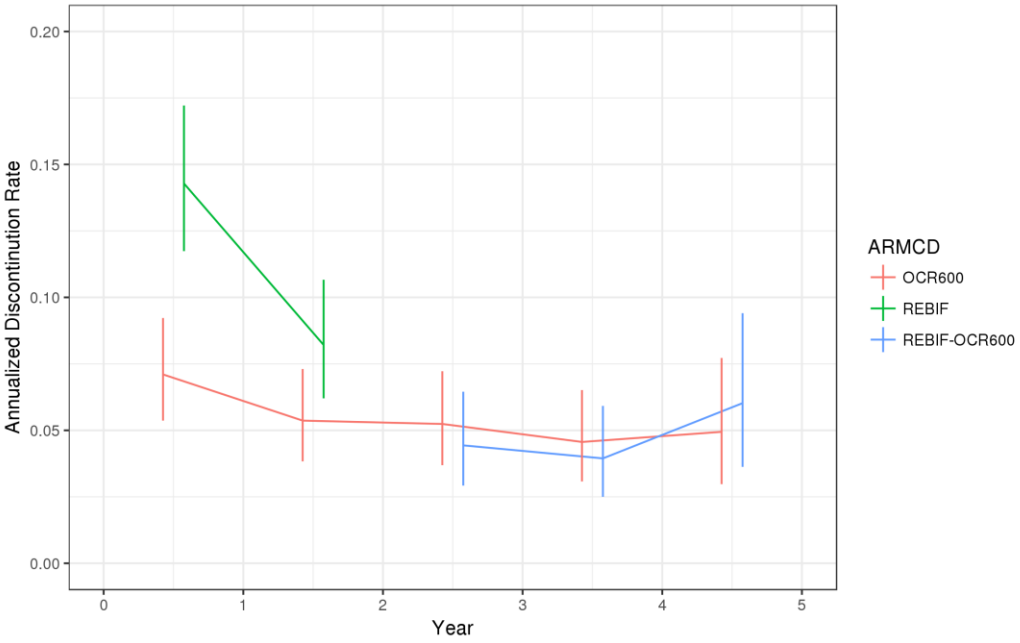

Annualized Discontinuation Rate
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
5
Year
ARMCD
OCR600
REBIF
REBIF-OCR600

Table 17 Annual all-cause discontinuation rates in OPERA I, II and OLE study

	Ocrelizumab				IFNB-1a (Rebif)				Ocrelizumab after IFNB-1a (Rebif)			
Year*	Discontinuations	Patient Years Exposure*	Annualized Discontinuation Rate	95% CI	Discontinuations	Patient Years Exposure*	Annualized Discontinuation Rate	95% CI	Discontinuations	Patient Years Exposure*	Annualized Discontinuation Rate	95% CI
0 - 1	56	788.5	0.071	0.054-0.092	110	770.1	0.143	0.117-0.172				
1 - 2	40	745.5	0.054	0.038-0.073	56	682	0.082	0.062-0.107				
2 - 3	37	706.2	0.052	0.037-0.072					27	608.9	0.044	0.029-0.065
3 - 4	30	657.5	0.046	0.031-0.065					23	583.1	0.039	0.025-0.059
4 - 5	19	384.3	0.049	0.03-0.077					19	315.5	0.06	0.036-0.094

* Note: for the purpose of this analysis a year was defined as 48 weeks consistent with assessments / dosing schedule.

A28. The submission section B.2.10 and Appendix L do not report any adverse events in the OPERA OLE study.

(a) Please provide information on all adverse events that have occurred in the OPERA OLE study.

Response:

Introduction

The primary analysis of safety and benefit risk of ocrelizumab is based on data from two Phase III active-controlled, double-blind, double-dummy studies in patients with relapsing multiple sclerosis (RMS) and one Phase III double-blind placebo-controlled study in patients with primary-progressive multiple sclerosis (PPMS). Additional supportive data are also provided from a Phase II study in patients with relapsing-remitting multiple sclerosis (RRMS). All of these studies have ongoing open-label extension (OLE) periods where all eligible patients are receiving ocrelizumab. Data from these MS studies have been pooled to provide a comprehensive assessment of safety of ocrelizumab in patients with MS (ocrelizumab all-exposure population).

With respect to safety, the purpose of the OLE studies is to collect and characterize long-term safety. There are limitations of OLE studies, such as bias due to the open-label design and drop-outs that are not random. However, by including all available patients exposed to ocrelizumab, the large patient population allows characterization of long-term safety and provide better estimates of less frequent adverse events. Thus, an integrated approach of including all patients exposed to ocrelizumab provides the most comprehensive overview of the safety profile.

Methods

In response to the question, two cohorts were assessed:

1. **ocrelizumab all-exposure population (Pool B)**, which included safety data from the Phase 2 study, Phase III OPERA trials and Phase III ORATORIO trial (both from controlled and OLE periods)

2. **ocrelizumab RMS exposure population (Pool C)**, which included safety data from the Phase III OPERA trials (both from controlled and OLE periods)

Data from all patients who received any part of an ocrelizumab dose are included in these pools. Thus, data from patients who were randomized to the IFN group in the OPERA trials or placebo in the ORATORIO trial are also included after the switch to open-label ocrelizumab treatment.

Results from Pool B and C is presented for two clinical cut-off dates (CCOD), 20-Jan-2016 and 17-Feb-2017 (latest available). Safety outcomes from these two cohorts have been presented at ECTRIMS 2017 (8, 9).

As of the CCOD of 17-Feb-2017, in the ocrelizumab all-exposure population (Pool B) a total of 2301 patients were exposed to any part of an ocrelizumab dose (Table 18)

contributing to 7748 patient-years of observation. The mean number of doses received totalled 7.3.

Table 18 Overview of exposure of ocrelizumab

Pool	Patient N	Exposure	Mean nr of Doses
OPERA Treatment Controlled Period			
Ocrelizumab	825	1448 PY	3.8
Inteferon beta-1a	826	1399 PY	3.6
ORATORIO Treatment Controlled Period			
Ocrelizumab	486	1416 PY	6.6
Placebo	239	660 PY	6.1
Ocrelizumab all-exposure population (Pool B), CCOD 20Jan2016			
Ocrelizumab	2279	5711	5.6
Ocrelizumab all-exposure population (Pool B), CCOD 17Feb2017			
Ocrelizumab	2301	7748	7.3
Ocrelizumab RMS exposure population (Pool C), CCOD 20Jan2016			
Ocrelizumab	1448	3233	5.4
Ocrelizumab RMS exposure population (Pool C), CCOD 17Feb2017			
Ocrelizumab	1448	4582	7.2

Safety Outcomes

As of February 2017, the overall rate of AEs in the ocrelizumab all-exposure population (Pool B) was 226 per 100 PY, which is lower compared with rates observed in January 2016 (242 per 100 PY) and rates at the completion of the controlled treatment periods of the OPERA and ORATORIO trials (290 and 261 per 100 PY, respectively) (Table 19). Deaths, serious AEs and serious infections had stable event rates during the OLE, and showed no increase compared with the controlled treatment periods. As of February 2017, no serious confirmed opportunistic infections have been reported. Over time, the crude incidence rate of malignancy per 100 PY fluctuated (CCOD 17Feb2017: 0.45 per 100 PY; 95% CI: 0.32-0.63,(8) and remained within epidemiological range for patients with MS (0.67 per 100 PY; 95% CI: 0.63-0.71, (10).

Conclusion

The OLE demonstrate that the safety profile for ocrelizumab is generally consistent with what was observed during the treatment controlled periods (with the exception of IRRs which decreased as expected).

Table 19 Overview of safety profile in MS patients treated with ocrelizumab – core and OLE periods

	OPERA Treatment Controlled Period[a]		ORATORIO Treatment Controlled Period[b]		Ocrelizumab all-exposure (Pool B), CCOD 20Jan2016 (PY=5711)[c]	Ocrelizumab all-exposure (Pool B), CCOD 17Feb2017 (PY=7748)[d]
	IFN (PY=1399)	OCR (PY=1448)	PLA (PY=660)	OCR (PY=1416)		
Overall total number of events	296.01 (287.06, 305.16)	289.66 (280.95, 298.56)	267.04 (254.72, 279.81	260.51 (252.18, 269.06)	241.65 (237.63, 245.72)	225.70 (222.37, 229.07)
Death	0.14 (0.02, 0.52)	0.07 (0.00, 0.38)	0.15 (0.00, 0.84)	0.28 (0.08, 0.72)	0.14 (0.06, 0.28)	0.17 (0.09, 0.29)
Serious AE	6.29 (5.05, 7.75)	5.39 (4.26, 6.72)	11.67 (9.21, 14.59)	10.24 (8.64, 12.05)	6.97 (6.30, 7.69)	7.18 (6.59, 7.80)
Serious infection*	1.79 (1.16, 2.64)	0.83 (0.43, 1.45)	2.88 (1.73, 4.50)	2.97 (2.14, 4.01)	1.80 (1.47, 2.19)	1.86 (1.57, 2.19)
Serious AE leading to withdrawal from treatment	0.64 (0.29, 1.22)	0.48 (0.19, 1.00)	0.91 (0.33, 1.98)	0.92 (0.49, 1.57)	0.63 (0.44, 0.87)	0.53 (0.38, 0.72)
Serious AE leading to dose modification/interruption	0.43 (0.16, 0.93)	0.76 (0.38, 1.36)	0.61 (0.17, 1.55)	0.85 (0.44, 1.48)	0.54 (0.37, 0.77)	0.48 (0.34, 0.66)
AE leading to withdrawal from treatment	3.93 (2.96, 5.12)	2.35 (1.63, 3.28)	1.21 (0.52, 2.39)	1.41 (0.86, 2.18)	1.40 (1.11, 1.74)	1.24 (1.00, 1.51)
AE leading to dose modification/interruption	8.65 (7.18, 10.33	3.38 (2.50, 4.47)	2.12 (1.16, 3.56)	4.59 (3.54, 5.85)	2.77 (2.35, 3.23)	2.44 (2.10, 2.81)
IRRs leading to withdrawal at the first infusion	0.00 (0, 0.26)	0.76 (0.38, 1.36)	0.00 (0.00, 0.56)	0.07 (0.00, 0.39)	0.32 (0.19, 0.50)	0.23 (0.14, 0.37)

[a] Source: t_ae_100py_profile_all_spa [b] Source: t_ae_100py_profile_CNTR_SE_046 [c] Source: t_ae_100py_profile_all_spb2_su [d] Source: t_ae_100py_profile_all_spb2_su4
Treatment controlled periods: Investigator text for AEs encoded using MedDRA version MedDRA v18.0. Pool B: Investigator text for AEs encoded using MedDRA version MedDRA v18.1
Multiple occurrences of the same AE in one patient will be counted multiple times. PY: Total patient years. 95% CI is calculated using an exact method based on the Poisson distribution.
*Serious infections are defined using Adverse events falling into the MedDRA System Organ Class 'Infections and infestations', and using 'Is the event non-serious or serious' from the Adverse events CRF page.

(b) The adverse events data as summarised in Table 40 of the submission do not appear to capture any events observed in the OLE study for ocrelizumab or (where conducted) the extension studies for the comparators. As such, the full available data on adverse events does not appear to have been utilised. Please explain this omission.

Response: As demonstrated in response to question A28.a, data from the ocrelizumab all-exposure population (up until 17-February-2017) demonstrate that the safety profile for ocrelizumab is generally consistent (with the exception of IRRs that decreased over time, which was to be expected) with that seen during the controlled treatment period of the pivotal trials.

The primary source for AEs for ocrelizumab in the economic model was the data from the treatment controlled period from the OPERA studies. The economic model included a specific set of adverse events, namely AEs that had an occurrence of ≥5% in either arm of the treatment controlled period of the OPERA trials (with exception of PML which was included due to high cost impact and ≥2% occurrence with natalizumab). During the OLE period the event rates for these specific AEs also remained stable in both CCODs, 20Jan2016 and 17Feb2017 (Table 20). As expected the IRR event rates decreased in the OLE period, as the frequency of IRRs is highest during the first infusion.

We believe that controlled data is the most relevant source for estimating AE event rates, which inform costs and utilities of adverse events. This is also consistent with other recent NICE submissions in MS. OLE studies are open-label without comparator arms, and can potentially introduce bias. Nevertheless, the OLE data provide insights into potential long-term safety effects, and since these data are consistent with the controlled data, except reduced rate of IRRs, we are confident that our initial submission provides a solid basis for the cost-effectiveness evaluation of ocrelizumab.

For comparators, AE data were derived from the daclizumab appraisal and no detailed information is provided in the daclizumab appraisal regarding the source of these data (see response to questions A23.a). It is therefore unclear whether OLE periods were included but it is more likely that only published AEs from controlled periods of pivotal studies formed the basis of this analysis. As such it is assumed to be comparable in nature to the ocrelizumab AE data set included in the submission.

Table 20 Updated safety profile including OLE data for AEs included in economic analysis

	OPERA Treatment Controlled Period (N=825, PY=1448)[a]		**Ocrelizumab RMS-exposure (Pool C), CCOD 20Jan2016 (N=1448, PY=3233)[b]**	**Ocrelizumab RMS-exposure (Pool C), CCOD 17Feb2017 (N=1448, PY=4582)[c]**
	Patients (%)	Events per 100 PY	Events per 100 PY	Events per 100 PY
INFUSION RELATED REACTION	283 (34.3)	34.88	27.44	21.13

UPPER RESPIRATORY TRACT INFECTION	125 (15.2)	13.26	13.70	12.83
NASOPHARYNGITIS	122 (14.8)	12.98	11.60	11.15
URINARY TRACT INFECTION	96 (11.6)	11.60	12.50	11.79
HEADACHE	93 (11.3)	9.53	6.43	5.30
FATIGUE	64 (7.8)	5.39	4.39	3.89
DEPRESSION	64 (7.8)	4.90	3.77	3.21
BACK PAIN	53 (6.4)	4.07	3.56	3.12
BRONCHITIS	42 (5.1)	3.52	4.02	3.65
ARTHRALGIA	46 (5.6)	3.45	3.12	2.90
SINUSITIS	46 (5.6)	4.01	3.46	3.25
INFLUENZA LIKE ILLNESS	38 (4.6)	2.76	1.64	1.24
INSOMNIA	46 (5.6)	3.59	2.32	1.83
INJECTION SITE REACTION	2 (0.2)	0.14	0.09	0.07
PML	0 (0.0)	0.00	0.00	0.00

Annualized risk of AEs are applied in economic model.
PML, progressive multifocal leukoencephalopathy
[a] t_ae_100py_ir_all_spa
[b] t_ae_100py_bsc_all_spc_su
[c] t_ae_100py_bsc_all_spc_su4

Section B: Clarification on cost effectiveness data

B1. The results of the economic analysis are presented using a 'blended ABCR' comparator, with costs and QALYs weighted according to market share (company submission Table 55, page 125). In previous appraisals, sensitivity analysis has been used to investigate the robustness of cost-effectiveness results to uncertainty over market share. Please explain how the market share estimates in Table 55 were derived, the extent of uncertainty over them, and the sensitivity of results to this uncertainty.

Response: The market share estimates are derived from confidential NHiS data. These data were based on freedom of information requests to all hospital Trusts in the UK. The information requested was the number of patients with MS currently treated with each of the DMTs. The data were collected in May-June 2017. 170 Trusts were contacted, out of these 92 Trusts provided current estimates of DMT patient shares, 64 did not treat patients with MS, 5 had pooled data with other Trusts, 3 did not have data available, and 6 were late with responding and data for these Trusts were based on a previous round of data collected in January 2017.

The extent of uncertainty over the estimates was not provided, but the results are relatively insensitive to changes in the split of ABCRs. For instance, if equal market share is assumed - i.e. 20% for IFNB-1a subcutaneous (Rebif), 20% for IFNB-1a intramuscular (Avonex), 20% for IFNB-1b (Betaferon or Extavia), 20% for pegIFN-1a (Plegridy), and 20% for glatiramer acetate (Copaxone) - the incremental ICER of ocrelizumab versus the blended ABCRs increases marginally by 1% (when excluding alemtuzumab to allow for patient choice).

B2. Treatments contained in a blended comparator must be mutually exclusive, it must be reasonable that they could be collectively displaced by ocrelizumab. Please

provide details of how this assumption was validated for 'blended ABCR', give details of any clinical expert opinion that was sought.

Response: The ABCRs are broadly similar but not identical. These treatments cannot be considered interchangeable as they have different modes of administration, dosing regimens, auto-immunogenicity, efficacy and safety profiles, and costs. These features all influence patient preferences and as such the market shares of these treatments are not equal, as you would expect with interchangeable treatments.

ABCRs used to be the treatment of choice for newly diagnosed patients with non-HA/RES disease. However, the emergence of newer treatment options in the last 5 years - e.g. with oral administration, or higher efficacy - has resulted in the steady decline of the use of ABCRs as a whole.

It is to be expected that ocrelizumab, with its unique features of broad licensed indication, high efficacy, manageable safety profile, and convenience of 6 monthly infusion, would further add to the displacement of the ABCRs collectively.

B4. Please provide economic analyses comparing ocrelizumab with glatiramer acetate alone and ocrelizumab compared with one interferon beta alone.

Response: Pairwise comparisons against individual ABCR treatments are provided in the NICE submission appendix J.

Incremental analyses with glatiramer acetate (Table 21 and Table 22) and IFNB-1a (Rebif) (Table 23 and Table 24) representing the ABCR treatments are provided below. IFNB-1a (Rebif) was chosen as it is the trial comparator and hence provides the most robust estimates of the IFNBs versus ocrelizumab. Results including alemtuzumab are not shown as alemtuzumab dominates all other DMTs apart from the cheapest ABCR.

The incremental results demonstrate that ocrelizumab is cost-effectiveness compared with glatiramer acetate or IFNB-1a (Rebif) at PAS price. All other DMTs are dominated or extendedly dominated and as such the incremental results are in fact the same as the pairwise comparisons of ocrelizumab against glatiramer acetate and IFNB-1a (Rebif).

Table 21 Incremental analysis with glatiramer acetate representing ABCRs, base case ITT excluding alemtuzumab (based on list prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Glatiramer acetate	[redacted]	[redacted]	[redacted]					
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 Incremental analysis with glatiramer acetate representing ABCRs, base case ITT excluding alemtuzumab (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Glatiramer acetate	[redacted]	[redacted]	[redacted]					
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	134,012	Extendedly dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,304	27,304
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	152,896	Dominated
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	399,860	Dominated

Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	108,455	Dominated

Table 23 Incremental analysis with IFNB-1a (Rebif) representing ABCRs, base case ITT excluding alemtuzumab (based on list prices)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]					
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24 Incremental analysis with IFNB-1a (Rebif) representing ABCRs, base case ITT excluding alemtuzumab (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]					
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,911	25,911
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	479,165	Dominated

Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	133,794	Dominated

Section C: Textual clarifications and additional points

C1. What does N/A mean for the outcomes in Table 6 of the company submission? The ocrelizumab phase II study did report outcomes relevant to the decision problem, so this may appear misleading.

Response: N/A was related to the phase II study not being included in the economic analysis due to lack of disease progression data. However, it did indeed report some outcomes relevant to the decision problem, namely annualised protocol-defined relapse rates and adverse events of treatments (both secondary endpoints).

Other outcomes reported in the phase II study but not relevant to the decision problem were:

- total number of gadolinium-enhancing T1 lesions observed on brain MRI scans for weeks 12, 16, 20, and 24 versus placebo (primary endpoint)
- proportion of relapse-free patients
- total number of gadolinium-enhancing T1 lesions
- total number of new gadolinium-enhancing T1 lesions
- change in total volume of T2 lesions from baseline to week 24

Appendix

Related to Question A5 (b)

Table 25 Included studies for intervention

Trial ID	Formatted record
Kappos et al, 2011	**Kappos L, Li D, Calabresi PA, 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(9805):1779-87**.
OPERA I	**F. Hoffmann-La Roche Ltd, Genentech Inc. Research report no. 1062034: primary clinical study report – protocol WA21092 – A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis. Basel: F. Hoffmann-La Roche Ltd; March 2016. 1-6491.**
OPERA II	**F. Hoffmann-La Roche Ltd, Genentech Inc. Research report no. 1062035: primary clinical study report – protocol WA21093 – A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif®) in patients with relapsing multiple sclerosis. Basel: F. Hoffmann-La Roche Ltd; March 2016. 1-6798.**

Table 26 Included studies for comparators

Trial ID	Author, year	Reference
ADVANCE	Calabresi, P.A. et al, 2014	**Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13(7):657-65.**
	Newsome, SD. et al, 2014	Newsome S, Balcer L, Boyko A, Pelletier J, Arnold D, Liu S, et al. Efficacy and safety of peginterferon beta-1a in relapsing-remitting multiple sclerosis: 2-year data from the ADVANCE study [poster]. In: Joint Meeting of the CMSC and ACTRIMS, Dallas, TX; 2014. DX57
	Arnold, DL. et al, 2014	Arnold DL, Calabresi PA, Kieseier BC, Sheikh SI, Deykin A, Zhu Y, et al. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol. 2014;14:240.
	Kieseier, B. et al, 2013	Kieseier B, Calabresi P, Liu S, Zhu Y, You X, Sperling B, et al. Effect of peginterferon beta-1a on disability progression in patients with relapsing remitting multiple sclerosis: Year 1 data from the pivotal phase 3 ADVANCE study. Mult Scler. 2013;19(Suppl 1):P540.
	Kieseier, B. et al, 2013	Kieseier B, Calabresi P, Song T, Zhu Y, Hung S, Deykin A, et al. Safety and tolerability of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: Data from the pivotal phase 3 ADVANCE study. Mult Scler. 2013;19(Suppl 1):P1061.
	NCT00906399	Biogen. Efficacy and safety study of peginterferon beta-1a in participants with relapsing multiple sclerosis. In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2009.

Trial ID	Author, year	Reference
		Available from https://ClinicalTrials.gov/show/NCT00906399. Identifier: NCT00906399
	Calabresi, P. et al, 2013	Calabresi P, Kiessier B, Arnold DL. Peginterferon beta-1a in relapsing multiple sclerosis: phase 3 advance. Int J MS Care. 2013;15(Suppl 3):DX05.
	Newsome, S. et al, 2015	Newsome S, Kieseier B, Shang S, Liu S, Hung S, Sperling B. Peginterferon beta-1a is effective as early as twelve weeks following treatment initiation in patients with relapsing multiple sclerosis. Neurology. 2015;84(Suppl 14):S4.
	Newsome, S. et al, 2014	Newsome S, Kiessier B, Balcer L. Efficacy and safety of peginterferon beta-1a in relapsing-remitting multiple sclerosis: 2-year data from the advance study Int J MS Care. 2014;16(Suppl 3):DX57
	Newsome, SD., 2017	Newsome SD, Kieseier BC, Liu S, You X, Kinter E, Hung S, et al. Peginterferon beta-1a reduces disability worsening in relapsing-remitting multiple sclerosis: 2-year results from ADVANCE. Ther Adv Neurol Disord. 2017;10(1):41-50.
	EMA 2014	European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Assessment report: Plegridy. International non-proprietary name: peginterferon beta-1a. London: 22 May 2014. 1-98. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002827/WC500170303.pdf.
	Scott 2016	Scott TF, Kieseier BC, Newsome SD, Arnold DL, You X, Hung S, et al. Improvement in relapse recovery with peginterferon beta-1a in patients with multiple sclerosis. Mult Scler J Exp Transl Clin. 2016;2:2055217316676644.
AFFIRM	Polman, C.H. et al, 2006	**Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899-910.**
	Miller, D.H. et al, 2007	Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology. 2007;68(17):1390-401.
	Rudick, R.A. et al, 2007	Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. Ann Neurol. 2007;62(4):335-46.
	Weinstock-Guttman, B. et al, 2012	Weinstock-Guttman B, Galetta SL, Giovannoni G, Havrdova E, Hutchinson M, Kappos L, et al. Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS. J Neurol. 2012;259(5):898-905.
BEYOND	O'Connor, P. et al, 2009	**O'Connor P. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8(10):889-97.**
Bornstein et al, 1987	Bornstein, M.B. et al, 1987	**Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med. 1987;317(7):408-14.**
BRAVO	Vollmer, T.L. et al, 2014	**Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol. 2014;261(4):773-83.**
Calabrese et al, 2012	Calabrese, M. et al, 2012	**Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012;18(4):418-24.**

Trial ID	Author, year	Reference
CAMMS223	Coles, A.J. et al, 2008	**Coles AJ, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359(17):1786-801.**
	Coles, A.J. et al, 2011	Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Lancet Neurol. 2011;10(4):338-48.
	Coles, A.J. et al, 2012	Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial. Neurology. 2012;78(14):1069-78.
	Wray, S. et al, 2011	Wray S. Alemtuzumab reduces risk of sustained accumulation of disability and relapse retreat at years 1 and 2 in CAMMS223. Int J MS Care. 2011;13(Suppl 3):S44.
CARE-MS I	Cohen, J.A. et al, 2012	**Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819-28.**
	Lycke, J. et al, 2013	Lycke J, Arnold DL, Cohen JA, Coles AJ, Confavreux C, Fox EJ, et al. Adverse event profile of alemtuzumab over time in treatment-naive patients with early, active relapsing-remitting multiple sclerosis (RRMS; CARE-MS I study). J Neurol Sci. 2013;333:e374-e75.
	Ionete, C. et al, 2014	Ionete C, Galetta S, Palmer J. Treatment-naive relapsing-remitting multiple sclerosis patients more likely to be disease activity free with alemtuzumab than subcutaneous interferon beta-1a across patient subgroups. Int J MS Care. 2014;16(Suppl 3):DX19.
	Havrdova, E. et al, 2012	Havrdova E, Arnold D, Cohen J, Coles A, Confavreux C, Fox E, et al. Infections phase 3 study: comparison of alemtuzumab and Rebif efficacy in multiple sclerosis I (CARE-MS I). Neurology. 2012;78(Suppl 1):S41.007.
CARE-MS II	Coles, A.J. et al, 2012	**Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1829-39.**
	Arroyo, R. et al, 2013	Arroyo R, Arnold DL, Cohen JA, Coles AJ, Confavreux C, Fox EJ, et al. Alemtuzumab improves quality of life compared to SC IFNB-1a in CARE-MS II. J Neurol. 2013;260:S121-S22.
	Twyman, C. et al, 2013	Twyman C, Montalban X, Arnold D, Cohen J, Coles A, Confavreux C, et al. Relapse Outcomes with Alemtuzumab vs IFNB-1a in Active Relapsing-Remitting Multiple Sclerosis Patients Who Experienced Disease Activity While on Prior Therapy (CARE-MS II). Neurology. 2013;80(Suppl 7):P07.098.
	NCT00548405	Genzyme, Bayer, Sanofi. Comparison of alemtuzumab and rebif® efficacy in multiple sclerosis, study two. In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2007. Available from https://ClinicalTrials.gov/show/NCT00548405. Identifier: NCT00548405
CLARITY	Giovannoni, G. et al	**Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010; 362(5): 416-26.**

Trial ID	Author, year	Reference
	Comi, G. et al, 2009	Comi G, Cook S, Giovannoni G, Rammohan K, Rieckmann P, Soelberg-Sorensen P, et al. Magnetic resonance imaging (MRI) outcomes in patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets: Results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial. J Neurol. 2009;256:S49-S50.
	Comi, G. et al, 2010	Comi G, Cook S, Giovannoni G. Reductions in magnetic resonance imaging activity in relapsing-remitting multiple sclerosis patients treated with cladribine tablets Int J MS Care. 2010;12(Suppl 1):S23.
	Cook, S. et al, 2009	Cook S, Vermersch P, Comi G, Giovannoni G, Rammohan K, Rieckmann P, et al. Safety of Cladribine tablets in the treatment of relapsing-remitting multiple sclerosis (RRMS): Results from the CLARITY study, a 96-week, phase iii, double-blind, placebo-controlled trial. J Neurol. 2009;256:S128.
	Cook, S. et al 2011	Cook S, Vermersch P, Comi G, Giovannoni G, Rammohan K, Rieckmann P, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: The CLARITY (claderibine tablets treating multiple sclerosis orally) study. Mult Scler J. 2011;17(5):578-93.
	Cook, S. et al, 2016	Cook S, Rammohan K, Rieckmann P, Soelberg-Sorensenn P, Vermersch P, Hicking C, et al. Slowing of disability progression based on 6-month confirmed edss in patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets in the clarity study: A post-hoc subgroup analysis. Neurology. 2016;86(Suppl 16):P3.058.
	Cook, S. et al, 2010	Cook S, Comi G, Vermersch P. Tolerability and retention with cladribine tablets for relapsing-remitting multiple sclerosis over 96 weeks. Int J MS Care. 2011;13(Suppl 3):S107.
	Cook, S. et al, 2010	Cook S, Comi G, Vermersch P. Safety and tolerability of cladribine tablets during the clarity study. Int J MS Care. 2010;12(Suppl 1):S24.
	Cook, S. et al 2009	Cook S, Vermersch P, Comi G. Safety and tolerability of cladribine tablets in relapsing-remitting multiple sclerosis. Int J MS Care. 2009;11(Suppl 2):S130.
	Giovannoni, G. 2010	Giovannoni G. The first on the stage: Cladribine. Eur J Neurol. 2010;17:14.
	Giovannoni, G. et al, 2009	Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg-Sorensen P, et al. Clinical efficacy of cladribine tablet therapy in patients with relapsing-remitting multiple sclerosis (RRMS): Results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial. J Neurol. 2009;256:S9-S10.
	Giovannoni, G. et al, 2010	Giovannoni G, Comi G, Cook S. Disease activity–free outcome with cladribine tablets during the clarity study. Int J MS Care. 2010;12(Suppl 1):S48.
	Giovannoni, G. et al, 2009	Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, et al. Clinical outcomes with cladribine tablets in the 96-week, phase III, double-blind, placebo-controlled CLARITY study in patients with relapsing-remitting multiple sclerosis. Mult Scler. 2009;15(9):S136-S37.
	Giovannoni, G. et al, 2017	Giovannoni G, Rammohan K, Cook S, Comi G, Rieckmann P, Soelberg-Sorensen P, et al. EP1157 Cladribine tablets in high disease activity (HDA) subgroups from the CLARITY study of patients with relapsing multiple sclerosis (RMS) In: 3rd Congress of the European Academy of Neurology, 2017.
	NCT00213135	EMD Serono. A safety and efficacy study of oral cladribine in subjects with relapsing-remitting multiple sclerosis (RRMS). In: ClinicalTrials.gov. [internet]. Bethesda. US National Library of Medicine. 2005. Available from

Trial ID	Author, year	Reference
		https://ClinicalTrials.gov/show/NCT00213135. Identifier: NCT00213135
	Rieckmann, P. et al, 2009	Rieckmann P, Giovannoni G, Comi G. The clarity study: efficacy of cladribine tablets for relapsing-remitting multiple sclerosis Int J MS Care. 2009;11(Suppl 2):P11.
	Vermersch, P. et al, 2010	Vermersch P, Comi G, Cook S. Early onset of effect with cladribine tablets in the clarity study. Int J MS Care. 2010;12(Suppl 1):S137.
	Vermersch, P. et al, 2009	Vermersch P, Comi G, Cook S, Giovannoni G, Rammohan K, Rieckmann P, et al. Rapid and sustained efficacy with cladribine tablet treatment in relapsing-remitting multiple sclerosis (RRMS): Results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial. J Neurol. 2009;256:S244-S45.
	Vermersch, P. et al, 2010	Vermersch P, Comi G, Cook S, Giovannoni G, Rammohan K, Rieckmann P, et al. Tolerability and retention on treatment with cladribine tablets for relapsing-remitting multiple sclerosis over 96 weeks in the phase III, double-blind, placebo-controlled CLARITY study. Mult Scler. 2010;16(Suppl):S298-S99.
CombiRx	Lublin, F.D. et al, 2013	**Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. Ann Neurol. 2013;73(3):327-40.**
	NCT00211887	Fred Lublin, National Institute of Neurological Disorders and Stroke. Combination therapy in patients with relapsing-remitting multiple sclerosis (MS) combiRx. In: ClinicalTrials.gov. [internet]. Bethesda. US National Library of Medicine. 2005. Available from https://ClinicalTrials.gov/show/NCT00211887. Identifier: NCT00211887
CONFIRM	Fox, E. et al, 2012	**Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087-97.**
	Kita, M. et al, 2014	Kita M, Fox RJ, Phillips JT, Hutchinson M, Havrdova E, Sarda SP, et al. Effects of BG-12 (dimethyl fumarate) on health-related quality of life in patients with relapsing-remitting multiple sclerosis: findings from the CONFIRM study. Mult Scler. 2014;20(2):253-7.
	Miller, D. et al, 2015	Miller DH, Fox RJ, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. Neurology. 2015; (11): 1145-52.
Copolymer 1 MS trial	Johnson, K.P. et al, 1995	**Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268-76.**
	Johnson, K.P. et al, 1998(11)(10)(6)(5)	Johnson KP, Brooks BR, Cohen JA, Ford C, Goldstein J, Lisak RP, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Neurology. 1998;50(3):701-08.
DECIDE	Kappos L. et al., 2014	**Kappos L, Selmaj K, Arnold D, Havrdova E, Boyko A, Kauffman M, et al. Primary results of DECIDE: a randomized, double-blind, double-dummy, active-controlled trial of daclizumab HYP vs. Interferon ?-1a in RRMS patients [PowerPoint]. In:**

Trial ID	Author, year	Reference
		Joint ACTRIMS-ECTRIMS Conference, Boston, MA; September 12. 2014. 1-20
	Arnold DL. et al., 2014	Arnold DL, Kappos L, Havrdova E, Selmaj K, Boyko A, Kaufman M, et al. Brain MRI results of DECIDE: a randomized, double-blind trial of DAC HYP vs. IFN?-1a in RRMS patients. Mult Scler. 2014;20(Suppl 1):P051.
	Arnold, DL. et al , 2015	Arnold DL, Kappos L, Wiendl H, Selmaj K, Havrdova E, Boyko A, et al. Benefits on brain MRI lesion activity with daclizumab HYP compared with intramuscular interferon beta-1a are maintained through 144 weeks' treatment: Results from the DECIDE study. Mult Scler. 2015;21(Suppl 11):255-56.
	Kappos, L. et al, 2015	Kappos L, Havrdova E, Giovannoni G, Khatri BO, Gauthier SA, Greenberg S, et al. Effect of daclizumab HYP versus intramuscular interferon beta-1a on no evidence of disease activity in patients with relapsing-remitting multiple sclerosis: Analysis of the DECIDE study. Mult Scler. 2015;21(Suppl 11):22 (A89).
	Kappos, L. et al, 2015	Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, et al. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2015;373(15):1418-28.
	Kappos, L. et al, 2015	Kappos L, Selmaj K, Arnold D, Havrdova E, Boyko A, Kaufman M, et al. Daclizumab HYP versus interferon beta1a in relapsing-remitting multiple sclerosis: primary results of the decide study. Neurology. 2015;84(Suppl 14):S4.
	NCT01064401	Biogen, AbbVie. Efficacy and safety of BIIB019 (daclizumab high yield process) versus interferon β 1a in participants with relapsing-remitting multiple sclerosis. In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2010. Available from https://ClinicalTrials.gov/show/NCT01064401. Identifier: NCT01064401
	Selmaj, K. et al, 2015	Selmaj K, Kappos L, Arnold D, Havrdova E, Boyko A, Kaufman M, et al. Safety and tolerability results from the decide study: A phase 3 active-comparator study of daclizumab HYP in relapsing-remitting multiple sclerosis. Neurology. 2015;84(Suppl 14):P7230.
	Ziemssen T, et al, 2017	Ziemssen T, Giovannoni G, Wiendl H, Greenberg S, Wang P, Aquino P, et al. PR3086 Consistent effects of daclizumab in disease-modifying therapy (DMT)-naïve relapsing-remitting multiple sclerosis (RRMS) patients in DECIDE. In: 3rd Congress of the European Academy of Neurology, 2017.
	NICE TA441, 2017	National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Daclizumab for treating relapsing-remitting multiple sclerosis [ID827]. Committee Papers. In: Technology appraisal guidance [TA441]. London. NICE. 2017. [cited: 08 August 2017]. Available from: https://www.nice.org.uk/guidance/ta441/documents/committee-papers.
	Lio Y, et al., 2017	Liu Y, Vollmer T, Havrdova E, Riester K, Lee A, Phillips G, et al. Impact of daclizumab versus interferon beta-1a on patient-reported outcomes in relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2017;11:18-24.
DEFINE	Gold, R. et al, 2012	**Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367(12):1098-107.**

Trial ID	Author, year	Reference
	Agarwal, S. et al, 2012	Agarwal S, Kappos L, Gold R, Arnold D, Bar-Or A, Giovannoni G, et al. Effects of BG-12 on Quality of Life in Patients with Relapsing-Remitting Multiple Sclerosis: Findings from the DEFINE Study. Neurology. 2012;78(Suppl 1):P07.102.
	Arnold, D. et al, 2012	Arnold D, Gold R, Kappos L, Bar-Or A, Giovannoni G, Selmaj K, et al. Effect of BG-12 on brain atrophy and lesions volume: MRI results from the define study during first and second year of treatment. Neurology. 2012;78(Suppl 1):S11.003.
	Giovannoni, G. et al, 2012	Giovannoni G, Gold R, Kappos L, Arnold DL, Bar-Or A, Selmaj K, et al. Analysis of clinical and radiological disease activity-free status in patients with relapsing-remitting multiple sclerosis treated with BG-12: findings from the DEFINE study. J Neurol. 2012;259:S106-S06.
	European Medicines Agency	European Medicines Agency. Assessment report: Tecfidera - Common Name: dimethyl fumarate. London: EMA; November 26 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002601/WC500162070.pdf.
	Arnold, DL. et al, 2014	Arnold DL, Gold R, Kappos L, Bar-Or A, Giovannoni G, Selmaj K, et al. Effects of delayed-release dimethyl fumarate on MRI measures in the Phase 3 DEFINE study. J Neurol. 2014;261(9):1794-802.
DMSG	Koch-Henriksen, N. et al, 2006	**Koch-Henriksen N, Sorensen PS, Christensen T, Frederiksen J, Ravnborg M, Jensen K, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006;66(7):1056-60.**
Etemadifir et al, 2006	Etemadifar et al, 2006	**Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand. 2006;113(5):283-7.**
European / Canadian Glatiramer Acetate trial	Comi, G. et al, 2001	**Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001;49(3):290-7.**
	Rovaris, M. et al, 2001	Rovaris M, Comi G, Rocca MA, Wolinsky JS, Filippi M, European/Canadian Glatiramer Acetate Study Group. Short-term brain volume change in relapsing-remitting multiple sclerosis: effect of glatiramer acetate and implications. Brain. 2001;124(Pt 9):1803-12.
	Rovaris, M. et al, 2003	Rovaris M, Comi G, Ladkani D, Wolinsky JS, Filippi M, European Canadian Glatiramer Aceta. Short-term correlations between clinical and MR imaging findings in relapsing-remitting multiple sclerosis. AJNR Am J Neuroradiol. 2003;24(1):75-81.
	Filippi, M. et al, 2001	Filippi M, Rovaris M, Rocca MA, Sormani MP, Wolinsky JS, Comi G, et al. Glatiramer acetate reduces the proportion of new MS lesions evolving into "black holes". Neurology. 2001;57(4):731-33.
EVIDENCE	Panitch, H. et al, 2002	**Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002;59(10):1496-506.**
	Schwid, SR. et al, 2007	Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. Clin Ther. 2007;29(9):2031-48.

Trial ID	Author, year	Reference
	Coyle, PK. et al, 2015	Coyle PK, Freedman MS, Dangond F, Fang J, Reder AT. Predictive value of early MRI measures for long-term disease activity in patients with relapsing-remitting multiple sclerosis receiving IFN beta-1a SC tiw or IFN beta-1a IM QW: Post hoc analyses of the EVIDENCE study. Mult Scler. 2015;86(Suppl 16):594-95.
	Reder, A. et al, 2016	Reder A, Freedman M, Fang J, Dangond F, Coyle P. MRI frequency and no evidence of disease activity status among patients with RRMS receiving IFN beta-1A SC tiw or IFN beta-1A IM QW: Post hoc analyses of evidence. Neurology. 2016;86(Suppl 16):P6.190.
	Panitch, H. et.al 2005	Panitch H, Goodin D, Francis G, Chang P, Coyle P, O'Connor P, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci. 2005;239(1):67-74.
	Coyle, PK. et.al., 2017	Coyle PK, Reder AT, Freedman MS, Fang J, Dangond F. Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon beta-1a in the EVIDENCE study. J Neurol Sci. 2017;379:151-56.
FREEDOMS	Kappos, L. et al, 2010	**Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387-401.**
	Radue, E.W. et al, 2012	Radue EW, O'Connor P, Polman CH, Hohlfeld R, Calabresi P, Selmaj K, et al. Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis. Arch Neurol. 2012;69(10):1259-69.
	Devonshire, V. et al, 2010	Devonshire V, O'Connor PW, Polman CH. Oral fingolimod (FTY720) versus placebo in relapsing-remitting multiple sclerosis: two-year efficacy results of the phase 3 freedoms trial. Int J MS Care. 2010;12(Suppl 1):S31.
	Francis, G. et al, 2011	Francis G, Calabresi P, O'Connor PW. Fingolimod improves expanded disability status scale–based outcomes in patients with multiple sclerosis Int J MS Care. 2011;13(Suppl 3):S63.
FREEDOMS II	Calabrese, M. et al, 2014	**Calabresi PA, Radue E-W, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545-56.**
	Vollmer, T. et al, 2012	Vollmer T, Goodin D, Jeffery D, Kappos L, Radue EW, Rammohan K, et al. Effect of fingolimod on severe relapses, healthcare utilisation and relapse recovery in patients with relapsing-remitting multiple sclerosis: results from the phase 3 FREEDOMS II study. Mult Scler J. 2012;18:438-39.
	Agius, M. et al., 2013	Agius M, Jeffrey D, Meng X. Fingolimod efficacy and safety vs. placebo: phase 3 freedoms II Study. Int J MS Care. 2013;15(Suppl 3):82.
GALA	Khan, O et al, 2013	**Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, Gala Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013;73(6):705-13.**
	Khan, O. et al, 2013	Khan O, Reckmann P, Boyko A. Efficacy of glatiramer acetate 40-mg injection three times weekly Int J MS Care. 2013;15(Suppl 3):DX41.

Trial ID	Author, year	Reference
	Khan, O. et al, 2013	Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. A multinational, multicenter, randomized, placebo-controlled, double-blind study to assess the efficacy, safety, and tolerability of glatiramer acetate 40 mg injection three times a week in subjects with RRMS: Efficacy and safety results of the gala study. Neurology. 2013;80(Suppl 7):S01.005.
	Khan, O. et al, 2012	Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. A phase 3 trial to assess the efficacy and safety of glatiramer acetate injections 40mg administered 3 times a week compared to placebo. Mult Scler J. 2012;18(Suppl 4):512-12.
	Rieckmann, P. et al, 2013	Rieckmann P, Boyko A, Selmaj K, Zivadinov R, Khan O. Reduction of RRMS Disease Activity with a Three Times Weekly Regimen of Glatiramer Acetate 40 mg Injection: A Post Hoc Analysis from the GALA Study. Neurology. 2013;80(Suppl 7):P07.090.
	Davis MD, et al., 2017	Davis MD, Ashtamker N, Steinerman JR, Knappertz V. Time course of glatiramer acetate efficacy in patients with RRMS in the GALA study. Neurol Neuroimmunol Neuroinflamm. 2017;4(2):e327.
	Khan O, et al., 2017	Khan O, Rieckmann P, Boyko A, Selmaj K, Ashtamker N, Davis MD, et al. Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study. Mult Scler. 2017;23(6):818-29.
GATE	Cohen, J et al	**Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberyé J, et al. Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial. JAMA Neurol. 2015; 72(12): 1433-41.**
	Cohen, JA. et al 2014	Cohen JA, Belova A, Selmaj K, Wolf C, Oberye JJL, Tweel ERW, et al. Generic glatiramer acetate is equivalent to copaxone on efficacy and safety: Results of the randomized doubleblind GATE trial in multiple sclerosis. Mult Scler. 2014; (1 suppl. 1): 38-9.
	NCT01489254	Synthon BV. Efficacy and Safety of GTR in Comparison to Copaxone®. In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2011. Available from https://ClinicalTrials.gov/show/NCT01489254. Identifier: NCT01489254
	Cohen, JA. et al, 2015	Cohen JA, Belova A, Barkhof F, Wolf C, Tweel ERW, Oberye JJL, et al. Switching from branded to generic glatiramer acetate: Two-year clinical data from the GATE trial further support the continued efficacy and tolerability of generic glatiramer acetate. Mult Scler. 2015; 11(Suppl 1): 536-7.
IFNB MS	Duquette, P. et al, 1993(12)(11)(7)(6)	**Duquette P, Girard M, Despault L, DuBois R, Knobler RL, Lublin FD, et al. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial. Neurology. 1993;43(4 I):655-61.**
	Paty, D.W. and Li et al, 1993	Paty DW, Li DKB. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo- controlled trial. Neurology. 1993;43(4 I):662-67.
	Sibley, W.A. et al, 1995	The IFNB Multiple Sclerosis Study Group, The University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology. 1995;45(7):1277-85.

Trial ID	Author, year	Reference
	Zhao, G.J. et al, 2000	Zhao GJ, Koopmans RA, Li DK, Bedell L, Paty DW. Effect of interferon beta-1b in MS: assessment of annual accumulation of PD/T2 activity on MRI. UBC MS/MRI Analysis Group and the MS Study Group. Neurology. 2000;54(1):200-6.
IMPROVE	De Stefano, N. et al, 2010	**De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler. 2010;16(7):888-92.**
	De Stefano, N. et al, 2012	De Stefano N, Sormani MP, Stubinski B, Blevins G, Drulovic JS, Issard D, et al. Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: Further outcomes from the IMPROVE study. J Neurol Sci. 2012;312(1-2):97-101.
	NCT00441103	Merck KGaA. A study to evaluate rebifÂ® new formulation (IFN-beta-1a) in relapsing remitting multiple sclerosis. In: ClinicalTrials.gov. [internet]. Bethesda. US National Library of Medicine. 2010. Available from https://clinicaltrials.gov/ct2/show/NCT00441103. Identifier: NCT00441103
INCOMIN	Durelli, L. et al, 2002	**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(9316):1453-60.**
	Barbero, P. et al, 2006	Barbero P, Bergui M, Versino E, Ricci A, Zhong JJ, Ferrero B, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis (INCOMIN Trial) II: Analysis of MRI responses to treatment and correlation with NAb. Mult Scler. 2006;12(1):72-76.
Knobler et al, 1993	Knobler, R.L. et al, 1993	**Knobler RL, Greenstein JI, Johnson KP, Lublin FD, Panitch HS, Conway K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. J Interferon Res. 1993;13(5):333-40.**
MSCRG	Jacobs, L. et al, 1996	**Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol. 1996;39(3):285-94.**
	Cookfair, D.L. et al, 1996	Cookfair DL, Fischer J, Rudick R, Bourdette D, OReilly K, Jacobs L, et al. Quality of life in low-disability multiple sclerosis patients participating in a phase III trial of interferon beta-1a for relapsing multiple sclerosis. Ann Neurol. 1996;40(3):T234-T34.
	Rudick, R.A. et al, 1997	Rudick RA, Goodkin DE, Jacobs LD, Cookfair DL, Herndon RM, Richert JR, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Neurology. 1997;49(2):358-63.
	Simon, J.H. et al, 1998	Simon JH, Jacobs LD, Campion M, Wende K, Simonian N, Cookfair DL, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. Ann Neurol. 1998;43(1):79-87.
	Simon, J.H. et al, 2000	Simon JH, Lull J, Jacobs LD, Rudick RA, Cookfair DL, Herndon RM, et al. A longitudinal study of T1 hypointense lesions in relapsing MS: MSCRG trial of interferon beta-1a. Multiple Sclerosis Collaborative Research Group. Neurology. 2000;55(2):185-92.

Trial ID	Author, year	Reference
	Simon, JH. Et al, 1995	Simon JH, Jacobs L, Cookfair D, Rudick R, Herndon R, Salazar A, et al. The natural history of MS based on an annual MR snapshot: results from the MSCRG study of intramuscular recombinant interferon beta-1a. Neurology. 1995; 45(Suppl 4): A418.
Polman et al, 2003	Polman, C. et al, 2003	**Polman C, Barkhof F, Kappos L, Pozzilli C, Sandbrink R, Dahlke F, et al. Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study. Mult Scler. 2003;9(4):342-8.**
PRISMS	Ebers, G.C. et al, 1998	**Ebers GC, Rice G, Lesaux J, Paty D, Oger J, Li DKB, et al. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998;352(9139):1498-504.**
	Liu, C. and Blumhardt et al, 1999	Liu C, Blumhardt LD. Randomised, double blind, placebo controlled study of interferon beta-1a in relapsing-remitting multiple sclerosis analysed by area under disability/time curves. J Neurol Neurosurg Psychiatry. 1999;67(4):451-6.
	Liu, C. and Blumhardt et al, 2002	Liu C, Blumhardt LD. Randomized, double-blind, placebo-controlled study of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: a categorical disability trend analysis. Mult Scler. 2002;8(1):10-4.
	Gold, R. et al, 2005	Gold R, Rieckmann P, Chang P, Abdalla J, Group PS. The long-term safety and tolerability of high-dose interferon beta-1a in relapsing-remitting multiple sclerosis: 4-year data from the PRISMS study. Eur J Neurol. 2005;12(8):649-56.
	Li, D.K. et al, 1999	Li DK, Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. Ann Neurol. 1999;46(2):197-206.
	David, L. et al, 2016	David L, Trabloulsee A, Williamson E, Zhang H, Dangond F. Interferon ß-1a SC tiw Reduces Cumulative MRI Lesions over 24 Months in Patients with Relapsing Multiple Sclerosis: Post Hoc Analyses of PRISMS Data. In: 2016 Annual Meeting of the Consortium of Multiple Sclerisis Centers (CMSC), National Harbor, MD, USA; 1st-4th June 2016. 2016. DX26
REFORMS	Singer, B. et al, 2012	**Singer B, Bandari D, Cascione M, LaGanke C, Huddlestone J, Bennett R, et al. Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonbeta-1a versus subcutaneous interferonbeta-1b: results of the randomized, multicenter, Phase IIIb REFORMS study. BMC Neurol. 2012;12:154.**
	NCT00428584	EMD Serono, Pfizer. RNF and betaseron® tolerability study. In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2006. Available from https://ClinicalTrials.gov/show/NCT00428584. Identifier: NCT00428584
REGARD	Mikol, D.D et al, 2008	**Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7(10):903-14.**
Saida et al, 2012	Saida, T. et al, 2012	**Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler. 2012;18(9):1269-77.**

Trial ID	Author, year	Reference
	NCT00537082	Novartis, Mitsubishi Tanabe Pharma Corporation. Efficacy and safety of FTY720 in patients with relapsing multiple sclerosis (MS). In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2007. Available from https://ClinicalTrials.gov/show/NCT00537082. Identifier: NCT00537082
	Saida T, et al., 2017	Saida T, Itoyama Y, Kikuchi S, Hao Q, Kurosawa T, Ueda K, et al. Long-term efficacy and safety of fingolimod in Japanese patients with relapsing multiple sclerosis: 3-year results of the phase 2 extension study. BMC Neurol. 2017;17(1):17.
Saida 2016	Saida, T. et al, 2016	**Saida T, Yamamura T, Kondo T, Yun J, Yang M, Li J, et al. Placebo-controlled Phase 3 study of delayed-release dimethyl fumarate in patients with relapsing multiple sclerosis from Asia-Pacific and other countries. Mult Scler. 2016;22:280.**
Saida 2017	Saidia, T. et.al.	**Saida T, Kira J-I, Kishida S, Yamamura T, Sudo Y, Ogiwara K, et al. Efficacy, safety, and pharmacokinetics of natalizumab in Japanese multiple sclerosis patients: A double-blind, randomized controlled trial and open-label pharmacokinetic study. Mult Scler Relat Disord. 2017;11:25-31.**
	NCT01440101	Biogen. Natalizumab (BG00002, Tysabri) study in Japanese participants with relapsing-remitting multiple sclerosis (RRMS). In: ClinicalTrials.gov. [internet]. Bethesda. US National Library of Medicine. 2010. Available from https://ClinicalTrials.gov/show/NCT01440101. Identifier: NCT01440101
	Saida T, et al., 2017 (#12168)	Saida T, Kira J-I, Kishida S, Yamamura T, Ohtsuka N, Dong Q, et al. Natalizumab for Achieving Relapse-Free, T1 Gadolinium-Enhancing-Lesion-Free, and T2 Lesion-Free Status in Japanese Multiple Sclerosis Patients: A Phase 2 Trial Subanalysis. Neurol. 2017;6(1):153-59.
SELECT	Gold, R. et al, 2013	**Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet. 2013;381(9884):2167-75.**
	Havrdova, E. et al, 2014	Havrdova E, Giovannoni G, Stefoski D, Forster S, Umans K, Mehta L, et al. Disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with daclizumab high-yield process in the SELECT study. Mult Scler. 2014;20(4):464-70.
	Radue, E.W. et al, 2012	Radue EW, Gold R, Giovannoni G, Stefoski D, Mueller-Lenke N, Glyman S, et al. Daclizumab HYP monotherapy reduces black holes and T2 burden of disease in relapsing-remitting multiple sclerosis: results of the SELECT trial. Mult Scler J. 2012;18:193-94.
	Radue, E.W. et al, 2013	Radue EW, Gold R, Giovannoni G, Stefoski D, Selmaj K, You XJ, et al. Daclizumab HYP Reduces the Evolution of New Gadolinium-Enhancing Lesions to T1-Black Holes: Results from the SELECT Study. Neurology. 2013;80(Suppl 7):P07.094.
	NCT00390221	Biogen, AbbVie. Safety and efficacy study of daclizumab high yield process (DAC HYP) to treat relapsing-remitting multiple sclerosis. In: ClinicalTrials.gov. [internet]. Besthesda. US National Library of Medicine. 2008. Available from https://ClinicalTrials.gov/show/NCT00390221. Identifier: NCT00390221
	Phillips, G. et al, 2016	Phillips G, Guo S, Bender R, Havrdova E, Proskorovsky I, Vollmer T. Assessing the impact of multiple sclerosis disease activity and daclizumab HYP treatment on patient-reported outcomes: Results from the SELECT trial. Mult Scler Relat Disord. 2016;6:66-72.

Trial ID	Author, year	Reference
Stepien et al, 2013	Stepien, A. et al, 2013	**Stepien A, Chalimoniuk M, Lubina-Dabrowska N, Chrapusta SJ, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study. Neuroimmunomodulation 2013;20(4):213-22.**
TEMSO	O'Connor, P. et al, 2011	**O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293-303.**
	O'Connor, P. et al, 2011	O"Connor P, Burrell A, Wang L, Wei L, Carita P, Zhang Q. Effect of teriflunomide on longitudinal patterns of relapse and relapse-related hospitalization in multiple sclerosis. Mult Scler J. 2011;17:S414-S14.
	O'Connor, P. et al, 2011	O'Connor P, Lublin F, Wolinsky J, Comi G, Kappos L, Freedman M, et al. Effect of teriflunomide on relapses leading to healthcare resource use: results from the TEMSO study. Mult Scler J. 2011;17:S95-S96.
	Freedman, M. et al, 2012	Freedman M, O'Connor P, Wolinsky J, Confavreux C, Comi G, Kappos L, et al. Teriflunomide Increases the Proportion of Patients Free from Disease Activity in the TEMSO Phase III Study. Neurology. 2012;78(Suppl 1):PD5.007.
	Miller, A. et al, 2012	Miller A, Lublin F, O'Connor P, Taniou C, Dive-Pouletty C. Impact of Relapses with Sequelae on Disability, Health-Related Quality of Life, and Fatigue in a Population with Relapsing Forms of Multiple Sclerosis Using Data from TEMSO, a Pivotal Phase III Teriflunomide Trial. Neurology. 2012;78(Suppl 1):P07.082.
	Wolinsky, J.S. et al, 2013	Wolinsky JS, Narayana PA, Nelson F, Datta S, O'Connor P, Confavreux C, et al. Magnetic resonance imaging outcomes from a phase III trial of teriflunomide. Mult Scler. 2013;19(10):1310-9.
	Chan, A. et al, 2015	Chan A, De Seze J, Truffinet P, Thangavelu K, Rufi P, Comabella M. Efficacy of teriflunomide treatment in achieving no evidence of disease activity over a 2-year period: Post hoc analysis of the TEMSO study. Eur J Neurol. 2015;22:298.
	Wolinsky, JS. et a;, 2015	Wolinsky JS, Freedman MS, Thangavelu K, Truffinet P, Rufi P, O'Connor PW. Efficacy of teriflunomide treatment in achieving no evidence of disease activity in the TEMSO long-term extension study. Mult Scler. 2015;1:534-35.
	Canadian Agency for Drugs and Technologies in Health	Canadian Agency for Drugs and Technologies in Health. Teriflunomide (Aubagio) (14 mg film-coated tablet): teriflunomide is indicated as monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Ottawa: CADTH; 2014. Available from: https://www.cadth.ca/media/cdr/clinical/SR0350_Aubagio_CL_Report_e.pdf.
TENERE	Vermersch, P. et al, 2014(13)(12)(8)(7)	**Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20(6):705-16.**
Teriflunomide MS Trial	O'Connor, P. et al, 2006	**O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GPA, Paty DW, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology. 2006;66(6):894-900.**

Trial ID	Author, year	Reference
TOWER	Confavreux, M. et al, 2014	**Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(3):247-56.**
TRANSFORMS	Cohen, J.A. et al, 2010	**Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-15.**
	Twiss J. et al., 2010	Twiss J, Doward LC, McKenna SP, Eckert B. Interpreting scores on multiple sclerosis-specific patient reported outcome measures (the PRIMUS and U-FIS). Health Qual Life Outcomes. 2010;8:117.
	Kappos, L. et al, 2015	Kappos L, Cohen J, Barkhof F, Khatri B, Hartung HP, Ritter S, et al. Effect of fingolimod versus interferon-beta1a on neda-4 (no evidence of disease activity or worsening) in the transforms study. J Neurol Sci. 2015;357:e315-16.
	Khatri, B. et al, 2010	Khatri B, Barkhof F, Comi G. Transforms: oral fingolimod (FTY720) versus interferon beta-1a in relapsing- remitting multiple sclerosis: clinical efficacy results Int J MS Care. 2010;12(Suppl 1):S74.
	Montalban, X. et al, 2015	Montalban X, Cohen J, Barkhof F, Khatri B, Hartung H, Ritter S, et al. Effect of fingolimod versus interferonbeta1a on no evidence of disease activity or worsening (NEDA-4) in the transforms study. Neurology. 2015;84(Suppl 14):P4.
Wroe et al, 2005	Wroe, S.J. et al, 2005	**Wroe SJ. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. J Int Med Res. 2005;33(3):309-18.**
CONFIRM and DEFINE	Viglietta, V. et al, 2014	Viglietta V, O'Gorman J, Yang M, Zhang R, Raghupathi K. Evaluation of disability progression as an endpoint in clinical trials for relapsing-remitting multiple sclerosis (RRMS): Comparison of the define and confirm studies. Value Health. 2014;17(7):A392.
	Havrdova E, et al., 2017	Havrdova E, Giovannoni G, Gold R, Fox RJ, Kappos L, Phillips JT, et al. Effect of delayed-release dimethyl fumarate on no evidence of disease activity in relapsing-remitting multiple sclerosis: integrated analysis of the phase III DEFINE and CONFIRM studies. Eur J Neurol. 2017;24(5):726-33.
DECIDE and SELECT	CADTH 2016	Canadian Agency for Drugs and Technologies in Health (CADTH). Common Drug review: Clinical Review Report. Daclizumab (Zinbryta). Ottawa: 2016. Available from: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0508_Zinbryta_CL_Report.pdf.
FREEDOMS and FREEDOMS II	Repovic, P. et al, 2016	Repovic P, Karlsson G, Merschhemke M, Haring DA, Bright J, Smith T. The effect of fongolimod on four measures of disease activity in patients with relapsing-remitting multiple sclerosis: a meta-analysis of the phase 3 freedoms trails. In: 2016 Annual Meeting of the Consortium of Multiple Sclerisis Centers (CMSC), National Harbor, MD, USA; 3 June. 2016. DX08
	Chin, P. et al, 2013	Chin P, Meng X, Hashmonay R. Early effect of fingolimod on clinical and mri outcomes in relapsing multiple sclerosis. Int J MS Care. 2013;15(Suppl 3):DX17.
OPERA I and II	Hauser, S. et al, 2015	Hauser SL, Comi CC, Hartung HP, Selmaj K, Traboulsee A, Bar-Or A, et al. Efficacy and safety of ocrelizumab in relapsing multiple sclerosis – results of the phase iii double-blind, interferon beta-1a-controlled opera i and ii studies [powerpoint presentation]. 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2015. Presentation 190.

Trial ID	Author, year	Reference
	Traboulsee, A. et al, 2016	Traboulsee A, Arnold D, Bar-or A, Comi G, Hartung HP, Kappos L, et al. Ocrelizumab no evidence of disease activity (NEDA) status at 96 weeks in relapsing multiple sclerosis patients: Analysis of the OPERA I and OPERA II studies. Eur J Neurol. 2016;23:58.
	Traboulsee, A. et al, 2016	Traboulsee A, Arnold D, Bar-Or A, Comi G, Hartung HP, Kappos L, et al. Ocrelizumab no evidence of disease activity (NEDA) status at 96 weeks in patients with relapsing multiple sclerosis: Analysis of the phase III double-blind, double-dummy, interferon beta-1a-controlled opera I and opera II studies. Neurology. 2016;86(Suppl 16):PL02.004.
	Lublin, F. et al, 2016	Lublin F, Arnold D, Bar-Or A, Comi G, Hauser SL, Selmaj K, et al. Efficacy and safety of ocrelizumab in relapsing multiple sclerosis: results of the phase III, interferon ß-1a-controlled opera I and opera II studies. In: 2016 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC), National Harbor, MD; 2 June. 2016. P4440
	Hauser SL, et al., 2017	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221-34.
TEMSO and TOWER	Comi, G. et al, 2015	Comi G, De Seze J, Thangavelu K, Truffinet P, Benamor M, Rufi P, et al. Teriflunomide safety in subsets of patients with relapsing MS: Results from the TEMSO and TOWER studies. Mult Scler. 2015;21(Suppl 11):541 (P1057).
	Freedman, M. et al, 2013	Freedman M, Confavreux C, Olsson T, Comi G, Miller A, Wolinsky J, et al. Teriflunomide efficacy and safety analyses: Results from TEMSO and tower. Mult Scler. 2013;19 (10):1399-400.
	Freedman, M. et al, 2013	Freedman M, Confavreux C, Olsson T. Teriflunomide efficacy and safety analyses: results from TEMSO and TOWER Int J MS Care. 2013;15(Suppl 3):P5.
	Honeycutt, W. et al, 2015	Honeycutt W, Frenay CL, King J, Chan A, Vukusic S, Gross J, et al. Teriflunomide significantly increased time to first relapse in Temso, tower and topic. Neurology. 2015;84(Suppl 14):P7.27.
	EMA 2013	European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. Assessment report: AUBAGIO. International non-proprietary name: TERIFLUNOMIDE. London: 27 June 2013. 1-150. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002514/WC500148684.pdf.
CARE I and CARE II	Arnold DL. et al., 2016	Arnold DL, Fisher E, Brinar VV, Cohen JA, Coles AJ, Giovannoni G, et al. Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon beta-1a in MS. Neurology. 2016;87(14):1464-72.
TRANSFORMS and FREEDOMS	Cohen, J.A. 2010	Cohen JA, Kappos L, Pelletier J. Oral Fingolimod (FTY720) In Relapsing-Remitting Multiple Sclerosis: Safety Findings from Transforms and Freedoms Trials [S22]. Int J MS Care. 2010;12(Suppl 1):19-20.

Related to Question A10

Table 27 Baseline characteristics for HA subgroup

Characteristic	OPERA I Trial	OPERA II Trial

	Ocrelizumab (n=66)	**IFNB-1a (Rebif) (n=72)**	**Ocrelizumab (n=77)**	**IFNB-1a (Rebif) (n=68)**
Female n, (%)	43 (65.2)	46 (63.9)	48 (62.3)	47 (69.1)
United States n, (%)	21 (31.8)	27 (37.5)	25 (32.5)	22 (32.4)
Rest of the World n, (%)	45 (68.2)	45 (62.5)	52 (67.5)	46 (67.6)
DMT n	66 (100)	72 (100)	77 (100)	68 (100)
No previous DMT n, (%)	0 (0)	0 (0)	0 (0)	0 (0)
Previous DMT n, (%)	66 (100)	72 (100)	77 (100)	68 (100)
Inteferon	50 (75.8)	57 (79.2)	53 (68.8)	51 (75)
Glatiramer acetate	24 (36.4)	21 (29.2)	26 (33.8)	28 (41.2)
Natalizumab	0 (0)	0 (0)	1 (1.3)	0 (0)
Fingolimod	0 (0)	0 (0)	0 (0)	0 (0)
Dimethyl fumarate	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (1.3)	0 (0)
No. of Gd-enhancing lesions on T1-weighted MRI, n (%)	66 (100)	72 (100)	77 (100)	68 (100)
0	32 (48.5)	47 (65.3)	53 (68.8)	44 (64.7)
1	9 (13.6)	8 (11.1)	8 (10.4)	5 (7.4)
2	7 (10.6)	5 (6.9)	5 (6.5)	6 (8.8)
3	4 (6.1)	3 (4.2)	2 (2.6)	1 (1.5)
>=4	14 (21.2)	9 (12.5)	9 (11.7)	12 (17.6)
Mean age, Years (SD)	37.8 (9.1)	37.1 (9.3)	38.1 (9.1)	38.2 (8.2)
Mean time since symptom onset, years (SD)	9.55 (5.99)	8.42 (5.44)	9.31 (5.09)	8.7 (5.81)
Mean time since diagnosis, years (SD)	6.71 (4.85)	6.57 (5.15)	6.99 (4.77)	6.24 (4.09)
Mean no. of relapses in previous 12 months (SD)	1.2 (0.47)	1.24 (0.57)	1.34 (0.72)	1.44 (0.8)
Mean EDSS score (SD)	3.11 (1.28)	2.83 (1.23)	3.07 (1.28)	3.07 (1.5)
Mean no. of lesions on T2-weighted MRI, (SD)	64.94 (40.75)	55.24 (37.94)	52.66 (41.15)	56.99 (29.67)
Mean volume of lesions on T2-weighted MRI, cm3 (SD)	14.02 (15.43)	10.34 (9.89)	12.75 (16.74)	14.29 (14.16)

Normalised brain volume, cm3 (SD)	1485.75 (79.47)	1483.01 (88.24)	1499.24 (98.71)	1488.41 (96.52)

Table 28 Baseline characteristics for RES subgroup

Characteristic	**OPERA I Trial**		**OPERA II Trial**	
	Ocrelizumab (n=75)	**IFNB-1a (Rebif) (n=69)**	**Ocrelizumab (n=75)**	**IFNB-1a (Rebif) (n=71)**
Female n, (%)	56 (74.7)	47 (68.1)	45 (60)	49 (69)
United States n, (%)	13 (17.3)	10 (14.5)	20 (26.7)	22 (31)
Rest of the World n, (%)	62 (82.7)	59 (85.5)	55 (73.3)	49 (69)
DMT n	75 (100)	69 (100)	75 (100)	71 (100)
No previous DMT n, (%)	59 (78.7)	54 (78.3)	52 (69.3)	53 (74.6)
Previous DMT n, (%)	16 (21.3)	15 (21.7)	23 (30.7)	18 (25.4)
Inteferon	9 (12)	12 (17.4)	15 (20)	12 (16.9)
Glatiramer acetate	8 (10.7)	3 (4.3)	10 (13.3)	10 (14.1)
Natalizumab	0 (0)	0 (0)	0 (0)	0 (0)
Fingolimod	1 (1.3)	0 (0)	1 (1.3)	0 (0)
Dimethyl fumarate	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (1.3)	0 (0)
No. of Gd-enhancing lesions on T1-weighted MRI, n (%)	75 (100)	69 (100)	75 (100)	71 (100)
0	14 (18.7)	21 (30.4)	18 (24)	16 (22.5)
1	22 (29.3)	13 (18.8)	19 (25.3)	18 (25.4)
2	14 (18.7)	11 (15.9)	15 (20)	9 (12.7)
3	7 (9.3)	6 (8.7)	2 (2.7)	4 (5.6)
>=4	18 (24)	18 (26.1)	21 (28)	24 (33.8)
Mean age, Years (SD)	35.7 (9.2)	35.6 (9.4)	34.5 (9)	34.4 (8.6)
Mean time since symptom onset, years (SD)	5.83 (6.8)	5.15 (5.01)	5.88 (6.08)	5.86 (5.88)
Mean time since diagnosis, years (SD)	2.89 (4.19)	2.92 (4.05)	3.97 (5.2)	3.73 (4.65)
Mean no. of relapses in previous 12 months (SD)	2.23 (0.56)	2.2 (0.53)	2.29 (0.59)	2.38 (0.76)

Mean EDSS score (SD)	2.77 (1.2)	2.72 (1.29)	2.9 (1.31)	2.95 (1.4)
Mean no. of lesions on T2-weighted MRI, (SD)	53.45 (39.5)	55.75 (40.09)	54.32 (44.64)	56.28 (33.14)
Mean volume of lesions on T2-weighted MRI, cm3 (SD)	11.7 (13.16)	10.09 (11.69)	13.33 (16.31)	16.07 (16.48)
Normalised brain volume, cm3 (SD)	1508.36 (91.1)	1507.06 (79.21)	1509.64 (96.58)	1505.43 (101.73)

Table 29 Baseline characteristics for non-HA/RES subgroup

Characteristic	**OPERA I Trial**		**OPERA II Trial**	
	Ocrelizumab (n=276)	**IFNB-1a (Rebif) (n=277)**	**Ocrelizumab (n=280)**	**IFNB-1a (Rebif) (n=290)**
Female n, (%)	177 (64.1)	183 (66.1)	186 (66.4)	192 (66.2)
United States n, (%)	73 (26.4)	72 (26)	72 (25.7)	75 (25.9)
Rest of the World n, (%)	203 (73.6)	205 (74)	208 (74.3)	215 (74.1)
DMT n	274 (100)	275 (100)	280 (100)	289 (100)
No previous DMT n, (%)	241 (88)	238 (86.5)	251 (89.6)	260 (90)
Previous DMT n, (%)	33 (12)	37 (13.5)	29 (10.4)	29 (10)
Inteferon	23 (8.4)	20 (7.3)	21 (7.5)	18 (6.2)
Glatiramer acetate	10 (3.6)	14 (5.1)	8 (2.9)	11 (3.8)
Natalizumab	0 (0)	1 (0.4)	0 (0)	0 (0)
Fingolimod	0 (0)	0 (0)	3 (1.1)	0 (0)
Dimethyl fumarate	1 (0.4)	0 (0)	0 (0)	0 (0)
Other	2 (0.7)	3 (1.1)	0 (0)	1 (0.3)
No. of Gd-enhancing lesions on T1-weighted MRI, n (%)	271 (100)	273 (100)	276 (100)	287 (100)
0	188 (69.4)	186 (68.1)	187 (67.8)	186 (64.8)
1	35 (12.9)	32 (11.7)	32 (11.6)	41 (14.3)
2	11 (4.1)	16 (5.9)	16 (5.8)	24 (8.4)
3	9 (3.3)	7 (2.6)	12 (4.3)	9 (3.1)
>=4	28 (10.3)	32 (11.7)	29 (10.5)	27 (9.4)
Mean age, Years (SD)	37.3 (9.4)	37.3 (9.4)	37.6 (9)	37.9 (9.1)
Mean time since symptom onset, years (SD)	6.39 (6.17)	6.01 (6.21)	6.45 (6.24)	6.6 (6.31)

Mean time since diagnosis, years (SD)	3.47 (4.75)	3.25 (4.42)	3.65 (4.8)	3.85 (5.31)
Mean no. of relapses in previous 12 months (SD)	1.11 (0.49)	1.16 (0.52)	1.12 (0.52)	1.11 (0.53)
Mean EDSS score (SD)	2.84 (1.23)	2.75 (1.31)	2.69 (1.27)	2.79 (1.37)
Mean no. of lesions on T2-weighted MRI, (SD)	47.22 (37.54)	48.71 (40.06)	46.9 (35.39)	48.69 (37.3)
Mean volume of lesions on T2-weighted MRI, cm3 (SD)	9.88 (13.49)	9.55 (11.61)	9.89 (13.46)	9.03 (10.9)
Normalised brain volume, cm3 (SD)	1502.29 (82.44)	1500.24 (89.1)	1503.25 (91.51)	1500.91 (89.31)

Related to Question A13

JAGS code for ARR base case analysis

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : GA 40 mg, TIW
# t = 10 : IM IFNB-1a 30 mcg, QW
# t = 11 : NAT 300 mg, Q4W
# t = 12 : OCR 600 mg
# t = 13 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
###############################################
# DATA                                        #
###############################################
list(
e  = structure(.Data =  c(500, 512, NA, 630, 1254, NA, 1776, 890, NA, 900,
894, NA, 94, 92, 96, 333, 336, NA, 374, 752, NA, 404, 852, NA, 874, 866,
912, 750, 777, NA, 726, 700, 718, 464, 454, NA, 2766, 2757, NA, 816, 820,
NA, 338, 339, NA, 836, 850, NA, 710, 716, NA, 461, 943, NA, 615, 620, NA,
184, 192, NA, 286, 316, NA, 822, 820, NA, 836, 834, NA, 772, 756, NA, 212,
217, NA, 54, 60, NA, 726, 730, 716, 208, 218, 222, 1228, 1288, 1171, 431,
429, NA) ,.Dim =  c(30, 3) ) ,
na  =  c(2, 2, 2, 2, 3, 2, 2, 2, 3, 2, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,
2, 2, 2, 2, 3, 3, 3, 2) ,
ns  =  30 ,
nt  =  17 ,
```

```
r  = structure(.Data =  c(198, 131, NA, 459, 288, NA, 639, 302, NA, 306,
232, NA, 47, 36, 48, 119, 36, NA, 145, 135, NA, 210, 221, NA, 288, 121,
136, 120, 85, NA, 290, 203, 157, 389, 267, NA, 1087, 595, NA, 293, 139, NA,
219, 183, NA, 334, 153, NA, 284, 150, NA, 232, 312, NA, 688, 483, NA, 128,
96, NA, 234, 211, NA, 240, 127, NA, 242, 129, NA, 231, 219, NA, 97, 45, NA,
23, 21, NA, 392, 270, 264, 45, 89, 57, 614, 502, 374, 142, 68, NA) ,.Dim =
c(30, 3) ) ,
t  = structure(.Data =  c(1, 13, NA, 1, 11, NA, 15, 8, NA, 1, 10, NA, 10,
14, 8, 14, 2, NA, 14, 2, NA, 14, 2, NA, 1, 3, 4, 10, 8, NA, 1, 8, 6, 1, 8,
NA, 10, 5, NA, 1, 6, NA, 10, 14, NA, 1, 7, NA, 1, 7, NA, 1, 9, NA, 1, 15,
NA, 10, 15, NA, 1, 10, NA, 14, 12, NA, 14, 12, NA, 14, 8, NA, 1, 5, NA, 15,
10, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 10, 7, NA) ,.Dim =  c(30, 3) ) ,
usehn  =  0
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
theta[i,j] <- lambda[i,j]*e[i,j]
lambda[i,j] <- exp(mu[i] + delta[i,j])
r[i,j] ~ dpois(theta[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
dev[i,j] <- 2*((theta[i,j]-r[i,j])+r[i,j]*log(r[i,j]/theta[i,j]))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sd ~ dunif(0,5)
tauhn <- 1/varhn
varhn <- pow(sdhn,2)
sdhn ~ dnorm(0,0.01)I(0,)
```

```
tau <- usehn*tauhn + (1-usehn)*pow(sd,-2)

}
###############################################
```

JAGS code for ARR sensitivity analysis (fixed effect model)

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : GA 40 mg, TIW
# t = 10 : IM IFNB-1a 30 mcg, QW
# t = 11 : NAT 300 mg, Q4W
# t = 12 : OCR 600 mg
# t = 13 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
###############################################
# DATA                                        #
###############################################
list(
e  = structure(.Data =  c(500, 512, NA, 630, 1254, NA, 1776, 890, NA, 900,
894, NA, 94, 92, 96, 333, 336, NA, 374, 752, NA, 404, 852, NA, 874, 866,
912, 750, 777, NA, 726, 700, 718, 464, 454, NA, 2766, 2757, NA, 816, 820,
NA, 338, 339, NA, 836, 850, NA, 710, 716, NA, 461, 943, NA, 615, 620, NA,
184, 192, NA, 286, 316, NA, 822, 820, NA, 836, 834, NA, 772, 756, NA, 212,
217, NA, 54, 60, NA, 726, 730, 716, 208, 218, 222, 1228, 1288, 1171, 431,
429, NA) ,.Dim =  c(30, 3) ) ,
na  =  c(2, 2, 2, 2, 3, 2, 2, 2, 3, 2, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,
2, 2, 2, 2, 3, 3, 3, 2) ,
ns  =  30 ,
nt  =  17 ,
r  = structure(.Data =  c(198, 131, NA, 459, 288, NA, 639, 302, NA, 306,
232, NA, 47, 36, 48, 119, 36, NA, 145, 135, NA, 210, 221, NA, 288, 121,
136, 120, 85, NA, 290, 203, 157, 389, 267, NA, 1087, 595, NA, 293, 139, NA,
219, 183, NA, 334, 153, NA, 284, 150, NA, 232, 312, NA, 688, 483, NA, 128,
96, NA, 234, 211, NA, 240, 127, NA, 242, 129, NA, 231, 219, NA, 97, 45, NA,
23, 21, NA, 392, 270, 264, 45, 89, 57, 614, 502, 374, 142, 68, NA) ,.Dim =
c(30, 3) ) ,
t  = structure(.Data =  c(1, 13, NA, 1, 11, NA, 15, 8, NA, 1, 10, NA, 10,
14, 8, 14, 2, NA, 14, 2, NA, 14, 2, NA, 1, 3, 4, 10, 8, NA, 1, 8, 6, 1, 8,
NA, 10, 5, NA, 1, 6, NA, 10, 14, NA, 1, 7, NA, 1, 7, NA, 1, 9, NA, 1, 15,
NA, 10, 15, NA, 1, 10, NA, 14, 12, NA, 14, 12, NA, 14, 8, NA, 1, 5, NA, 15,
10, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 10, 7, NA) ,.Dim =  c(30, 3) )
)

###############################################
# MODEL                                       #
###############################################
```

```
model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
theta[i,j] <- lambda[i,j]*e[i,j]
lambda[i,j] <- exp(mu[i] + delta[i,j])
r[i,j] ~ dpois(theta[i,j])
}

delta[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] <- beta[t[i,j]] - beta[t[i,1]]
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
dev[i,j] <- 2*((theta[i,j]-r[i,j])+r[i,j]*log(r[i,j]/theta[i,j]))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

}
##############################################
```

JAGS code for ARR sensitivity analysis (random effects model with alternative prior)

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : GA 40 mg, TIW
# t = 10 : IM IFNB-1a 30 mcg, QW
# t = 11 : NAT 300 mg, Q4W
# t = 12 : OCR 600 mg
# t = 13 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
```

```
list(
e  = structure(.Data =  c(500, 512, NA, 630, 1254, NA, 1776, 890, NA, 900,
894, NA, 94, 92, 96, 333, 336, NA, 374, 752, NA, 404, 852, NA, 874, 866,
912, 750, 777, NA, 726, 700, 718, 464, 454, NA, 2766, 2757, NA, 816, 820,
NA, 338, 339, NA, 836, 850, NA, 710, 716, NA, 461, 943, NA, 615, 620, NA,
184, 192, NA, 286, 316, NA, 822, 820, NA, 836, 834, NA, 772, 756, NA, 212,
217, NA, 54, 60, NA, 726, 730, 716, 208, 218, 222, 1228, 1288, 1171, 431,
429, NA) ,.Dim =  c(30, 3) ) ,
na  =  c(2, 2, 2, 2, 3, 2, 2, 2, 3, 2, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,
2, 2, 2, 3, 3, 3, 2) ,
ns  =  30 ,
nt  =  17 ,
r  = structure(.Data =  c(198, 131, NA, 459, 288, NA, 639, 302, NA, 306,
232, NA, 47, 36, 48, 119, 36, NA, 145, 135, NA, 210, 221, NA, 288, 121,
136, 120, 85, NA, 290, 203, 157, 389, 267, NA, 1087, 595, NA, 293, 139, NA,
219, 183, NA, 334, 153, NA, 284, 150, NA, 232, 312, NA, 688, 483, NA, 128,
96, NA, 234, 211, NA, 240, 127, NA, 242, 129, NA, 231, 219, NA, 97, 45, NA,
23, 21, NA, 392, 270, 264, 45, 89, 57, 614, 502, 374, 142, 68, NA) ,.Dim =
c(30, 3) ) ,
t  = structure(.Data =  c(1, 13, NA, 1, 11, NA, 15, 8, NA, 1, 10, NA, 10,
14, 8, 14, 2, NA, 14, 2, NA, 14, 2, NA, 1, 3, 4, 10, 8, NA, 1, 8, 6, 1, 8,
NA, 10, 5, NA, 1, 6, NA, 10, 14, NA, 1, 7, NA, 1, 7, NA, 1, 9, NA, 1, 15,
NA, 10, 15, NA, 1, 10, NA, 14, 12, NA, 14, 12, NA, 14, 8, NA, 1, 5, NA, 15,
10, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 10, 7, NA) ,.Dim =  c(30, 3) ) ,
usehn  =  1
)

################################################
# MODEL                                        #
################################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
theta[i,j] <- lambda[i,j]*e[i,j]
lambda[i,j] <- exp(mu[i] + delta[i,j])
r[i,j] ~ dpois(theta[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
dev[i,j] <- 2*((theta[i,j]-r[i,j])+r[i,j]*log(r[i,j]/theta[i,j]))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
```

```
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sd ~ dunif(0,5)
tauhn <- 1/varhn
varhn <- pow(sdhn,2)
sdhn ~ dnorm(0,0.01)I(0,)

tau <- usehn*tauhn + (1-usehn)*pow(sd,-2)

}
##############################################
```

JAGS code for ARR (Meta-Regression on Study Duration)

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : GA 40 mg, TIW
# t = 10 : IM IFNB-1a 30 mcg, QW
# t = 11 : NAT 300 mg, Q4W
# t = 12 : OCR 600 mg
# t = 13 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
e  = structure(.Data =  c(500, 512, NA, 630, 1254, NA, 1776, 890, NA, 900,
894, NA, 94, 92, 96, 333, 336, NA, 374, 752, NA, 404, 852, NA, 874, 866,
912, 750, 777, NA, 726, 700, 718, 464, 454, NA, 2766, 2757, NA, 816, 820,
NA, 338, 339, NA, 836, 850, NA, 710, 716, NA, 461, 943, NA, 615, 620, NA,
184, 192, NA, 286, 316, NA, 822, 820, NA, 836, 834, NA, 772, 756, NA, 212,
217, NA, 54, 60, NA, 726, 730, 716, 208, 218, 222, 1228, 1288, 1171, 431,
429, NA) ,.Dim =  c(30, 3) ) ,
na  =  c(2, 2, 2, 2, 3, 2, 2, 2, 3, 2, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,
2, 2, 2, 2, 3, 3, 3, 2) ,
ns  =  30 ,
nt  =  17 ,
r  = structure(.Data =  c(198, 131, NA, 459, 288, NA, 639, 302, NA, 306,
232, NA, 47, 36, 48, 119, 36, NA, 145, 135, NA, 210, 221, NA, 288, 121,
136, 120, 85, NA, 290, 203, 157, 389, 267, NA, 1087, 595, NA, 293, 139, NA,
219, 183, NA, 334, 153, NA, 284, 150, NA, 232, 312, NA, 688, 483, NA, 128,
96, NA, 234, 211, NA, 240, 127, NA, 242, 129, NA, 231, 219, NA, 97, 45, NA,
23, 21, NA, 392, 270, 264, 45, 89, 57, 614, 502, 374, 142, 68, NA) ,.Dim =
c(30, 3) ) ,
```

```
t  = structure(.Data =  c(1, 13, NA, 1, 11, NA, 15, 8, NA, 1, 10, NA, 10,
14, 8, 14, 2, NA, 14, 2, NA, 14, 2, NA, 1, 3, 4, 10, 8, NA, 1, 8, 6, 1, 8,
NA, 10, 5, NA, 1, 6, NA, 10, 14, NA, 1, 7, NA, 1, 7, NA, 1, 9, NA, 1, 15,
NA, 10, 15, NA, 1, 10, NA, 14, 12, NA, 14, 12, NA, 14, 8, NA, 1, 5, NA, 15,
10, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 10, 7, NA) ,.Dim =  c(30, 3) ) ,
usehn  =  0 ,
x  =  c(-53.2, -5.2, -5.2, -5.2, -5.2, 42.8, -5.2, -5.2, -5.2, 42.8, -5.2,
-5.2, 42.8, -5.2, -53.2, -5.2, -5.2, -53.2, 138.8, -5.2, -5.2, -5.2, -5.2,
-5.2, -49.2, 42.8, -5.2, -5.2, 50.8, -53.2)
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
theta[i,j] <- lambda[i,j]*e[i,j]
lambda[i,j] <- exp(mu[i] + delta[i,j] + (covbeta[t[i,j]] -
covbeta[t[i,1]])*x[i])
r[i,j] ~ dpois(theta[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
dev[i,j] <- 2*((theta[i,j]-r[i,j])+r[i,j]*log(r[i,j]/theta[i,j]))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sd ~ dunif(0,5)
tauhn <- 1/varhn
varhn <- pow(sdhn,2)
sdhn ~ dnorm(0,0.01)I(0,)

tau <- usehn*tauhn + (1-usehn)*pow(sd,-2)

covbeta[1] <- 0
```

```
for (i in 2:nt){
covbeta[i] <- B
}
B ~ dnorm(0,0.0001)

}
###############################################
```

JAGS code for ARR in HA subgroup

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : DAC 150 mg , Q4W
# t = 4 : FINGO 0.5 mg, QD
# t = 5 : GA 20 mg, QD
# t = 6 : GA 40 mg, TIW
# t = 7 : IM IFNB-1a 30 mcg, QW
# t = 8 : OCR 600 mg
# t = 9 : SC IFNB-1a 44 mcg, TIW
# t = 10 : SC IFNB-1b 250 mcg, EOD
###############################################
# DATA                                        #
###############################################
list(
e  = structure(.Data =  c(1776, 890, NA, 900, 894, NA, 94, 92, 96, 288,
554, NA, 750, 777, NA, 726, 700, NA, 464, 454, NA, 1158, 1074, NA, 338,
339, NA, 461, 943, NA, 615, 620, NA, 184, 192, NA, 286, 316, NA, 514, 498,
NA, 280, 286, NA, 772, 756, NA, 40, 49, NA, 54, 60, NA, 149, 160, NA) ,.Dim
=  c(19, 3) ) ,
na  =  c(2, 2, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2) ,
ns  =  19 ,
nt  =  10 ,
r  = structure(.Data =  c(639, 302, NA, 306, 232, NA, 47, 36, 48, 152, 119,
NA, 120, 85, NA, 290, 203, NA, 389, 267, NA, 613, 279, NA, 219, 183, NA,
232, 312, NA, 688, 483, NA, 128, 96, NA, 234, 211, NA, 236, 119, NA, 87,
28, NA, 231, 219, NA, 21, 12, NA, 23, 21, NA, 76, 32, NA) ,.Dim =  c(19, 3)
) ,
t  = structure(.Data =  c(10, 5, NA, 1, 7, NA, 7, 9, 5, 9, 2, NA, 7, 5, NA,
1, 5, NA, 1, 5, NA, 7, 3, NA, 7, 9, NA, 1, 6, NA, 1, 10, NA, 7, 10, NA, 1,
7, NA, 1, 4, NA, 9, 8, NA, 9, 5, NA, 1, 3, NA, 10, 7, NA, 7, 4, NA) ,.Dim =
c(19, 3) ) ,
usehn  =  0
)

###############################################
# MODEL                                       #
###############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
theta[i,j] <- lambda[i,j]*e[i,j]
lambda[i,j] <- exp(mu[i] + delta[i,j])
r[i,j] ~ dpois(theta[i,j])
}
```

```
delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
dev[i,j] <- 2*((theta[i,j]-r[i,j])+r[i,j]*log(r[i,j]/theta[i,j]))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sd ~ dunif(0,5)
tauhn <- 1/varhn
varhn <- pow(sdhn,2)
sdhn ~ dnorm(0,0.01)I(0,)

tau <- usehn*tauhn + (1-usehn)*pow(sd,-2)

}
##############################################
```

JAGS code for ARR in RES subgroup

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : DAC 150 mg , Q4W
# t = 4 : FINGO 0.5 mg, QD
# t = 5 : GA 20 mg, QD
# t = 6 : GA 40 mg, TIW
# t = 7 : IM IFNB-1a 30 mcg, QW
# t = 8 : NAT 300 mg, Q4W
# t = 9 : OCR 600 mg
# t = 10 : SC IFNB-1a 44 mcg, TIW
# t = 11 : SC IFNB-1b 250 mcg, EOD
##############################################
# DATA                                       #
##############################################
list(
e  = structure(.Data =  c(122, 296, NA, 1776, 890, NA, 900, 894, NA, 94,
92, 96, 122, 210, NA, 84, 202, NA, 750, 777, NA, 726, 700, NA, 464, 454,
NA, 408, 368, NA, 338, 339, NA, 126, 154, NA, 461, 943, NA, 615, 620, NA,
184, 192, NA, 286, 316, NA, 280, 300, NA, 772, 756, NA, 32, 62, NA, 54, 60,
```

```
NA, 30, 27, NA) ,.Dim =  c(21, 3) ) ,
na  =  c(2, 2, 2, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2) ,
ns  =  21 ,
nt  =  11 ,
r  = structure(.Data =  c(178, 82, NA, 639, 302, NA, 306, 232, NA, 47, 36,
48, 50, 42, NA, 54, 66, NA, 120, 85, NA, 290, 203, NA, 389, 267, NA, 276,
103, NA, 219, 183, NA, 117, 53, NA, 232, 312, NA, 688, 483, NA, 128, 96,
NA, 234, 211, NA, 110, 45, NA, 231, 219, NA, 19, 18, NA, 23, 21, NA, 9, 6,
NA) ,.Dim =  c(21, 3) ) ,
t  = structure(.Data =  c(1, 8, NA, 11, 5, NA, 1, 7, NA, 7, 10, 5, 10, 2,
NA, 10, 2, NA, 7, 5, NA, 1, 5, NA, 1, 5, NA, 7, 3, NA, 7, 10, NA, 1, 4, NA,
1, 6, NA, 1, 11, NA, 7, 11, NA, 1, 7, NA, 10, 9, NA, 10, 5, NA, 1, 3, NA,
11, 7, NA, 7, 4, NA) ,.Dim =  c(21, 3) ) ,
usehn  =  0
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
theta[i,j] <- lambda[i,j]*e[i,j]
lambda[i,j] <- exp(mu[i] + delta[i,j])
r[i,j] ~ dpois(theta[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
dev[i,j] <- 2*((theta[i,j]-r[i,j])+r[i,j]*log(r[i,j]/theta[i,j]))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sd ~ dunif(0,5)
tauhn <- 1/varhn
varhn <- pow(sdhn,2)
sdhn ~ dnorm(0,0.01)I(0,)
```

```
tau <- usehn*tauhn + (1-usehn)*pow(sd,-2)

}
#############################################
```

JAGS code for CDP-12 Base-case analysis

```
#############################################
# TREATMENT DECODE                          #
#############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
#############################################
# DATA                                      #
#############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3, 3,
3) ,
ns  =  22 ,
ns2  =  17 ,
nt  =  17 ,
se  = structure(.Data =  c(1, 0.226, NA, 1, 0.1486, NA, 1, 0.1291, NA, 1,
0.5431, NA, 1, 0.1938, NA, 1, 0.264, NA, 1, 0.1233, NA, 1, 0.1739, NA, 1,
0.2078, NA, 1, 0.1564, NA, 1, 0.155, NA, 1, 0.1465, NA, 1, 0.2051, NA, 1,
0.2268, NA, 1, 0.2, NA, 1, 0.3655, NA, 1, 0.2624, NA, 1, 0.1687, 0.1716, 1,
0.1982, 0.2112, 1, 0.1821, 0.1912, 1, 0.1604, 0.164, 1, 0.1749,
0.1926) ,.Dim =  c(22, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 1, 8, NA, 1, 9,
NA, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14, NA, 1, 7, NA, 1, 7, NA, 14, 2, NA,
1, 15, NA, 14, 11, NA, 14, 11, NA, 1, 5, NA, 9, 7, NA, 1, 3, 4, 1, 8, 6, 1,
13, 14, 1, 17, 16, 1, 17, 16) ,.Dim =  c(22, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.02553, 0.01104, 0.008335, 0.1475, 0.01877, 0.03485, 0.007596,
0.01512, 0.0216, 0.01223, 0.01201, 0.01072, 0.02103, 0.02571, 0.02001,
0.0668, 0.03443, 0.01448, 0.02097, 0.01743, 0.01315, 0.01693) ,
y  = structure(.Data =  c(0, -0.4734, NA, 0, -0.5527, NA, 0, -0.05484, NA,
0, -1.07, NA, 0, -0.2936, NA, 0, -0.1487, NA, 0, -0.1739, NA, 0, -0.4801,
NA, 0, -0.1374, NA, 0, -0.3474, NA, 0, -0.1905, NA, 0, -0.4263, NA, 0, -
0.3462, NA, 0, -0.5498, NA, 0, -0.4754, NA, 0, -0.8442, NA, 0, -0.3025, NA,
0, -0.4033, -0.3771, 0, -0.07361, -0.24, 0, -0.3771, -0.4691, 0, -0.2655, -
0.3519, 0, -0.04278, -0.3775) ,.Dim =  c(22, 3) )
)
```

```
###############################################
# MODEL                                       #
###############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
###############################################
```

JAGS code for CDP-12 Sensitivity analysis (Fixed effect (FE))

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
```

```
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3, 3,
3) ,
ns  =  22 ,
ns2  =  17 ,
nt  =  17 ,
se  = structure(.Data =  c(1, 0.226, NA, 1, 0.1486, NA, 1, 0.1291, NA, 1,
0.5431, NA, 1, 0.1938, NA, 1, 0.264, NA, 1, 0.1233, NA, 1, 0.1739, NA, 1,
0.2078, NA, 1, 0.1564, NA, 1, 0.155, NA, 1, 0.1465, NA, 1, 0.2051, NA, 1,
0.2268, NA, 1, 0.2, NA, 1, 0.3655, NA, 1, 0.2624, NA, 1, 0.1687, 0.1716, 1,
0.1982, 0.2112, 1, 0.1821, 0.1912, 1, 0.1604, 0.164, 1, 0.1749,
0.1926) ,.Dim =  c(22, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 1, 8, NA, 1, 9,
NA, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14, NA, 1, 7, NA, 1, 7, NA, 14, 2, NA,
1, 15, NA, 14, 11, NA, 14, 11, NA, 1, 5, NA, 9, 7, NA, 1, 3, 4, 1, 8, 6, 1,
13, 14, 1, 17, 16, 1, 17, 16) ,.Dim =  c(22, 3) ) ,
v  =  c(0.02553, 0.01104, 0.008335, 0.1475, 0.01877, 0.03485, 0.007596,
0.01512, 0.0216, 0.01223, 0.01201, 0.01072, 0.02103, 0.02571, 0.02001,
0.0668, 0.03443, 0.01448, 0.02097, 0.01743, 0.01315, 0.01693) ,
y  = structure(.Data =  c(0, -0.4734, NA, 0, -0.5527, NA, 0, -0.05484, NA,
0, -1.07, NA, 0, -0.2936, NA, 0, -0.1487, NA, 0, -0.1739, NA, 0, -0.4801,
NA, 0, -0.1374, NA, 0, -0.3474, NA, 0, -0.1905, NA, 0, -0.4263, NA, 0, -
0.3462, NA, 0, -0.5498, NA, 0, -0.4754, NA, 0, -0.8442, NA, 0, -0.3025, NA,
0, -0.4033, -0.3771, 0, -0.07361, -0.24, 0, -0.3771, -0.4691, 0, -0.2655, -
0.3519, 0, -0.04278, -0.3775) ,.Dim =  c(22, 3) )
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
delta[i,j] <- beta[t[i,j]] - beta[t[i,1]]
vr[i,j]    <- pow(se[i,j], 2)
prec[i,j]  <- pow(vr[i,j],-1)
}
}

for (i in 1: ns2){
```

```
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

}
##############################################
```

JAGS code for CDP-12 Sensitivity analysis (Random effects (RE) alternative prior)

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3, 3,
3) ,
ns  =  22 ,
```

```
ns2  =  17 ,
nt  =  17 ,
se  = structure(.Data =  c(1, 0.226, NA, 1, 0.1486, NA, 1, 0.1291, NA, 1,
0.5431, NA, 1, 0.1938, NA, 1, 0.264, NA, 1, 0.1233, NA, 1, 0.1739, NA, 1,
0.2078, NA, 1, 0.1564, NA, 1, 0.155, NA, 1, 0.1465, NA, 1, 0.2051, NA, 1,
0.2268, NA, 1, 0.2, NA, 1, 0.3655, NA, 1, 0.2624, NA, 1, 0.1687, 0.1716, 1,
0.1982, 0.2112, 1, 0.1821, 0.1912, 1, 0.1604, 0.164, 1, 0.1749,
0.1926) ,.Dim =  c(22, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 1, 8, NA, 1, 9,
NA, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14, NA, 1, 7, NA, 1, 7, NA, 14, 2, NA,
1, 15, NA, 14, 11, NA, 14, 11, NA, 1, 5, NA, 9, 7, NA, 1, 3, 4, 1, 8, 6, 1,
13, 14, 1, 17, 16, 1, 17, 16) ,.Dim =  c(22, 3) ) ,
taulmn  =  0.5 ,
taulprec  =  1 ,
tauuup  =  5 ,
usevag  =  1 ,
v  =  c(0.02553, 0.01104, 0.008335, 0.1475, 0.01877, 0.03485, 0.007596,
0.01512, 0.0216, 0.01223, 0.01201, 0.01072, 0.02103, 0.02571, 0.02001,
0.0668, 0.03443, 0.01448, 0.02097, 0.01743, 0.01315, 0.01693) ,
y  = structure(.Data =  c(0, -0.4734, NA, 0, -0.5527, NA, 0, -0.05484, NA,
0, -1.07, NA, 0, -0.2936, NA, 0, -0.1487, NA, 0, -0.1739, NA, 0, -0.4801,
NA, 0, -0.1374, NA, 0, -0.3474, NA, 0, -0.1905, NA, 0, -0.4263, NA, 0, -
0.3462, NA, 0, -0.5498, NA, 0, -0.4754, NA, 0, -0.8442, NA, 0, -0.3025, NA,
0, -0.4033, -0.3771, 0, -0.07361, -0.24, 0, -0.3771, -0.4691, 0, -0.2655, -
0.3519, 0, -0.04278, -0.3775) ,.Dim =  c(22, 3) )
)

################################################
# MODEL                                        #
################################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
```

```
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
###############################################
```

JAGS code for CDP-12 (Meta-Regression on Duration)

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
###############################################
# DATA                                        #
###############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3, 3, 3)
,
ns  =  22 ,
ns2  =  17 ,
nt  =  17 ,
se  = structure(.Data =  c(1, 0.226, NA, 1, 0.1486, NA, 1, 0.1291, NA, 1,
0.5431, NA, 1, 0.1938, NA, 1, 0.264, NA, 1, 0.1233, NA, 1, 0.1739, NA, 1,
0.2078, NA, 1, 0.1564, NA, 1, 0.155, NA, 1, 0.1465, NA, 1, 0.2051, NA, 1,
0.2268, NA, 1, 0.2, NA, 1, 0.3655, NA, 1, 0.2624, NA, 1, 0.1687, 0.1716, 1,
0.1982, 0.2112, 1, 0.1821, 0.1912, 1, 0.1604, 0.164, 1, 0.1749, 0.1926)
,.Dim =  c(22, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 1, 8, NA, 1, 9,
NA, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14, NA, 1, 7, NA, 1, 7, NA, 14, 2, NA,
1, 15, NA, 14, 11, NA, 14, 11, NA, 1, 5, NA, 9, 7, NA, 1, 3, 4, 1, 8, 6, 1,
```

```
13, 14, 1, 17, 16, 1, 17, 16) ,.Dim =  c(22, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.02553, 0.01104, 0.008335, 0.1475, 0.01877, 0.03485, 0.007596,
0.01512, 0.0216, 0.01223, 0.01201, 0.01072, 0.02103, 0.02571, 0.02001,
0.0668, 0.03443, 0.01448, 0.02097, 0.01743, 0.01315, 0.01693) ,
x  =  c(-52.91, -4.909, -4.909, -4.909, -4.909, -4.909, -4.909, -4.909,
43.09, -4.909, -52.91, -4.909, -4.909, 43.09, 139.1, -4.909, -4.909, -
4.909, -48.91, -4.909, 51.09, -52.91) ,
y  = structure(.Data =  c(0, -0.4734, NA, 0, -0.5527, NA, 0, -0.05484, NA,
0, -1.07, NA, 0, -0.2936, NA, 0, -0.1487, NA, 0, -0.1739, NA, 0, -0.4801,
NA, 0, -0.1374, NA, 0, -0.3474, NA, 0, -0.1905, NA, 0, -0.4263, NA, 0, -
0.3462, NA, 0, -0.5498, NA, 0, -0.4754, NA, 0, -0.8442, NA, 0, -0.3025, NA,
0, -0.4033, -0.3771, 0, -0.07361, -0.24, 0, -0.3771, -0.4691, 0, -0.2655, -
0.3519, 0, -0.04278, -0.3775) ,.Dim =  c(22, 3) )
)

################################################
# MODEL                                        #
################################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)
theta[i,j] <- delta[i,j] + (covbeta[t[i,j]] - covbeta[t[i,1]])*x[i]
}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(theta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(theta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
```

```
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

covbeta[1] <- 0
for (i in 2:nt){
covbeta[i] <- B
}
B ~ dnorm(0,0.0001)

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

}
##############################################
```

JAGS code for CDP-12 in HA subgroup

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : DMF 240 mg, BID
# t = 3 : FINGO 0.5 mg, QD
# t = 4 : GA 20 mg, QD
# t = 5 : IM IFNB-1a 30 mcg, QW
# t = 6 : OCR 600 mg
# t = 7 : SC IFNB-1a 22 mcg, TIW
# t = 8 : SC IFNB-1a 44 mcg, TIW
# t = 9 : SC IFNB-1b 250 mcg, EOD
# t = 10 : TERI 14 mg, QD
##############################################
# DATA                                       #
##############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3) ,
ns  =  13 ,
ns2  =  12 ,
nt  =  10 ,
se  = structure(.Data =  c(1, 0.1291, NA, 1, 0.5431, NA, 1, 0.1938, NA, 1,
0.1982, NA, 1, 0.264, NA, 1, 0.2078, NA, 1, 0.2051, NA, 1, 0.3013, NA, 1,
0.2035, NA, 1, 0.3618, NA, 1, 0.2024, NA, 1, 0.4313, NA, 1, 0.1821, 0.1912)
,.Dim =  c(13, 3) ) ,
t  = structure(.Data =  c(9, 4, NA, 1, 4, NA, 1, 5, NA, 1, 4, NA, 1, 4, NA,
5, 8, NA, 1, 9, NA, 1, 2, NA, 1, 3, NA, 8, 6, NA, 1, 10, NA, 5, 3, NA, 1,
7, 8) ,.Dim =  c(13, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.008335, 0.1475, 0.01877, 0.01964, 0.03485, 0.0216, 0.02103,
0.04538, 0.0207, 0.06546, 0.02048, 0.09301, 0.01743) ,
y  = structure(.Data =  c(0, -0.05484, NA, 0, -1.07, NA, 0, -0.2936, NA, 0,
-0.07361, NA, 0, -0.1487, NA, 0, -0.1374, NA, 0, -0.3462, NA, 0, 0.175, NA,
0, -0.4546, NA, 0, -0.7605, NA, 0, -0.6255, NA, 0, -0.5017, NA, 0, -0.3771,
-0.4691) ,.Dim =  c(13, 3) )
)

##############################################
# MODEL                                      #
```

```
##############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
##############################################
```

JAGS code for CDP-12 in RES subgroup

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : DAC 150 mg , Q4W
# t = 3 : DMF 240 mg, BID
# t = 4 : FINGO 0.5 mg, QD
```

```
# t = 5 : GA 20 mg, QD
# t = 6 : IM IFNB-1a 30 mcg, QW
# t = 7 : NAT 300 mg, Q4W
# t = 8 : OCR 600 mg
# t = 9 : SC IFNB-1a 22 mcg, TIW
# t = 10 : SC IFNB-1a 44 mcg, TIW
# t = 11 : SC IFNB-1b 250 mcg, EOD
# t = 12 : TERI 14 mg, QD
# t = 13 : TERI 7 mg, QD
#############################################
# DATA                                      #
#############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3) ,
ns  =  15 ,
ns2  =  13 ,
nt  =  13 ,
se  = structure(.Data =  c(1, 0.3455, NA, 1, 0.1291, NA, 1, 0.5431, NA, 1,
0.1938, NA, 1, 0.1982, NA, 1, 0.264, NA, 1, 0.2078, NA, 1, 0.5392, NA, 1,
0.2051, NA, 1, 0.4364, NA, 1, 0.3478, NA, 1, 1.118, NA, 1, 1.49, NA, 1,
0.1821, 0.1912, 1, 0.4615, 0.4584) ,.Dim =  c(15, 3) ) ,
t  = structure(.Data =  c(1, 7, NA, 11, 5, NA, 1, 5, NA, 1, 6, NA, 1, 5,
NA, 1, 5, NA, 6, 10, NA, 1, 4, NA, 1, 11, NA, 1, 3, NA, 10, 8, NA, 1, 2,
NA, 6, 4, NA, 1, 9, 10, 1, 13, 12) ,.Dim =  c(15, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.0597, 0.008335, 0.1475, 0.01877, 0.01964, 0.03485, 0.0216,
0.1454, 0.02103, 0.09521, 0.06048, 0.6252, 1.11, 0.01743, 0.1058) ,
y  = structure(.Data =  c(0, -0.7498, NA, 0, -0.05484, NA, 0, -1.07, NA, 0,
-0.2936, NA, 0, -0.07361, NA, 0, -0.1487, NA, 0, -0.1374, NA, 0, -0.3294,
NA, 0, -0.3462, NA, 0, 0.1002, NA, 0, -0.427, NA, 0, -2.108, NA, 0, -2.176,
NA, 0, -0.3771, -0.4691, 0, -0.4938, -0.4334) ,.Dim =  c(15, 3) )
)

#############################################
# MODEL                                     #
#############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
```

```
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
###############################################
```

JAGS code for CDP-24 Base-case analysis

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 44 mcg, TIW
# t = 14 : TERI 14 mg, QD
# t = 15 : TERI 7 mg, QD
###############################################
# DATA                                        #
###############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3) ,
ns  =  21 ,
ns2  =  18 ,
nt  =  15 ,
se  = structure(.Data =  c(1, 0.2899, NA, 1, 0.169, NA, 1, 0.226, NA, 1,
0.4197, NA, 1, 0.2866, NA, 1, 0.2113, NA, 1, 0.1893, NA, 1, 0.1474, NA, 1,
0.2002, NA, 1, 0.2971, NA, 1, 0.1826, NA, 1, 0.2045, NA, 1, 0.2222, NA, 1,
0.2621, NA, 1, 0.2286, NA, 1, 0.2293, NA, 1, 0.4964, NA, 1, 0.1984, NA, 1,
```

```
0.2005, 0.1848, 1, 0.2347, 0.2612, 1, 0.2161, 0.234) ,.Dim =  c(21, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 1, 9, NA, 13, 2, NA, 13, 2,
NA, 13, 2, NA, 9, 8, NA, 9, 5, NA, 1, 6, NA, 9, 13, NA, 1, 7, NA, 1, 7, NA,
1, 9, NA, 13, 11, NA, 13, 11, NA, 13, 8, NA, 1, 5, NA, 1, 14, NA, 1, 3, 4,
1, 8, 6, 1, 15, 14) ,.Dim =  c(21, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.04202, 0.01428, 0.02555, 0.08807, 0.04106, 0.02233, 0.01792,
0.01086, 0.02005, 0.04414, 0.01666, 0.02091, 0.0247, 0.03435, 0.02613,
0.02629, 0.1232, 0.01968, 0.01859, 0.03082, 0.02537) ,
y  = structure(.Data =  c(0, -0.7789, NA, 0, -0.7775, NA, 0, -0.312, NA, 0,
-1.385, NA, 0, -0.3546, NA, 0, -0.5534, NA, 0, 0.1591, NA, 0, -0.309, NA,
0, -0.2614, NA, 0, -0.3592, NA, 0, -0.4632, NA, 0, -0.3332, NA, 0, -0.5519,
NA, 0, -0.5651, NA, 0, -0.4682, NA, 0, -0.3052, NA, 0, -1.435, NA, 0, -
0.2845, NA, 0, -0.6287, -0.3927, 0, -0.1379, -0.4823, 0, 0.05259, -
0.1705) ,.Dim =  c(21, 3) )
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])
```

```
beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
##############################################
```

JAGS code for CDP-24 Sensitivity analysis (Fixed effect (FE))

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 44 mcg, TIW
# t = 14 : TERI 14 mg, QD
# t = 15 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3) ,
ns  =  21 ,
ns2  =  18 ,
nt  =  15 ,
se  = structure(.Data =  c(1, 0.2899, NA, 1, 0.169, NA, 1, 0.226, NA, 1,
0.4197, NA, 1, 0.2866, NA, 1, 0.2113, NA, 1, 0.1893, NA, 1, 0.1474, NA, 1,
0.2002, NA, 1, 0.2971, NA, 1, 0.1826, NA, 1, 0.2045, NA, 1, 0.2222, NA, 1,
0.2621, NA, 1, 0.2286, NA, 1, 0.2293, NA, 1, 0.4964, NA, 1, 0.1984, NA, 1,
0.2005, 0.1848, 1, 0.2347, 0.2612, 1, 0.2161, 0.234) ,.Dim =  c(21, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 1, 9, NA, 13, 2, NA, 13, 2,
NA, 13, 2, NA, 9, 8, NA, 9, 5, NA, 1, 6, NA, 9, 13, NA, 1, 7, NA, 1, 7, NA,
1, 9, NA, 13, 11, NA, 13, 11, NA, 13, 8, NA, 1, 5, NA, 1, 14, NA, 1, 3, 4,
1, 8, 6, 1, 15, 14) ,.Dim =  c(21, 3) ) ,
v  =  c(0.04202, 0.01428, 0.02555, 0.08807, 0.04106, 0.02233, 0.01792,
0.01086, 0.02005, 0.04414, 0.01666, 0.02091, 0.0247, 0.03435, 0.02613,
0.02629, 0.1232, 0.01968, 0.01859, 0.03082, 0.02537) ,
y  = structure(.Data =  c(0, -0.7789, NA, 0, -0.7775, NA, 0, -0.312, NA, 0,
-1.385, NA, 0, -0.3546, NA, 0, -0.5534, NA, 0, 0.1591, NA, 0, -0.309, NA,
0, -0.2614, NA, 0, -0.3592, NA, 0, -0.4632, NA, 0, -0.3332, NA, 0, -0.5519,
NA, 0, -0.5651, NA, 0, -0.4682, NA, 0, -0.3052, NA, 0, -1.435, NA, 0, -
0.2845, NA, 0, -0.6287, -0.3927, 0, -0.1379, -0.4823, 0, 0.05259, -
0.1705) ,.Dim =  c(21, 3) )
)
```

```
################################################
# MODEL                                        #
################################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
delta[i,j] <- beta[t[i,j]] - beta[t[i,1]]
vr[i,j]    <- pow(se[i,j], 2)
prec[i,j]  <- pow(vr[i,j],-1)
}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

}
################################################
```

JAGS code for CDP-24 Sensitivity analysis (Random effects (RE) alternative prior)

```
################################################
# TREATMENT DECODE                             #
################################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
```

```
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 44 mcg, TIW
# t = 14 : TERI 14 mg, QD
# t = 15 : TERI 7 mg, QD
#############################################
# DATA                                      #
#############################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3) ,
ns  =  21 ,
ns2  =  18 ,
nt  =  15 ,
se  = structure(.Data =  c(1, 0.2899, NA, 1, 0.169, NA, 1, 0.226, NA, 1,
0.4197, NA, 1, 0.2866, NA, 1, 0.2113, NA, 1, 0.1893, NA, 1, 0.1474, NA, 1,
0.2002, NA, 1, 0.2971, NA, 1, 0.1826, NA, 1, 0.2045, NA, 1, 0.2222, NA, 1,
0.2621, NA, 1, 0.2286, NA, 1, 0.2293, NA, 1, 0.4964, NA, 1, 0.1984, NA, 1,
0.2005, 0.1848, 1, 0.2347, 0.2612, 1, 0.2161, 0.234) ,.Dim =  c(21, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 1, 9, NA, 13, 2, NA, 13, 2,
NA, 13, 2, NA, 9, 8, NA, 9, 5, NA, 1, 6, NA, 9, 13, NA, 1, 7, NA, 1, 7, NA,
1, 9, NA, 13, 11, NA, 13, 11, NA, 13, 8, NA, 1, 5, NA, 1, 14, NA, 1, 3, 4,
1, 8, 6, 1, 15, 14) ,.Dim =  c(21, 3) ) ,
taulmn  =  0.5 ,
taulprec  =  1 ,
tauuup  =  5 ,
usevag  =  1 ,
v  =  c(0.04202, 0.01428, 0.02555, 0.08807, 0.04106, 0.02233, 0.01792,
0.01086, 0.02005, 0.04414, 0.01666, 0.02091, 0.0247, 0.03435, 0.02613,
0.02629, 0.1232, 0.01968, 0.01859, 0.03082, 0.02537) ,
y  = structure(.Data =  c(0, -0.7789, NA, 0, -0.7775, NA, 0, -0.312, NA, 0,
-1.385, NA, 0, -0.3546, NA, 0, -0.5534, NA, 0, 0.1591, NA, 0, -0.309, NA,
0, -0.2614, NA, 0, -0.3592, NA, 0, -0.4632, NA, 0, -0.3332, NA, 0, -0.5519,
NA, 0, -0.5651, NA, 0, -0.4682, NA, 0, -0.3052, NA, 0, -1.435, NA, 0, -
0.2845, NA, 0, -0.6287, -0.3927, 0, -0.1379, -0.4823, 0, 0.05259, -
0.1705) ,.Dim =  c(21, 3) )
)

#############################################
# MODEL                                     #
#############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
```

```
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
################################################
```

JAGS code for CDP-24 (Meta-Regression on Duration)

```
################################################
# TREATMENT DECODE                             #
################################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 44 mcg, TIW
# t = 14 : TERI 14 mg, QD
# t = 15 : TERI 7 mg, QD
################################################
# DATA                                         #
################################################
list(
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3) ,
ns  =  21 ,
ns2  =  18 ,
nt  =  15 ,
se  = structure(.Data =  c(1, 0.2899, NA, 1, 0.169, NA, 1, 0.226, NA, 1,
```

```
0.4197, NA, 1, 0.2866, NA, 1, 0.2113, NA, 1, 0.1893, NA, 1, 0.1474, NA, 1,
0.2002, NA, 1, 0.2971, NA, 1, 0.1826, NA, 1, 0.2045, NA, 1, 0.2222, NA, 1,
0.2621, NA, 1, 0.2286, NA, 1, 0.2293, NA, 1, 0.4964, NA, 1, 0.1984, NA, 1,
0.2005, 0.1848, 1, 0.2347, 0.2612, 1, 0.2161, 0.234) ,.Dim =  c(21, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 1, 9, NA, 13, 2, NA, 13, 2,
NA, 13, 2, NA, 9, 8, NA, 9, 5, NA, 1, 6, NA, 9, 13, NA, 1, 7, NA, 1, 7, NA,
1, 9, NA, 13, 11, NA, 13, 11, NA, 13, 8, NA, 1, 5, NA, 1, 14, NA, 1, 3, 4,
1, 8, 6, 1, 15, 14) ,.Dim =  c(21, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.04202, 0.01428, 0.02555, 0.08807, 0.04106, 0.02233, 0.01792,
0.01086, 0.02005, 0.04414, 0.01666, 0.02091, 0.0247, 0.03435, 0.02613,
0.02629, 0.1232, 0.01968, 0.01859, 0.03082, 0.02537) ,
x  =  c(-50.86, -2.857, -2.857, 45.14, -2.857, -2.857, -2.857, 45.14, -
2.857, 45.14, -2.857, -50.86, -2.857, -2.857, -2.857, -2.857, -2.857, -
2.857, -46.86, -2.857, 53.14) ,
y  = structure(.Data =  c(0, -0.7789, NA, 0, -0.7775, NA, 0, -0.312, NA, 0,
-1.385, NA, 0, -0.3546, NA, 0, -0.5534, NA, 0, 0.1591, NA, 0, -0.309, NA,
0, -0.2614, NA, 0, -0.3592, NA, 0, -0.4632, NA, 0, -0.3332, NA, 0, -0.5519,
NA, 0, -0.5651, NA, 0, -0.4682, NA, 0, -0.3052, NA, 0, -1.435, NA, 0, -
0.2845, NA, 0, -0.6287, -0.3927, 0, -0.1379, -0.4823, 0, 0.05259, -0.1705)
,.Dim =  c(21, 3) )
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)
theta[i,j] <- delta[i,j] + (covbeta[t[i,j]] - covbeta[t[i,1]])*x[i]
}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(theta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(theta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}

for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
```

```
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

covbeta[1] <- 0
for (i in 2:nt){
covbeta[i] <- B
}
B ~ dnorm(0,0.0001)

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

}
#############################################
```

JAGS code for CDP-24 in HA subgroup

```
#############################################
# TREATMENT DECODE                          #
#############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : DAC 150 mg , Q4W
# t = 4 : FINGO 0.5 mg, QD
# t = 5 : GA 20 mg, QD
# t = 6 : IM IFNB-1a 30 mcg, QW
# t = 7 : OCR 600 mg
# t = 8 : SC IFNB-1a 44 mcg, TIW
# t = 9 : TERI 14 mg, QD
#############################################
# DATA                                      #
#############################################
list(
ns  =  12 ,
nt  =  9 ,
se  = structure(.Data =  c(1, 0.226, 1, 0.2524, 1, 0.1893, 1, 0.2347, 1,
0.2181, 1, 0.2971, 1, 0.2222, 1, 0.2483, 1, 0.3969, 1, 0.2369, 1, 0.2293,
1, 1.198) ,.Dim =  c(12, 2) ) ,
t  = structure(.Data =  c(1, 6, 8, 2, 6, 5, 1, 5, 6, 3, 6, 8, 1, 6, 1, 4,
8, 7, 1, 9, 8, 5, 1, 3) ,.Dim =  c(12, 2) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
y  = structure(.Data =  c(0, -0.312, 0, -0.6031, 0, 0.1591, 0, -0.1379, 0,
-0.5668, 0, -0.3592, 0, -0.5519, 0, -0.5921, 0, -0.6917, 0, -0.5142, 0, -
0.3052, 0, -1.564) ,.Dim =  c(12, 2) )
)

#############################################
# MODEL                                     #
#############################################
```

```
model{

for(i in 1:ns) {
for (j in 2:2){
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)
y[i,j] ~ dnorm(delta[i,j], prec[i,j])
}
}

for(i in 1 : ns) {
dev[i,2] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
resdev[i] <- sum(dev[i,2:2])
}

totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

}
###############################################
```

JAGS code for CDP-24 in RES subgroup

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : GA 20 mg, QD
# t = 4 : IM IFNB-1a 30 mcg, QW
# t = 5 : NAT 300 mg, Q4W
# t = 6 : OCR 600 mg
# t = 7 : SC IFNB-1a 44 mcg, TIW
###############################################
# DATA                                        #
###############################################
list(
ns  =  9 ,
nt  =  7 ,
se  = structure(.Data =  c(1, 0.382, 1, 0.226, 1, 0.4234, 1, 0.1893, 1,
0.2347, 1, 0.2971, 1, 0.2222, 1, 0.3495, 1, 0.2293) ,.Dim =  c(9, 2) ) ,
t  = structure(.Data =  c(1, 5, 1, 4, 7, 2, 4, 3, 1, 3, 4, 7, 1, 4, 7, 6,
7, 3) ,.Dim =  c(9, 2) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
y  = structure(.Data =  c(0, -1.023, 0, -0.312, 0, -0.543, 0, 0.1591, 0, -
0.1379, 0, -0.3592, 0, -0.5519, 0, -0.4862, 0, -0.3052) ,.Dim =  c(9, 2) )
)
```

```
################################################
# MODEL                                        #
################################################

model{

for(i in 1:ns) {
for (j in 2:2){
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)
y[i,j] ~ dnorm(delta[i,j], prec[i,j])
}
}

for(i in 1 : ns) {
dev[i,2] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
resdev[i] <- sum(dev[i,2:2])
}

totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

}
################################################
```

JAGS code for CDP-24 (sensitivity analysis including INCOMIN)

```
################################################
# TREATMENT DECODE                             #
################################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 44 mcg, TIW
# t = 14 : SC IFNB-1b 250 mcg, EOD
# t = 15 : TERI 14 mg, QD
# t = 16 : TERI 7 mg, QD
################################################
# DATA                                         #
################################################
list(
```

```
na  =  c(2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 3, 3)
,
ns  =  22 ,
ns2  =  19 ,
nt  =  16 ,
se  = structure(.Data =  c(1, 0.2899, NA, 1, 0.169, NA, 1, 0.226, NA, 1,
0.4197, NA, 1, 0.2866, NA, 1, 0.2113, NA, 1, 0.1893, NA, 1, 0.1474, NA, 1,
0.2002, NA, 1, 0.2971, NA, 1, 0.1826, NA, 1, 0.2045, NA, 1, 0.2967, NA, 1,
0.2222, NA, 1, 0.2621, NA, 1, 0.2286, NA, 1, 0.2293, NA, 1, 0.4964, NA, 1,
0.1984, NA, 1, 0.2005, 0.1848, 1, 0.2347, 0.2612, 1, 0.2161, 0.234) ,.Dim =
c(22, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 1, 9, NA, 13, 2, NA, 13, 2,
NA, 13, 2, NA, 9, 8, NA, 9, 5, NA, 1, 6, NA, 9, 13, NA, 1, 7, NA, 1, 7, NA,
9, 14, NA, 1, 9, NA, 13, 11, NA, 13, 11, NA, 13, 8, NA, 1, 5, NA, 1, 15,
NA, 1, 3, 4, 1, 8, 6, 1, 16, 15) ,.Dim =  c(22, 3) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
v  =  c(0.04202, 0.01428, 0.02555, 0.08807, 0.04106, 0.02233, 0.01792,
0.01086, 0.02005, 0.04414, 0.01666, 0.02091, 0.04402, 0.0247, 0.03435,
0.02613, 0.02629, 0.1232, 0.01968, 0.01859, 0.03082, 0.02537) ,
y  = structure(.Data =  c(0, -0.7789, NA, 0, -0.7775, NA, 0, -0.312, NA, 0,
-1.385, NA, 0, -0.3546, NA, 0, -0.5534, NA, 0, 0.1591, NA, 0, -0.309, NA,
0, -0.2614, NA, 0, -0.3592, NA, 0, -0.4632, NA, 0, -0.3332, NA, 0, -0.8047,
NA, 0, -0.5519, NA, 0, -0.5651, NA, 0, -0.4682, NA, 0, -0.3052, NA, 0, -
1.435, NA, 0, -0.2845, NA, 0, -0.6287, -0.3927, 0, -0.1379, -0.4823, 0,
0.05259, -0.1705) ,.Dim =  c(22, 3) )
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {
for(j in 2:na[i]) {
md[i,j]<- beta[t[i,j]] - beta[t[i,1]]
delta[i,j]~dnorm(md[i,j],tau)
vr[i,j]   <- pow(se[i,j], 2)
prec[i,j] <- pow(vr[i,j],-1)

}
}

for (i in 1: ns2){
omega[i,1,1] <- prec[i,2]
y[i,2] ~ dnorm(delta[i,2],  omega[i,1,1])
}

for (i in (ns2+1):ns){
for (j in 1:(na[i]-1)){
for (k in 1:(na[i]-1)){
sigma[i,j,k] <- equals(j,k)*vr[i,j+1]+(1-equals(j,k))*(v[i])
}
}
omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(sigma[i,,])
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],omega[i,1:(na[i]-1),1:(na[i]-1)])
}
```

```
for(i in 1 : ns) {
for(j in 1:(na[i]-1)) {
yd[i,j] <- (y[i,j+1]-delta[i,j+1])
z[i,j]  <- inprod(omega[i,j,1:(na[i]-1)], yd[i,1:(na[i]-1)])
dev[i,j] <- z[i,j] * yd[i,j]
}
resdev[i] <- sum(dev[i,1:(na[i]-1)])
}
totresdev <- sum(resdev[])

beta[1] <- 0
for (i in 2:nt){
beta[i]~ dnorm(0,0.0001)
}

sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)


}
##############################################
```

JAGS code for All-cause discontinuation Base-case analysis

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
n  = structure(.Data =  c(500, 512, NA, 315, 627, NA, 888, 445, NA, 111,
113, NA, 187, 376, NA, 202, 426, NA, 437, 433, 456, 363, 350, 359, 126,
125, NA, 922, 919, NA, 408, 410, NA, 338, 339, NA, 418, 425, NA, 355, 358,
NA, 123, 124, NA, 92, 96, NA, 143, 158, NA, 411, 410, NA, 418, 417, NA,
187, 189, 184, 386, 378, NA, 204, 208, NA, 363, 365, 358, 104, 109, 111,
388, 407, 370, 431, 429, NA) ,.Dim =  c(26, 3) ) ,
na  =  c(2, 2, 2, 2, 2, 2, 3, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 2, 2,
3, 3, 3, 2) ,
ns  =  26 ,
nt  =  17 ,
r  = structure(.Data =  c(44, 74, NA, 76, 46, NA, 104, 71, NA, 41, 14, NA,
23, 14, NA, 44, 27, NA, 60, 38, 63, 129, 86, 106, 17, 19, NA, 278, 266, NA,
```

```
143, 126, NA, 21, 25, NA, 115, 80, NA, 123, 116, NA, 23, 24, NA, 15, 9, NA,
9, 14, NA, 71, 44, NA, 98, 57, NA, 17, 22, 19, 80, 51, NA, 18, 19, NA, 104,
91, 95, 30, 20, 22, 125, 134, 126, 45, 31, NA) ,.Dim =  c(26, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 14, 2, NA, 14,
2, NA, 14, 2, NA, 1, 3, 4, 1, 8, 6, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14,
NA, 1, 7, NA, 1, 7, NA, 1, 15, NA, 9, 15, NA, 1, 9, NA, 14, 11, NA, 14, 11,
NA, 1, 13, 14, 14, 8, NA, 1, 5, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 9, 7,
NA) ,.Dim =  c(26, 3) ) ,
taulmn  =  -3.23 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {

logit(p[i,j])  <- mu[i] + delta[i,j]
r[i,j] ~ dbin(p[i,j],n[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
rhat[i,j] <- p[i,j] * n[i,j]
dev[i,j] <- 2*(r[i,j] * (log(r[i,j]) - log(rhat[i,j])) + (n[i,j] -
r[i,j])*(log(n[i,j]-r[i,j])-log(n[i,j]-rhat[i,j])))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sdvag ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <- usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)
```

```
}
##############################################
```

JAGS code for All-cause discontinuation Sensitivity analysis (Fixed effect (FE))

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
n  = structure(.Data =  c(500, 512, NA, 315, 627, NA, 888, 445, NA, 111,
113, NA, 187, 376, NA, 202, 426, NA, 437, 433, 456, 363, 350, 359, 126,
125, NA, 922, 919, NA, 408, 410, NA, 338, 339, NA, 418, 425, NA, 355, 358,
NA, 123, 124, NA, 92, 96, NA, 143, 158, NA, 411, 410, NA, 418, 417, NA,
187, 189, 184, 386, 378, NA, 204, 208, NA, 363, 365, 358, 104, 109, 111,
388, 407, 370, 431, 429, NA) ,.Dim =  c(26, 3) ) ,
na  =  c(2, 2, 2, 2, 2, 2, 3, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 2, 2,
3, 3, 3, 2) ,
ns  =  26 ,
nt  =  17 ,
r  = structure(.Data =  c(44, 74, NA, 76, 46, NA, 104, 71, NA, 41, 14, NA,
23, 14, NA, 44, 27, NA, 60, 38, 63, 129, 86, 106, 17, 19, NA, 278, 266, NA,
143, 126, NA, 21, 25, NA, 115, 80, NA, 123, 116, NA, 23, 24, NA, 15, 9, NA,
9, 14, NA, 71, 44, NA, 98, 57, NA, 17, 22, 19, 80, 51, NA, 18, 19, NA, 104,
91, 95, 30, 20, 22, 125, 134, 126, 45, 31, NA) ,.Dim =  c(26, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 14, 2, NA, 14,
2, NA, 14, 2, NA, 1, 3, 4, 1, 8, 6, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14,
NA, 1, 7, NA, 1, 7, NA, 1, 15, NA, 9, 15, NA, 1, 9, NA, 14, 11, NA, 14, 11,
NA, 1, 13, 14, 14, 8, NA, 1, 5, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 9, 7,
NA) ,.Dim =  c(26, 3) )
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {
```

```
logit(p[i,j])  <- mu[i] + delta[i,j]
r[i,j] ~ dbin(p[i,j],n[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] <- beta[t[i,j]] - beta[t[i,1]]
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
rhat[i,j] <- p[i,j] * n[i,j]
dev[i,j] <- 2*(r[i,j] * (log(r[i,j]) - log(rhat[i,j])) + (n[i,j] -
r[i,j])*(log(n[i,j]-r[i,j])-log(n[i,j]-rhat[i,j])))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

}
###############################################
```

JAGS code for All-cause discontinuation Sensitivity analysis (Random effects (RE) alternative prior)

```
###############################################
# TREATMENT DECODE                            #
###############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
###############################################
# DATA                                        #
###############################################
list(
```

```
n  = structure(.Data =  c(500, 512, NA, 315, 627, NA, 888, 445, NA, 111,
113, NA, 187, 376, NA, 202, 426, NA, 437, 433, 456, 363, 350, 359, 126,
125, NA, 922, 919, NA, 408, 410, NA, 338, 339, NA, 418, 425, NA, 355, 358,
NA, 123, 124, NA, 92, 96, NA, 143, 158, NA, 411, 410, NA, 418, 417, NA,
187, 189, 184, 386, 378, NA, 204, 208, NA, 363, 365, 358, 104, 109, 111,
388, 407, 370, 431, 429, NA) ,.Dim =  c(26, 3) ) ,
na  =  c(2, 2, 2, 2, 2, 2, 3, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 2, 2,
3, 3, 3, 2) ,
ns  =  26 ,
nt  =  17 ,
r  = structure(.Data =  c(44, 74, NA, 76, 46, NA, 104, 71, NA, 41, 14, NA,
23, 14, NA, 44, 27, NA, 60, 38, 63, 129, 86, 106, 17, 19, NA, 278, 266, NA,
143, 126, NA, 21, 25, NA, 115, 80, NA, 123, 116, NA, 23, 24, NA, 15, 9, NA,
9, 14, NA, 71, 44, NA, 98, 57, NA, 17, 22, 19, 80, 51, NA, 18, 19, NA, 104,
91, 95, 30, 20, 22, 125, 134, 126, 45, 31, NA) ,.Dim =  c(26, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 14, 2, NA, 14,
2, NA, 14, 2, NA, 1, 3, 4, 1, 8, 6, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14,
NA, 1, 7, NA, 1, 7, NA, 1, 15, NA, 9, 15, NA, 1, 9, NA, 14, 11, NA, 14, 11,
NA, 1, 13, 14, 14, 8, NA, 1, 5, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 9, 7,
NA) ,.Dim =  c(26, 3) ) ,
taulmn  =  0.5 ,
taulprec  =  1 ,
tauuup  =  5 ,
usevag  =  1
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {

logit(p[i,j])  <- mu[i] + delta[i,j]
r[i,j] ~ dbin(p[i,j],n[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
rhat[i,j] <- p[i,j] * n[i,j]
dev[i,j] <- 2*(r[i,j] * (log(r[i,j]) - log(rhat[i,j])) + (n[i,j] -
r[i,j])*(log(n[i,j]-r[i,j])-log(n[i,j]-rhat[i,j])))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])
```

```
for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sdvag ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <- usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

}
#############################################
```

JAGS code for All-cause discontinuation (Meta-Regression on Duration)

```
#############################################
# TREATMENT DECODE                          #
#############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
#############################################
# DATA                                      #
#############################################
list(
n  = structure(.Data =  c(500, 512, NA, 315, 627, NA, 888, 445, NA, 111,
113, NA, 187, 376, NA, 202, 426, NA, 437, 433, 456, 363, 350, 359, 126,
125, NA, 922, 919, NA, 408, 410, NA, 338, 339, NA, 418, 425, NA, 355, 358,
NA, 123, 124, NA, 92, 96, NA, 143, 158, NA, 411, 410, NA, 418, 417, NA,
187, 189, 184, 386, 378, NA, 204, 208, NA, 363, 365, 358, 104, 109, 111,
388, 407, 370, 431, 429, NA) ,.Dim =  c(26, 3) ) ,
na  =  c(2, 2, 2, 2, 2, 2, 3, 3, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 3, 2, 2,
3, 3, 3, 2) ,
ns  =  26 ,
nt  =  17 ,
r  = structure(.Data =  c(44, 74, NA, 76, 46, NA, 104, 71, NA, 41, 14, NA,
23, 14, NA, 44, 27, NA, 60, 38, 63, 129, 86, 106, 17, 19, NA, 278, 266, NA,
143, 126, NA, 21, 25, NA, 115, 80, NA, 123, 116, NA, 23, 24, NA, 15, 9, NA,
9, 14, NA, 71, 44, NA, 98, 57, NA, 17, 22, 19, 80, 51, NA, 18, 19, NA, 104,
91, 95, 30, 20, 22, 125, 134, 126, 45, 31, NA) ,.Dim =  c(26, 3) ) ,
t  = structure(.Data =  c(1, 12, NA, 1, 10, NA, 15, 8, NA, 14, 2, NA, 14,
2, NA, 14, 2, NA, 1, 3, 4, 1, 8, 6, 1, 8, NA, 9, 5, NA, 1, 6, NA, 9, 14,
NA, 1, 7, NA, 1, 7, NA, 1, 15, NA, 9, 15, NA, 1, 9, NA, 14, 11, NA, 14, 11,
NA, 1, 13, 14, 14, 8, NA, 1, 5, NA, 1, 17, 16, 14, 17, 16, 1, 17, 16, 9, 7,
NA) ,.Dim =  c(26, 3) ) ,
```

```
taulmn  =  -3.23 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
x  =  c(-46.58, 1.423, 1.423, 49.42, 1.423, 1.423, 1.423, 1.423, 1.423,
49.42, 1.423, -46.58, 1.423, 1.423, 1.423, 1.423, 1.423, 1.423, 1.423,
1.423, 1.423, -42.58, 1.423, 20.42, 37.42, -46.58)
)

##############################################
# MODEL                                      #
##############################################

model{

for(i in 1 : ns) {

for(j in 1:na[i]) {

logit(p[i,j])  <- mu[i] + delta[i,j] + (covbeta[t[i,j]] -
covbeta[t[i,1]])*x[i]
r[i,j] ~ dbin(p[i,j],n[i,j])
}

delta[i,1] <- 0
w[i,1] <- 0
for (j in 2:na[i]) {
delta[i,j] ~ dnorm(md[i,j],taud[i,j])
md[i,j] <- beta[t[i,j]] - beta[t[i,1]] + sw[i,j]
taud[i,j] <- tau*2*(j-1)/j
w[i,j] <- delta[i,j] - (beta[t[i,j]] - beta[t[i,1]])
sw[i,j] <- sum(w[i,1:(j-1)])/(j-1)
}
}

for(i in 1 : ns) {
for(j in 1:na[i]) {
rhat[i,j] <- p[i,j] * n[i,j]
dev[i,j] <- 2*(r[i,j] * (log(r[i,j]) - log(rhat[i,j])) + (n[i,j] -
r[i,j])*(log(n[i,j]-r[i,j])-log(n[i,j]-rhat[i,j])))
}
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])

for (i in 1:ns){
mu[i] ~ dnorm(0,0.001)
}
beta[1]<-0
for (i in 2:nt){
beta[i] ~ dnorm(0,.0001)
}

sdvag ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)

tau <- usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

covbeta[1] <- 0
for (i in 2:nt){
covbeta[i] <- B
```

```
}
B ~ dnorm(0,0.0001)

}
##############################################
```

Related to Question A15

Table 30 Input table for ARR ITT, base case and meta-regression on duration

				Reported Data			Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**	**Meta Regression Covariate**
ADVANCE	48	1	Placebo	0.397	500	48	198.50	500.00	-53.2
ADVANCE	48	2	PEG-INFB-1A 2W 125 mcg, Q2W	0.256	512	48	131.07	512.00	-53.2
AFFIRM	96	1	Placebo	0.73	315	96	459.90	630.00	-5.2
AFFIRM	96	2	NAT 300 mg, Q4W	0.23	627	96	288.42	1254.00	-5.2
BEYOND	96	1	SC IFNB-1b 250 mcg, EOD	0.36	888 (assumed based on AE reported numbers)	96	639.36	1776.00	-5.2
BEYOND	96	2	GA 20 mg, QD	0.34	445 (assumed based on AE reported numbers)	96	302.60	890.00	-5.2
BRAVO	96	1	Placebo	0.34	450	96	306.00	900.00	-5.2
BRAVO	96	2	IM IFNB-1a 30 mcg, QW	0.26	447	96	232.44	894.00	-5.2
Calabrese 2012	96	1	IM IFNB-1a 30 mcg, QW	0.5	47	96	47.00	94.00	-5.2
Calabrese 2012	96	2	SC IFNB-1a 44 mcg, TIW	0.4	46	96	36.80	92.00	-5.2

				Reported Data			Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**	**Meta Regression Covariate**
Calabrese 2012	96	3	GA 20 mg, QD	0.5	48	96	48.00	96.00	-5.2
CAMMS223	144	1	SC IFNB-1a 44 mcg, TIW	0.36	111	144	119.88	333.00	42.8
CAMMS223	144	2	ALEM 12 mg	0.11	112	144	36.96	336.00	42.8
CARE-MS I	96	1	SC IFNB-1a 44 mcg, TIW	0.39	187	96	145.86	374.00	-5.2
CARE-MS I	96	2	ALEM 12 mg	0.18	376	96	135.36	752.00	-5.2
CARE-MS II	96	1	SC IFNB-1a 44 mcg, TIW	0.52	202	96	210.08	404.00	-5.2
CARE-MS II	96	2	ALEM 12 mg	0.26	426	96	221.52	852.00	-5.2
CLARITY	96	1	Placebo	0.33	437	96	288.42	874.00	-5.2
CLARITY	96	2	CLAD 3.5mg/kg	0.14	433	96	121.24	866.00	-5.2
CLARITY	96	3	CLAD 5.25mg/kg	0.15	456	96	136.80	912.00	-5.2
CombiRx	144	1	IM IFNB-1a 30 mcg, QW	0.16	250	144	120.00	750.00	42.8
CombiRx	144	2	GA 20 mg, QD	0.11	259	144	85.47	777.00	42.8
CONFIRM	96	1	Placebo	0.4	363	96	290.40	726.00	-5.2
CONFIRM	96	2	GA 20 mg, QD	0.29	350	96	203.00	700.00	-5.2
CONFIRM	96	3	DMF 240 mg, BID	0.22	359	96	157.96	718.00	-5.2

				Reported Data			Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**	**Meta Regression Covariate**
Copolymer 1 MS trial	96	1	Placebo	0.84	232	96	389.76	464.00	-5.2
Copolymer 1 MS trial	96	2	GA 20 mg, QD	0.59	227	96	267.86	454.00	-5.2
DECIDE	144	1	IM IFNB-1a 30 mcg, QW	0.393	922	144	1087.04	2766.00	42.8
DECIDE	144	2	DAC 150 mg , Q4W	0.216	919	144	595.51	2757.00	42.8
DEFINE	96	1	Placebo	0.36	408	96	293.76	816.00	-5.2
DEFINE	96	2	DMF 240 mg, BID	0.17	410	96	139.40	820.00	-5.2
EVIDENCE	48	1	IM IFNB-1a 30 mcg, QW	0.65	338	48	219.70	338.00	-53.2
EVIDENCE	48	2	SC IFNB-1a 44 mcg, TIW	0.54	339	48	183.06	339.00	-53.2
FREEDOMS	96	1	Placebo	0.4	418	96	334.40	836.00	-5.2
FREEDOMS	96	2	FINGO 0.5 mg, QD	0.18	425	96	153.00	850.00	-5.2
FREEDOMS II	96	1	Placebo	0.4	355	96	284.00	710.00	-5.2
FREEDOMS II	96	2	FINGO 0.5 mg, QD	0.21	358	96	150.36	716.00	-5.2
GALA	48	1	Placebo	0.505	461	48	232.81	461.00	-53.2
GALA	48	2	GA 40 mg, TIW	0.331	943	48	312.13	943.00	-53.2
IFNB MS	240	1	Placebo	1.12	123	240	688.80	615.00	138.8
IFNB MS	240	2	SC IFNB-1b 250 mcg, EOD	0.78	124	240	483.60	620.00	138.8

				Reported Data			Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**	**Meta Regression Covariate**
INCOMIN	96	1	IM IFNB-1a 30 mcg, QW	0.7	92	96	128.80	184.00	-5.2
INCOMIN	96	2	SC IFNB-1b 250 mcg, EOD	0.5	96	96	96.00	192.00	-5.2
MSCRG	96	1	Placebo	0.82	143	96	234.52	286.00	-5.2
MSCRG	96	2	IM IFNB-1a 30 mcg, QW	0.67	158	96	211.72	316.00	-5.2
OPERA I	96	1	SC IFNB-1a 44 mcg, TIW	0.292	411	96	240.02	822.00	-5.2
OPERA I	96	2	OCR 600 mg	0.156	410	96	127.92	820.00	-5.2
OPERA II	96	1	SC IFNB-1a 44 mcg, TIW	0.29	418	96	242.44	836.00	-5.2
OPERA II	96	2	OCR 600 mg	0.155	417	96	129.27	834.00	-5.2
REGARD	96	1	SC IFNB-1a 44 mcg, TIW	0.3	386	96	231.60	772.00	-5.2
REGARD	96	2	GA 20 mg, QD	0.29	378	96	219.24	756.00	-5.2
SELECT	52	1	Placebo	0.46	196	52	97.67	212.33	-49.2
SELECT	52	2	DAC 150 mg , Q4W	0.21	201	52	45.73	217.75	-49.2
Stepien 2013	144	1	SC IFNB-1b 250 mcg, EOD	0.43	18	144	23.22	54.00	42.8
Stepien 2013	144	2	IM IFNB-1a 30 mcg, QW	0.35	20	144	21.00	60.00	42.8

				Reported Data			Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**	**Meta Regression Covariate**
TEMSO	96	1	Placebo	0.54	363	96	392.04	726.00	-5.2
TEMSO	96	2	TERI 7 mg, QD	0.37	365	96	270.10	730.00	-5.2
TEMSO	96	3	TERI 14 mg, QD	0.37	358	96	264.92	716.00	-5.2
TENERE	96	1	SC IFNB-1a 44 mcg, TIW	0.22	104	96	45.76	208.00	-5.2
TENERE	96	2	TERI 7 mg, QD	0.41	109	96	89.38	218.00	-5.2
TENERE	96	3	TERI 14 mg, QD	0.26	111	96	57.72	222.00	-5.2
TOWER	152	1	Placebo	0.5	388	152	614.33	1228.67	50.8
TOWER	152	2	TERI 7 mg, QD	0.39	407	152	502.64	1288.83	50.8
TOWER	152	3	TERI 14 mg, QD	0.32	370	152	374.93	1171.67	50.8
TRANSFORMS	48	1	IM IFNB-1a 30 mcg, QW	0.33	431	48	142.23	431.00	-53.2
TRANSFORMS	48	2	FINGO 0.5 mg, QD	0.16	429	48	68.64	429.00	-53.2

Table 31 Input table for CDP-12 ITT, base case & meta-regression

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
ADVANCE	48	1	Placebo					NA	NA	NA
ADVANCE	48	2	PEG-INFB-1A 2W 125 mcg, Q2W	95% CI Lower Limit	0.4	95% CI Upper Limit	0.97	-0.47	0.226	-52.91
AFFIRM	96	1	Placebo					NA	NA	NA
AFFIRM	96	2	NAT 300 mg, Q4W	95% CI Lower Limit	0.43	95% CI Upper Limit	0.77	-0.55	0.149	-4.91
BEYOND	96	1	SC IFNB-1b 250 mcg, EOD	N patients	888	% event	21	NA	NA	NA
BEYOND	96	2	GA 20 mg, QD	N patients	445	% event	20	-0.05	0.129	-4.91
Bornstein 1987	96	1	Placebo	N patients	23	n event	11	NA	NA	NA
Bornstein 1987	96	2	GA 20 mg, QD	N patients	25	n event	5	-1.07	0.543	-4.91
BRAVO	96	1	Placebo					NA	NA	NA
BRAVO	96	2	IM IFNB-1a 30 mcg, QW	95% CI Lower Limit	0.51	95% CI Upper Limit	1.09	-0.29	0.194	-4.91
CLARITY	96	1	Placebo					NA	NA	NA
CLARITY	96	2	CLAD 3.5mg/kg	95% CI Lower Limit	0.48	95% CI Upper Limit	0.93	-0.40	0.169	-4.91

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
CLARITY	96	3	CLAD 5.25mg/kg	95% CI Lower Limit	0.49	95% CI Upper Limit	0.96	-0.38	0.172	-4.91
CONFIRM	96	1	Placebo					NA	NA	NA
CONFIRM	96	2	GA 20 mg, QD	95% CI Lower Limit	0.63	95% CI Upper Limit	1.37	-0.07	0.198	-4.91
CONFIRM	96	3	DMF 240 mg, BID	95% CI Lower Limit	0.52	95% CI Upper Limit	1.19	-0.24	0.211	-4.91
Copolymer 1 MS trial	96	1	Placebo	N patients	126	% event	24.6	NA	NA	NA
Copolymer 1 MS trial	96	2	GA 20 mg, QD	N patients	125	% event	21.6	-0.15	0.264	-4.91
DECIDE	144	1	IM IFNB-1a 30 mcg, QW					NA	NA	NA
DECIDE	144	2	DAC 150 mg , Q4W	95% CI Lower Limit	0.66	95% CI Upper Limit	1.07	-0.17	0.123	43.09
DEFINE	96	1	Placebo					NA	NA	NA
DEFINE	96	2	DMF 240 mg, BID	95% CI Lower Limit	0.44	95% CI Upper Limit	0.87	-0.48	0.174	-4.91

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
EVIDENCE	48	1	IM IFNB-1a 30 mcg, QW					NA	NA	NA
EVIDENCE	48	2	SC IFNB-1a 44 mcg, TIW	95% CI Lower Limit	0.58	95% CI Upper Limit	1.31	-0.14	0.208	-52.91
FREEDOMS	96	1	Placebo					NA	NA	NA
FREEDOMS	96	2	FINGO 0.5 mg, QD	95% CI Lower Limit	0.52	95% CI Upper Limit	0.96	-0.35	0.156	-4.91
FREEDOMS II	96	1	Placebo					NA	NA	NA
FREEDOMS II	96	2	FINGO 0.5 mg, QD	95% CI Lower Limit	0.61	95% CI Upper Limit	1.12	-0.19	0.155	-4.91
HAS Meta Analysis	144	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
HAS Meta Analysis	144	2	ALEM 12 mg	95% CI Lower Limit	0.49	95% CI Upper Limit	0.87	-0.43	0.146	43.09
IFNB MS	240	1	Placebo	N patients	122	n event	56	NA	NA	NA
IFNB MS	240	2	SC IFNB-1b 250 mcg, EOD	N patients	122	n event	43	-0.35	0.205	139.09
OPERA I	96	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
OPERA I	96	2	OCR 600 mg	95% CI Lower Limit	0.37	95% CI Upper Limit	0.9	-0.55	0.227	-4.91
OPERA II	96	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
OPERA II	96	2	OCR 600 mg	95% CI Lower Limit	0.42	95% CI Upper Limit	0.92	-0.48	0.200	-4.91
PRISMS	96	1	Placebo					NA	NA	NA
PRISMS	96	2	SC IFNB-1a 22 mcg, TIW	95% CI Lower Limit	0.48	95% CI Upper Limit	0.98	-0.38	0.182	-4.91
PRISMS	96	3	SC IFNB-1a 44 mcg, TIW	95% CI Lower Limit	0.43	95% CI Upper Limit	0.91	-0.47	0.191	-4.91
SELECT	52	1	Placebo					NA	NA	NA
SELECT	52	2	DAC 150 mg , Q4W	95% CI Lower Limit	0.21	95% CI Upper Limit	0.88	-0.84	0.366	-48.91
TEMSO	96	1	Placebo					NA	NA	NA
TEMSO	96	2	TERI 7 mg, QD	95% CI Lower Limit	0.56	95% CI Upper Limit	1.05	-0.27	0.160	-4.91

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
TEMSO	96	3	TERI 14 mg, QD	95% CI Lower Limit	0.51	95% CI Upper Limit	0.97	-0.35	0.164	-4.91
TOWER	152	1	Placebo					NA	NA	NA
TOWER	152	2	TERI 7 mg, QD	95% CI Lower Limit	0.68	95% CI Upper Limit	1.35	-0.04	0.175	51.09
TOWER	152	3	TERI 14 mg, QD	95% CI Lower Limit	0.47	95% CI Upper Limit	1	-0.38	0.193	51.09
TRANSFORMS	48	1	IM IFNB-1a 30 mcg, QW	N patients	429	% event	7.9	NA	NA	NA
TRANSFORMS	48	2	FINGO 0.5 mg, QD	N patients	431	% event	5.9	-0.30	0.262	-52.91

Table 32 Input table for CDP-24 ITT, base case & meta-regression

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
ADVANCE	48	1	Placebo					NA	NA	NA
ADVANCE	48	2	PEG-INFB-1A 2W 125 mcg, Q2W	95% CI Lower Limit	0.26	95% CI Upper Limit	0.81	-0.78	0.290	-50.86
AFFIRM	96	1	Placebo					NA	NA	NA
AFFIRM	96	2	NAT 300 mg, Q4W	95% CI Lower Limit	0.33	95% CI Upper Limit	0.64	-0.78	0.169	-2.86
BRAVO	96	1	Placebo					NA	NA	NA
BRAVO	96	2	IM IFNB-1a 30 mcg, QW	95% CI Lower Limit	0.47	95% CI Upper Limit	1.14	-0.31	0.226	-2.86
CAMMS223	144	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
CAMMS223	144	2	ALEM 12 mg	95% CI Lower Limit	0.11	95% CI Upper Limit	0.57	-1.38	0.420	45.14
CARE-MS I	96	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
CARE-MS I	96	2	ALEM 12 mg	95% CI Lower Limit	0.4	95% CI Upper Limit	1.23	-0.35	0.287	-2.86
CARE-MS II	96	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
CARE-MS II	96	2	ALEM 12 mg	95% CI Lower Limit	0.38	95% CI Upper Limit	0.87	-0.55	0.211	-2.86

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
CLARITY	96	1	Placebo					NA	NA	NA
CLARITY	96	2	CLAD 3.5mg/kg	95% CI Lower Limit	0.36	95% CI Upper Limit	0.79	-0.63	0.200	-2.86
CLARITY	96	3	CLAD 5.25mg/kg	95% CI Lower Limit	0.47	95% CI Upper Limit	0.97	-0.39	0.185	-2.86
CombiRx	144	1	IM IFNB-1a 30 mcg, QW	N patients	241	n event	52	NA	NA	NA
CombiRx	144	2	GA 20 mg, QD	N patients	246	n event	61	0.16	0.189	45.14
CONFIRM	96	1	Placebo					NA	NA	NA
CONFIRM	96	2	GA 20 mg, QD	95% CI Lower Limit	0.55	95% CI Upper Limit	1.38	-0.14	0.235	-2.86
CONFIRM	96	3	DMF 240 mg, BID	95% CI Lower Limit	0.37	95% CI Upper Limit	1.03	-0.48	0.261	-2.86
DECIDE	144	1	IM IFNB-1a 30 mcg, QW					NA	NA	NA
DECIDE	144	2	DAC 150 mg , Q4W	95% CI Lower Limit	0.55	95% CI Upper Limit	0.98	-0.31	0.147	45.14
DEFINE	96	1	Placebo					NA	NA	NA
DEFINE	96	2	DMF 240 mg, BID	95% CI Lower Limit	0.52	95% CI Upper Limit	1.14	-0.26	0.200	-2.86
EVIDENCE	48	1	IM IFNB-1a 30 mcg, QW					NA	NA	NA

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
EVIDENCE	48	2	SC IFNB-1a 44 mcg, TIW	95% CI Lower Limit	0.39	95% CI Upper Limit	1.25	-0.36	0.297	-50.86
FREEDOMS	96	1	Placebo					NA	NA	NA
FREEDOMS	96	2	FINGO 0.5 mg, QD	95% CI Lower Limit	0.44	95% CI Upper Limit	0.9	-0.46	0.183	-2.86
FREEDOMS II	96	1	Placebo					NA	NA	NA
FREEDOMS II	96	2	FINGO 0.5 mg, QD	95% CI Lower Limit	0.48	95% CI Upper Limit	1.07	-0.33	0.204	-2.86
MSCRG	96	1	Placebo	N patients	143	% event	34.9	NA	NA	NA
MSCRG	96	2	IM IFNB-1a 30 mcg, QW	N patients	158	% event	21.9	-0.55	0.222	-2.86
OPERA I	96	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
OPERA I	96	2	OCR 600 mg	95% CI Lower Limit	0.34	95% CI Upper Limit	0.95	-0.57	0.262	-2.86
OPERA II	96	1	SC IFNB-1a 44 mcg, TIW					NA	NA	NA
OPERA II	96	2	OCR 600 mg	95% CI Lower Limit	0.4	95% CI Upper Limit	0.98	-0.47	0.229	-2.86
REGARD	96	1	SC IFNB-1a 44 mcg, TIW	N patients	386	n event	45	NA	NA	NA
REGARD	96	2	GA 20 mg, QD	N patients	378	n event	33	-0.31	0.229	-2.86

				Reported Data						
				Source 1		Source 2		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**	**Meta Regression Covariate**
SELECT	52	1	Placebo					NA	NA	NA
SELECT	52	2	DAC 150 mg , Q4W	95% CI Lower Limit	0.09	95% CI Upper Limit	0.63	-1.43	0.496	-46.86
TEMSO	96	1	Placebo					NA	NA	NA
TEMSO	96	2	TERI 14 mg, QD	95% CI Lower Limit	0.51	95% CI Upper Limit	1.11	-0.28	0.198	-2.86
TOWER	152	1	Placebo					NA	NA	NA
TOWER	152	2	TERI 7 mg, QD	95% CI Lower Limit	0.69	95% CI Upper Limit	1.61	0.05	0.216	53.14
TOWER	152	3	TERI 14 mg, QD	95% CI Lower Limit	0.533	95% CI Upper Limit	1.334	-0.17	0.234	53.14

Table 33 Input table for all-cause discontinuation ITT, base case & meta-regression

				Reported Data		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**N**	**n**	**N patients**	**n events**	**Meta Regression Covariate**
ADVANCE	48	1	Placebo	500	44	500	44	-46.58
ADVANCE	48	2	PEG-INFB-1A 2W 125 mcg, Q2W	512	74	512	74	-46.58
AFFIRM	96	1	Placebo	315	76	315	76	1.42
AFFIRM	96	2	NAT 300 mg, Q4W	627	46	627	46	1.42
BEYOND	96	1	SC IFNB-1b 250 mcg, EOD	888	104	888	104	1.42
BEYOND	96	2	GA 20 mg, QD	445	71	445	71	1.42
CAMMS223	144	1	SC IFNB-1a 44 mcg, TIW	111	41	111	41	49.42
CAMMS223	144	2	ALEM 12 mg	113	14	113	14	49.42
CARE-MS I	96	1	SC IFNB-1a 44 mcg, TIW	187	23	187	23	1.42
CARE-MS I	96	2	ALEM 12 mg	376	14	376	14	1.42
CARE-MS II	96	1	SC IFNB-1a 44 mcg, TIW	202	44	202	44	1.42
CARE-MS II	96	2	ALEM 12 mg	426	27	426	27	1.42
CLARITY	96	1	Placebo	437	60	437	60	1.42
CLARITY	96	2	CLAD 3.5mg/kg	433	38	433	38	1.42
CLARITY	96	3	CLAD 5.25mg/kg	456	63	456	63	1.42
CONFIRM	96	1	Placebo	363	129	363	129	1.42
CONFIRM	96	2	GA 20 mg, QD	350	86	350	86	1.42
CONFIRM	96	3	DMF 240 mg, BID	359	106	359	106	1.42
Copolymer 1 MS trial	96	1	Placebo	126	17	126	17	1.42
Copolymer 1 MS trial	96	2	GA 20 mg, QD	125	19	125	19	1.42
DECIDE	144	1	IM IFNB-1a 30 mcg, QW	922	278	922	278	49.42
DECIDE	144	2	DAC 150 mg , Q4W	919	266	919	266	49.42
DEFINE	96	1	Placebo	408	143	408	143	1.42
DEFINE	96	2	DMF 240 mg, BID	410	126	410	126	1.42

				Reported Data		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**N**	**n**	**N patients**	**n events**	**Meta Regression Covariate**
EVIDENCE	48	1	IM IFNB-1a 30 mcg, QW	338	21	338	21	-46.58
EVIDENCE	48	2	SC IFNB-1a 44 mcg, TIW	339	25	339	25	-46.58
FREEDOMS	96	1	Placebo	418	115	418	115	1.42
FREEDOMS	96	2	FINGO 0.5 mg, QD	425	80	425	80	1.42
FREEDOMS II	96	1	Placebo	355	123	355	123	1.42
FREEDOMS II	96	2	FINGO 0.5 mg, QD	358	116	358	116	1.42
IFNB MS	96	1	Placebo	123	23	123	23	1.42
IFNB MS	96	2	SC IFNB-1b 250 mcg, EOD	124	24	124	24	1.42
INCOMIN	96	1	IM IFNB-1a 30 mcg, QW	92	15	92	15	1.42
INCOMIN	96	2	SC IFNB-1b 250 mcg, EOD	96	9	96	9	1.42
MSCRG	96	1	Placebo	143	9	143	9	1.42
MSCRG	96	2	IM IFNB-1a 30 mcg, QW	158	14	158	14	1.42
OPERA I	96	1	SC IFNB-1a 44 mcg, TIW	411	71	411	71	1.42
OPERA I	96	2	OCR 600 mg	410	44	410	44	1.42
OPERA II	96	1	SC IFNB-1a 44 mcg, TIW	418	98	418	98	1.42
OPERA II	96	2	OCR 600 mg	417	57	417	57	1.42
PRISMS	96	1	Placebo	187	17	187	17	1.42
PRISMS	96	2	SC IFNB-1a 22 mcg, TIW	189	22	189	22	1.42
PRISMS	96	3	SC IFNB-1a 44 mcg, TIW	184	19	184	19	1.42
REGARD	96	1	SC IFNB-1a 44 mcg, TIW	386	80	386	80	1.42
REGARD	96	2	GA 20 mg, QD	378	51	378	51	1.42
SELECT	52	1	Placebo	204	18	204	18	-42.58
SELECT	52	2	DAC 150 mg , Q4W	208	19	208	19	-42.58
TEMSO	96	1	Placebo	363	104	363	104	1.42
TEMSO	96	2	TERI 7 mg, QD	365	91	365	91	1.42
TEMSO	96	3	TERI 14 mg, QD	358	95	358	95	1.42
TENERE	115	1	SC IFNB-1a 44 mcg, TIW	104	30	104	30	20.42
TENERE	115	2	TERI 7 mg, QD	109	20	109	20	20.42
TENERE	115	3	TERI 14 mg, QD	111	22	111	22	20.42

				Reported Data		Derived Data used in NMA		
Trial	**Duration/Timepoint**	**Arm**	**Intervention**	**N**	**n**	**N patients**	**n events**	**Meta Regression Covariate**
TOWER	132	1	Placebo	388	125	388	125	37.42
TOWER	132	2	TERI 7 mg, QD	407	134	407	134	37.42
TOWER	132	3	TERI 14 mg, QD	370	126	370	126	37.42
TRANSFORMS	48	1	IM IFNB-1a 30 mcg, QW	431	45	431	45	-46.58
TRANSFORMS	48	2	FINGO 0.5 mg, QD	429	31	429	31	-46.58

Table 34 Input table for ARR in HA subgroup

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
CARE-MS II	Prior GA therapy: Yes: Sous-groupe des patients issus de l'étude CAMMS324 ayant eu au moins une poussée sous traitement par acétate de glatiramère d'au moins 1 an. Les patients avaient au moins 9 lésions en T2 à l'inclusion.	1	SC IFNB-1a 44 mcg, TIW	0.43	26	96	NA	NA
		2	ALEM 12 mg	0.29	48	96	NA	NA
	Prior Interferon therapy: Yes: Sous-groupe des patients issus de l'étude CAMMS324 ayant eu au moins une poussée sous traitement par interféron β d'au moins 1 an. Les patients avaient au moins 9 lésions en T2 à l'inclusion	1	SC IFNB-1a 44 mcg, TIW	0.55	118	96	NA	NA
		2	ALEM 12 mg	0.2	229	96	NA	NA
	Summed values	1	SC IFNB-1a 44 mcg, TIW	Derived exposure and relapses summed			152.16	288.00
		2	ALEM 12 mg				119.44	554.00
DECIDE	Previously treated with IFNB: Highly active disease or failure to respond to ≥1 year of interferon beta treatment (≥1 relapse in the previous year while on therapy with ≥9 T2 lesions or ≥1 gadolinium-enhancing lesion at baseline, or unchanged/ increased relapse rate in the previous year vs. preceding 2 years.	1	IM IFNB-1a 30 mcg, QW	0.53	386	144	613.74	1158.00
		2	DAC 150 mg , Q4W	0.26	358	144	279.24	1074.00
Pool: FREEDOMS, FREEDOMS II	HAD despite previous DMT: (1) ≥1 relapse in the previous year and either ≥1 gadolinium (Gd) enhancing T1 lesion or ≥9 T2 lesions at baseline	1	Placebo	0.46	257	96	236.44	514.00
		2	FINGO 0.5 mg, QD	0.24	249	96	119.52	498.00

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
	and/or (2) as many or more relapses in the year before baseline as in the previous year.							
Pool: OPERA I, OPERA II	Highly Active Inadequate Responders: Treated with interferon or glatiramer acetate for at least 1 year and – had at least one relapse in the previous year AND – had at least nine T2 hyperintense lesions or at least one T1 Gd-enhancing lesion at baseline	1	SC IFNB-1a 44 mcg, TIW	0.313	140	96	87.64	280.00
		2	OCR 600 mg	0.099	143	96	28.31	286.00
SELECT	Previously treated with IFNB: Highly active disease or failure to respond to ≥1 year of interferon beta treatment (≥1 relapse in the previous year while on therapy with ≥9 T2 lesions or ≥1 gadolinium-enhancing lesion at baseline, or unchanged/ increased relapse rate in the previous year vs. preceding 2 years.	1	Placebo	0.54	37	52	21.64	40.08
		2	DAC 150 mg , Q4W	0.26	46	52	12.96	49.83
TRANSFORMS	Group C: Patients who had been previously treated with interferon in the past year and had at least 1 relapse in the past year and (either at least 1 GD+ lesion at baseline or T2 lesion count >= 9).	2	FINGO 0.5 mg, QD	0.201	160	48	32.16	160.00
		1	IM IFNB-1a 30 mcg, QW	0.514	149	48	76.59	149.00
BEYOND	ITT	1	SC IFNB-1b 250 mcg, EOD	0.36	888 (assumed based on AE reported numbers)	96	639.36	1776.00

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
		3	GA 20 mg, QD	0.34	445 (assumed based on AE reported numbers)	96	302.60	890.00
BRAVO	ITT	1	Placebo	0.34	450	96	306.00	900.00
		2	IM IFNB-1a 30 mcg, QW	0.26	447	96	232.44	894.00
Calabrese 2012	ITT	2	IM IFNB-1a 30 mcg, QW	0.5	47	96	47.00	94.00
		3	SC IFNB-1a 44 mcg, TIW	0.4	46	96	36.80	92.00
		4	GA 20 mg, QD	0.5	48	96	48.00	96.00
CombiRx	ITT	1	IM IFNB-1a 30 mcg, QW	0.16	250	144	120.00	750.00
		2	GA 20 mg, QD	0.11	259	144	85.47	777.00
CONFIRM	ITT	1	Placebo	0.4	363	96	290.40	726.00
		2	GA 20 mg, QD	0.29	350	96	203.00	700.00
Copolymer 1 MS trial	ITT	1	Placebo	0.84	232	96	389.76	464.00
		2	GA 20 mg, QD	0.59	227	96	267.86	454.00
EVIDENCE	ITT	1	IM IFNB-1a 30 mcg, QW	0.65	338	48	219.70	338.00
		2	SC IFNB-1a 44 mcg, TIW	0.54	339	48	183.06	339.00
GALA	ITT	1	Placebo	0.505	461	48	232.81	461.00

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
		2	GA 40 mg, TIW	0.331	943	48	312.13	943.00
IFNB MS	ITT	1	Placebo	1.12	123	240	688.80	615.00
		2	SC IFNB-1b 250 mcg, EOD	0.78	124	240	483.60	620.00
INCOMIN	ITT	1	IM IFNB-1a 30 mcg, QW	0.7	92	96	128.80	184.00
		2	SC IFNB-1b 250 mcg, EOD	0.5	96	96	96.00	192.00
MSCRG	ITT	1	Placebo	0.82	143	96	234.52	286.00
		2	IM IFNB-1a 30 mcg, QW	0.67	158	96	211.72	316.00
REGARD	ITT	1	SC IFNB-1a 44 mcg, TIW	0.3	386	96	231.60	772.00
		2	GA 20 mg, QD	0.29	378	96	219.24	756.00
Stepien 2013	ITT	1	SC IFNB-1b 250 mcg, EOD	0.43	18	144	23.22	54.00
		2	IM IFNB-1a 30 mcg, QW	0.35	20	144	21.00	60.00

Grey highlighting signifies ABCR ITT data applied to connect the subgroup network

Table 35 Input table for ARR in RES subgroup

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
AFFIRM	Patients with HAD: Highly active relapsing MS had ≥ 2 relapses in the year prior to study entry and ≥ 1 Gd+ lesion on T1-weighted MRI at study entry	1	Placebo	1.46	61	96	178.12	122.00
		2	NAT 300 mg, Q4W	0.28	148	96	82.88	296.00
CARE-MS I	Patients with highly active RRMS: Patients with highly active RRMS had >= 2 relapses the year before randomization and >= 1 gadolinium (Gd)-enhancing lesion at baseline.	1	SC IFNB-1a 44 mcg, TIW	0.41	61	96	50.02	122.00
		2	ALEM 12 mg	0.2	105	96	42.00	210.00
CARE-MS II	Highly-active disease: Highly-active patients had >= 2 relapses per year before randomization and >= 1 baseline gadolinium-enhancing lesion. s.	1	SC IFNB-1a 44 mcg, TIW	0.65	42	96	54.60	84.00
		2	ALEM 12 mg	0.33	101	96	66.66	202.00
DECIDE	Patients with HAD: Patients with ≥2 relapses in prior Y and ≥1 Gd+ lesions at BL	1	IM IFNB-1a 30 mcg, QW	0.677	204	96	276.22	408.00
		2	DAC 150 mg , Q4W	0.282	184	96	103.78	368.00
FREEDOMS	Patients with HAD: Patients with ≥2 relapses in prior Y and ≥1 Gd+ lesions at BL	1	Placebo	0.93	63	96	117.18	126.00
		2	FINGO 0.5 mg, QD	0.35	77	96	53.90	154.00
Pool: OPERA I, OPERA II	RES: Had at least two relapses in the last year prior to randomization AND - had at least one baseline T1 Gd-enhancing lesion OR - an increase in T2 hyperintense lesion count at baseline visit	1	SC IFNB-1a 44 mcg, TIW	0.394	140	96	110.32	280.00
		2	OCR 600 mg	0.151	150	96	45.30	300.00

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
	(changing from 0-5 to 6-9, >9 lesions or from 6-9 lesions to > 9 lesions), as compared to the prior (recorded at screening) MRI							
SELECT	Highly active RRMS: Patients with >= 2 relapses in the year before randomization and >= 1 gadolinium-enhancing (Gd+) lesion at baseline.	1	Placebo	0.6	30	52	19.50	32.50
		2	DAC 150 mg , Q4W	0.3	58	52	18.85	62.83
TRANSFORMS	Pat. mit rasch fortschr. RRMS: Patients with rapidly evolving severe RRMS, defined as ≥2 relapses/year and ≥1 Gd-enhancing T1 lesion at baseline	1	IM IFNB-1a 30 mcg, QW	0.303	30	48	9.09	30.00
		2	FINGO 0.5 mg, QD	0.226	27	48	6.10	27.00
BEYOND	ITT	1	SC IFNB-1b 250 mcg, EOD	0.36	888 (assumed based on AE reported numbers)	96	639.36	1776.00
		3	GA 20 mg, QD	0.34	445 (assumed based on AE reported numbers)	96	302.60	890.00
BRAVO	ITT	1	Placebo	0.34	450	96	306.00	900.00
		2	IM IFNB-1a 30 mcg, QW	0.26	447	96	232.44	894.00
Calabrese 2012	ITT	2	IM IFNB-1a 30 mcg, QW	0.5	47	96	47.00	94.00
		3	SC IFNB-1a 44 mcg, TIW	0.4	46	96	36.80	92.00
		4	GA 20 mg, QD	0.5	48	96	48.00	96.00

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
CombiRx	ITT	1	IM IFNB-1a 30 mcg, QW	0.16	250	144	120.00	750.00
		2	GA 20 mg, QD	0.11	259	144	85.47	777.00
CONFIRM	ITT	1	Placebo	0.4	363	96	290.40	726.00
		2	GA 20 mg, QD	0.29	350	96	203.00	700.00
Copolymer 1 MS trial	ITT	1	Placebo	0.84	232	96	389.76	464.00
		2	GA 20 mg, QD	0.59	227	96	267.86	454.00
EVIDENCE	ITT	1	IM IFNB-1a 30 mcg, QW	0.65	338	48	219.70	338.00
		2	SC IFNB-1a 44 mcg, TIW	0.54	339	48	183.06	339.00
GALA	ITT	1	Placebo	0.505	461	48	232.81	461.00
		2	GA 40 mg, TIW	0.331	943	48	312.13	943.00
IFNB MS	ITT	1	Placebo	1.12	123	240	688.80	615.00
		2	SC IFNB-1b 250 mcg, EOD	0.78	124	240	483.60	620.00
INCOMIN	ITT	1	IM IFNB-1a 30 mcg, QW	0.7	92	96	128.80	184.00
		2	SC IFNB-1b 250 mcg, EOD	0.5	96	96	96.00	192.00
MSCRG	ITT	1	Placebo	0.82	143	96	234.52	286.00
		2	IM IFNB-1a 30 mcg, QW	0.67	158	96	211.72	316.00
REGARD	ITT	1	SC IFNB-1a 44 mcg, TIW	0.3	386	96	231.60	772.00
		2	GA 20 mg, QD	0.29	378	96	219.24	756.00
Stepien 2013	ITT	1	SC IFNB-1b 250 mcg, EOD	0.43	18	144	23.22	54.00

				Reported Data			Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**ARR**	**N**	**Duration/Timepoint**	**Relapses**	**Exposure**
		2	IM IFNB-1a 30 mcg, QW	0.35	20	144	21.00	60.00

Grey highlighting signifies ABCR ITT data applied to connect the subgroup network

Table 36 Input table for CDP-12 in HA subgroup

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
Pool: DEFINE, CONFIRM	High disease activity despite pre-treatment: Patients who received IFN for a minimum of 12 months AND had at least 1 relapse on IFN AND >= 9 T2 lesions or unchanged or increased relapse rate	1	Placebo					NA	NA
		2	DMF 240 mg, BID	Hazard Ratio 95% CI Lower Limit	0.66	Hazard Ratio 95% CI Upper Limit	2.15	0.17	0.301
Pool: FREEDOMS, FREEDOMS II	GA1: GA failures (patients previously treated with GA in the 1 year prior to Screening with relapse in the year before Screening and with either at least 1 Gd-enhancing T1 lesion or at least 9 T2 lesions at Baseline)	1	Placebo	N patients	76	% events	38.4 %	NA	NA
		2	FINGO 0.5 mg, QD	N patients	57	% events	15.3 %	NA	NA
	IFN1: IFN failures (patients previously treated with IFN in the 1 year prior to Screening with relapse in the year before Screening and with either at least 1 Gd-enhancing T1 lesion or at least 9 T2 lesions at Baseline)	1	Placebo	N patients	124	% events	24.7 %	NA	NA
		2	FINGO 0.5 mg, QD	N patients	146	% events	22.1 %	NA	NA
	Summed values	1	Placebo	N patients and derived n events summed				NA	NA
		2	FINGO 0.5 mg, QD					-0.45	0.203
Pool: OPERA I, OPERA II	Highly Active Inadequate Responders: Treated with interferon or glatiramer acetate for at least 1 year and – had at least one relapse in the previous year AND – had at least nine T2 hyperintense lesions or at least one T1 Gd-enhancing lesion at baseline	1	SC IFNB-1a 44 mcg, TIW					NA	NA
		2	OCR 600 mg	Hazard Ratio 95% CI Lower Limit	0.23	Hazard Ratio 95% CI Upper Limit	0.95	-0.76	0.362

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
Pool: TEMSO, TOWER	Subgroup B : Patients with disease modifiying therapy (DMT) use in the prior 2 years and either >= 1 relapse in the year before study entry or >= 1 gadolinium enhancing (Gd+) lesion on baseline MRI	1	Placebo					NA	NA
		3	TERI 14 mg, QD	Hazard Ratio	0.535	p-value	0.001	-0.63	0.202
TRANSFORMS	IFN Non - Resp. Def I: IFN Non-Responder, at least 1 relapse/year and >= 9 T2 lesions or presence of Gd-enhancing lesion	1	IM IFNB-1a 30 mcg, QW					NA	NA
		2	FINGO 0.5 mg, QD	Hazard Ratio 95% CI Lower Limit	0.26	Hazard Ratio 95% CI Upper Limit	1.41	-0.50	0.431
BEYOND	ITT	1	SC IFNB-1b 250 mcg, EOD	N patients	888	% events	21	NA	NA
		3	GA 20 mg, QD	N patients	445	% events	20	-0.05	0.129
Bornstein 1987	ITT	1	Placebo	N patients	23	n events	11	NA	NA
		2	GA 20 mg, QD	N patients	25	n events	5	-1.07	0.543
BRAVO	ITT	1	Placebo					NA	NA
		2	IM IFNB-1a 30 mcg, QW	Hazard Ratio 95% CI Lower Limit	0.51	Hazard Ratio 95% CI Upper Limit	1.09	-0.29	0.194
CONFIRM	ITT	1	Placebo					NA	NA
		2	GA 20 mg, QD	Hazard Ratio 95% CI Lower Limit	0.63	Hazard Ratio 95% CI Upper Limit	1.37	-0.07	0.198
Copolymer 1 MS trial	ITT	1	Placebo	N patients	126	% events	24.6	NA	NA
		2	GA 20 mg, QD	N patients	125	% events	21.6	-0.15	0.264

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
EVIDENCE	ITT	1	IM IFNB-1a 30 mcg, QW					NA	NA
		2	SC IFNB-1a 44 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.58	Hazard Ratio 95% CI Upper Limit	1.31	-0.14	0.208
IFNB MS	ITT	1	Placebo	N patients	122	n events	56	NA	NA
		2	SC IFNB-1b 250 mcg, EOD	N patients	122	n events	43	-0.35	0.205
PRISMS	ITT	1	Placebo					NA	NA
		2	SC IFNB-1a 22 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.48	Hazard Ratio 95% CI Upper Limit	0.98	-0.38	0.182
		3	SC IFNB-1a 44 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.43	Hazard Ratio 95% CI Upper Limit	0.91	-0.47	0.191

Grey highlighting signifies ABCR ITT data applied to connect the subgroup network

Table 37 Input table for CDP-12 in RES subgroup

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
AFFIRM	Patients with HAD: Highly active relapsing MS had ≥ 2 relapses in the year prior to study entry and ≥ 1 Gd+ lesion on T1-weighted MRI at study entry	1	Placebo					NA	NA
		2	NAT 300 mg, Q4W	Hazard Ratio 95% CI Lower Limit	0.24	Hazard Ratio 95% CI Upper Limit	0.93	-0.75	0.346
FREEDOMS	Group E: Treatment-naive rapidly evolving severe relapsing-remitting multiple sclerosis: ≥2 relapses within the year before baseline and ≥1 gadolinium-enhancing lesion at baseline	1	Placebo					NA	NA
		2	FINGO 0.5 mg, QD	Hazard Ratio 95% CI Lower Limit	0.25	Hazard Ratio 95% CI Upper Limit	2.07	-0.33	0.539
Pool: DEFINE, CONFIRM	Patients with high disease activity as defined by manufacturer: Patients with at least 2 relapses in prior year, and presence of Gd enhancing lesions; regardless of pre-treatment status	1	Placebo					NA	NA
		2	DMF 240 mg, BID	Hazard Ratio 95% CI Lower Limit	0.47	Hazard Ratio 95% CI Upper Limit	2.6	0.10	0.436
Pool: OPERA I, OPERA II	RES: Had at least two relapses in the last year prior to randomization AND - had at least one baseline T1 Gd-enhancing lesion OR - an increase in T2 hyperintense lesion count at baseline visit (changing from 0-5 to 6-9, >9 lesions or from 6-9 lesions to > 9 lesions), as compared to the prior (recorded at screening) MRI	1	SC IFNB-1a 44 mcg, TIW					NA	NA
		2	OCR 600 mg	Hazard Ratio 95% CI Lower Limit	0.33	Hazard Ratio 95% CI Upper Limit	1.29	-0.43	0.348
SELECT	Highly active RRMS: Patients with >= 2 relapses in the year before randomization and >= 1 gadolinium-enhancing (Gd+) lesion at baseline.	1	Placebo	N patients	30	n events	4	NA	NA
		2	DAC 150 mg , Q4W	N patients	58	n events	1	-2.11	1.118

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
TEMSO	High: Definition of high disease activity: patients with at least 2 relapses in past year and 1 Gd lesion at baseline.	1	Placebo					NA	NA
		2	TERI 7 mg, QD	Hazard Ratio 95% CI Lower Limit	0.247	Hazard Ratio 95% CI Upper Limit	1.508	-0.49	0.462
		3	TERI 14 mg, QD	Hazard Ratio 95% CI Lower Limit	0.264	Hazard Ratio 95% CI Upper Limit	1.592	-0.43	0.458
TRANSFORMS	Pat. mit schnell fortschr. RRMS: Patients with rapidly evolving severe RRMS, defined as ≥2 relapses/year and ≥1 Gd-enhancing T1 lesion at baseline	1	IM IFNB-1a 30 mcg, QW	N patients	30	% events	13.5 %	NA	NA
		2	FINGO 0.5 mg, QD	N patients	27	% events	0 %	-2.18	1.490
BEYOND	ITT	1	SC IFNB-1b 250 mcg, EOD	N patients	888	% events	21	NA	NA
		3	GA 20 mg, QD	N patients	445	% events	20	-0.05	0.129
Bornstein 1987	ITT	1	Placebo	N patients	23	n events	11	NA	NA
		2	GA 20 mg, QD	N patients	25	n events	5	-1.07	0.543
BRAVO	ITT	1	Placebo					NA	NA
		2	IM IFNB-1a 30 mcg, QW	Hazard Ratio 95% CI Lower Limit	0.51	Hazard Ratio 95% CI Upper Limit	1.09	-0.29	0.194
CONFIRM	ITT	1	Placebo					NA	NA
		2	GA 20 mg, QD	Hazard Ratio 95% CI Lower Limit	0.63	Hazard Ratio 95% CI Upper Limit	1.37	-0.07	0.198

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
Copolymer 1 MS trial	ITT	1	Placebo	N patients	126	% events	24.6	NA	NA
		2	GA 20 mg, QD	N patients	125	% events	21.6	-0.15	0.264
EVIDENCE	ITT	1	IM IFNB-1a 30 mcg, QW					NA	NA
		2	SC IFNB-1a 44 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.58	Hazard Ratio 95% CI Upper Limit	1.31	-0.14	0.208
IFNB MS	ITT	1	Placebo	N patients	122	n events	56	NA	NA
		2	SC IFNB-1b 250 mcg, EOD	N patients	122	n events	43	-0.35	0.205
PRISMS	ITT	1	Placebo					NA	NA
		2	SC IFNB-1a 22 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.48	Hazard Ratio 95% CI Upper Limit	0.98	-0.38	0.182
		3	SC IFNB-1a 44 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.43	Hazard Ratio 95% CI Upper Limit	0.91	-0.47	0.191

Grey highlighting signifies ABCR ITT data applied to connect the subgroup network

Table 38 Input table for CDP-24 in HA subgroup

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
CARE-MS II	Prior GA therapy: Yes: Sous-groupe des patients issus de l'étude CAMMS324 ayant eu au moins une poussée sous traitement par acétate de glatiramère d'au moins 1 an. Les patients avaient au moins 9 lésions en T2 à l'inclusion.	1	SC IFNB-1a 44 mcg, TIW	N patients	26	% events	23.08 %	NA	NA
		2	ALEM 12 mg	N patients	48	% events	6.25 %	NA	NA
	Prior Interferon therapy: Yes: Sous-groupe des patients issus de l'étude CAMMS324 ayant eu au moins une poussée sous traitement par interféron β d'au moins 1 an. Les patients avaient au moins 9 lésions en T2 à l'inclusion	1	SC IFNB-1a 44 mcg, TIW	N patients	118	% events	20.3 %	NA	NA
		2	ALEM 12 mg	N patients	229	% events	13.18 %	NA	NA
	Summed values	1	SC IFNB-1a 44 mcg, TIW	N patients and derived n events summed				NA	NA
		2	ALEM 12 mg					-0.60	0.252
DECIDE	Previously treated with IFNB: Highly active disease or failure to respond to ≥1 year of interferon beta treatment (≥1 relapse in the previous year while on therapy with ≥9 T2 lesions or ≥1 gadolinium-enhancing lesion at baseline, or unchanged/ increased relapse rate in the previous year vs. preceding 2 years.	1	IM IFNB-1a 30 mcg, QW					NA	NA
		2	DAC 150 mg , Q4W	Hazard Ratio 95% CI Lower Limit	0.37	Hazard Ratio 95% CI Upper Limit	0.87	-0.57	0.218
Pool: FREEDOMS, FREEDOMS II	HAD despite previous DMT: (1) ≥1 relapse in the previous year and either ≥1 gadolinium (Gd) enhancing T1 lesion or ≥9 T2 lesions at baseline and/or (2) as many or more relapses in the year before baseline as in the previous year.	1	Placebo					NA	NA
		2	FINGO 0.5 mg, QD	Hazard Ratio 95% CI Lower Limit	0.34	Hazard Ratio 95% CI Upper Limit	0.9	-0.59	0.248

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
Pool: OPERA I, OPERA II	Highly Active Inadequate Responders: Treated with interferon or glatiramer acetate for at least 1 year and – had at least one relapse in the previous year AND – had at least nine T2 hyperintense lesions or at least one T1 Gd-enhancing lesion at baseline	1	SC IFNB-1a 44 mcg, TIW					NA	NA
		2	OCR 600 mg	Hazard Ratio 95% CI Lower Limit	0.23	Hazard Ratio 95% CI Upper Limit	1.09	-0.69	0.397
Pool: TEMSO, TOWER	Subgroup B : Patients with disease modifiying therapy (DMT) use in the prior 2 years and either >= 1 relapse in the year before study entry or >= 1 gadolinium enhancing (Gd+) lesion on baseline MRI	1	Placebo					NA	NA
		3	TERI 14 mg, QD	Hazard Ratio	0.598	p-value	0.015	-0.51	0.237
SELECT	Previously treated with IFNB: Highly active disease or failure to respond to ≥1 year of interferon beta treatment (≥1 relapse in the previous year while on therapy with ≥9 T2 lesions or ≥1 gadolinium-enhancing lesion at baseline, or unchanged/ increased relapse rate in the previous year vs. preceding 2 years.	1	Placebo					NA	NA
		2	DAC 150 mg , Q4W	Hazard Ratio 95% CI Lower Limit	0.02	Hazard Ratio 95% CI Upper Limit	2.19	-1.56	1.198
BRAVO	ITT	1	Placebo					NA	NA
		2	IM IFNB-1a 30 mcg, QW	Hazard Ratio 95% CI Lower Limit	0.47	Hazard Ratio 95% CI Upper Limit	1.14	-0.31	0.226
CombiRx	ITT	1	IM IFNB-1a 30 mcg, QW	N patients	241	n events	52	NA	NA

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
		2	GA 20 mg, QD	N patients	246	n events	61	0.16	0.189
CONFIRM	ITT	1	Placebo					NA	NA
		2	GA 20 mg, QD	Hazard Ratio 95% CI Lower Limit	0.55	Hazard Ratio 95% CI Upper Limit	1.38	-0.14	0.235
EVIDENCE	ITT	1	IM IFNB-1a 30 mcg, QW					NA	NA
		2	SC IFNB-1a 44 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.39	Hazard Ratio 95% CI Upper Limit	1.25	-0.36	0.297
MSCRG	ITT	1	Placebo	N patients	143	% events	34.9	NA	NA
		2	IM IFNB-1a 30 mcg, QW	N patients	158	% events	21.9	-0.55	0.222
REGARD	ITT	1	SC IFNB-1a 44 mcg, TIW	N patients	386	n events	45	NA	NA
		2	GA 20 mg, QD	N patients	378	n events	33	-0.31	0.229

Grey highlighting signifies ABCR ITT data applied to connect the subgroup network

Table 39 Input table for CDP-24 in RES subgroup

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
AFFIRM	Rapidly Evolving Severe (RES): Patients with 2 or more relapses and 1 or more Gd-enhancing lesions	1	Placebo					NA	NA
		2	NAT 300 mg, Q4W	Hazard Ratio 95% CI Lower Limit	0.17	Hazard Ratio 95% CI Upper Limit	0.76	-1.02	0.382
CARE-MS II	Highly-active disease: Highly-active patients had >= 2 relapses per year before randomization and >= 1 baseline gadolinium-enhancing lesion. s.	1	SC IFNB-1a 44 mcg, TIW	N patients	42	% events	22.4 %	NA	NA
		2	ALEM 12 mg	N patients	101	% events	13.7 %	-0.54	0.423
Pool: OPERA I, OPERA II	RES: Had at least two relapses in the last year prior to randomization AND - had at least one baseline T1 Gd-enhancing lesion OR - an increase in T2 hyperintense lesion count at baseline visit (changing from 0-5 to 6-9, >9 lesions or from 6-9 lesions to > 9 lesions), as compared to the prior (recorded at screening) MRI	1	SC IFNB-1a 44 mcg, TIW					NA	NA
		2	OCR 600 mg	Hazard Ratio 95% CI Lower Limit	0.31	Hazard Ratio 95% CI Upper Limit	1.22	-0.49	0.349
BRAVO	ITT	1	Placebo					NA	NA
		2	IM IFNB-1a 30 mcg, QW	Hazard Ratio 95% CI Lower Limit	0.47	Hazard Ratio 95% CI Upper Limit	1.14	-0.31	0.226
CombiRx	ITT	1	IM IFNB-1a 30 mcg, QW	N patients	241	n events	52	NA	NA
		2	GA 20 mg, QD	N patients	246	n events	61	0.16	0.189
CONFIRM		1	Placebo					NA	NA

				Reported Data					
				Source 1		Source 2		Derived Data used in NMA	
Trial	**Subgroup Definition**	**Arm**	**Intervention**	**Type**	**Value**	**Type**	**Value**	**log(HR)**	**SE(log(HR))**
	ITT	2	GA 20 mg, QD	Hazard Ratio 95% CI Lower Limit	0.55	Hazard Ratio 95% CI Upper Limit	1.38	-0.14	0.235
EVIDENCE	ITT	1	IM IFNB-1a 30 mcg, QW					NA	NA
		2	SC IFNB-1a 44 mcg, TIW	Hazard Ratio 95% CI Lower Limit	0.39	Hazard Ratio 95% CI Upper Limit	1.25	-0.36	0.297
MSCRG	ITT	1	Placebo	N patients	143	% events	34.9	NA	NA
		2	IM IFNB-1a 30 mcg, QW	N patients	158	% events	21.9	-0.55	0.222
REGARD	ITT	1	SC IFNB-1a 44 mcg, TIW	N patients	386	n events	45	NA	NA
		2	GA 20 mg, QD	N patients	378	n events	33	-0.31	0.229

Grey highlighting signifies ABCR ITT data applied to connect the subgroup network

Related to Question A16 (d)

Table 40 Summary table for ARR: definition of outcome, definition of relapse and time point of assessment

Study ID	Time point	Definition of outcome in study	Relapse definition
ADVANCE	48 weeks	Annualized relapse rate: total number of relapses divided by patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis drugs	New or recurrent neurological symptoms not associated with fever or infection, lasting for at least 24 h, accompanied by new objective neurological findings confirmed by the independent neurological evaluation committee, and separated from the onset of other confirmed relapses by at least 30 days.
AFFIRM	48 and 96 weeks (reported as 1 and 2 years)	Annualized relapse rate: Total number of relapses divided by the total number of patient-years followed for each treatment group. Relapses that occurred after sustained progression of disability was reached and rescue treatment was initiated (per protocol) were censored	New or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurologic signs found by the examining neurologist.
BEYOND	96 weeks	Annualized relapsed rate	New or recurrent neurological abnormalities that were separated by at least 30 days from the onset of the preceding event, lasted at least 24 h, and occurred without fever or infection.
BRAVO	96 weeks (reported as 24 months)	Annualized relapse rate estimated from primary endpoint cumulative number of confirmed relapses on-study	The appearance of one or more new neurological abnormalities, or reappearance of one or more previously observed neurological abnormalities, in the absence of fever, persisting for $\geq$48 h, preceded by >30 days of a stable or improving condition, and accompanied by at least one of the following: an increase of at least 0.5 point in EDSS score, an increase of one grade in the score of two of the seven functional systems on the EDSS, or an increase of two grades in one functional systems.

Study ID	Time point	Definition of outcome in study	Relapse definition
Calabrese (2012)	96 weeks (reported as 2 years)	Annualized relapse rate	NR
CAMMS223	144 weeks (reported as 36 months)	Annualized relapse rate	New or worsening symptoms with an objective change in neurologic examination attributable to MS that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability.
CARE-MS I	96 weeks (reported as 24 months)	Yearly relapse rate	New or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater.
CARE-MS II	48 weeks (reported as 1 year)	Yearly relapse rate	New or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater.
CLARITY	96 weeks	Annualized relapse rate.	An increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement.
CombiRx	144 weeks (results refer to	Annualized relapse rate - protocol defined exacerbations	The appearance of a new symptom or worsening of an old symptom, attributable to MS; accompanied by a change in the neurologic examination (demonstrated by a 0.5 or greater increase in the EDSS or a 2 point change in one functional system or a 1 point change on two functional systems, excluding bladder and cognitive changes); lasting at least 24 hours in the absence of

Study ID	Time point	Definition of outcome in study	Relapse definition
	36 months)		fever; preceded by stability or improvement for at least 30 days; and confirmed by the examining physician within 7 days of onset.
CONFIRM	96 weeks (reported at 2 years)	Annualized relapse rate	New or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days that were confirmed by the independent neurologic evaluation committee.
Copolymer 1 MS trial	96 weeks (reported as 24 months)	Annualized relapse rate	Objective changes on the neurologic examination consistent with an increase of at least a half a step on the EDSS, two points on one of the seven functional systems, or one point on two or more of the functional systems. Events associated with fever were excluded.
DECIDE	144 weeks	Annualized relapse rate over a period of 144 weeks	New or recurrent neurologic symptoms that were not associated with fever or infection and that lasted at least 24 hours; the symptoms had to be accompanied by new objective neurologic findings on examination by the examining neurologist that were confirmed by the independent neurologic evaluation committee.
DEFINE	96 weeks	Annualized relapse rate	New or recurrent neurologic symptoms, not associated with fever or infection that lasted for at least 24 hours and that were accompanied by new objective neurologic findings.
Etemadifar (2006)	96 weeks	Mean relapse rate	Acute relapse: Appearance of a new neurologic symptom, or severe deterioration in a pre-existing symptom that lasted for at least 24 h causing the deterioration in the EDSS with 1 point. Assessment of the course of the disease was made by monitoring the relapse rate and change in the EDSS score.
EVIDENCE	48 weeks	Annualized relapse rate	Appearance of a new symptom or worsening of an old symptom, accompanied by an appropriate objective finding on neurologic examination by the blinded evaluator, lasting at least 24 hours in the absence of fever and preceded by at

Study ID	Time point	Definition of outcome in study	Relapse definition
			least 30 days of clinical stability or improvement. An objective finding was defined as an abnormality on examination that was consistent with the reported neurologic symptom. A relapse was recorded only if the blinded evaluator described new findings consistent with the patient's reported symptoms, and if the treating physician had excluded the possibility of a pseudo-relapse.
FREEDOMS	96 weeks (reported at 24 months)	Annualized relapse rate - defined as the number of confirmed relapses per year	Increase of at least half a point in the EDSS score, of one point in each of two EDSS functional system scores, or of two points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems).
FREEDOMS II	96 weeks (reported at 24 months)	Annualized relapse rate	Increase of at least half a step (0·5) on the EDSS, an increase of 1 point on two different functional systems of the EDSS, or 2 points on one of the functional systems (excluding bowel, bladder, or cerebral functional systems).
GALA	48 (reported as 12 months)	Annualized relapse rate.	Appearance of 1 new neurological abnormality or the reappearance of 1 previously observed neurological abnormalities lasting at least 48 hours and preceded by an improving neurological state of at least 30 days from the onset of previous relapse accompanied by neurological changes consistent with an increase of 0.5 points in the EDSS score compared with previous evaluation, or an increase of 1 grade in the actual score of 2 or more of the 7 Functional Systems; or an increase of 2 grades in the score of 1 Functional Systems, compared with the previous assessment.
IFNB MS	48, 96, 144 and 240 weeks	Exacerbation rate	Appearance of a new symptom or worsening of an old symptom, attributable to MS and an appropriate new neurologic abnormality; lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days.
INCOMIN	96 weeks	Annualized relapse rate	Score of three or more in at least one, or of two in at least three, KFSS.

Study ID	Time point	Definition of outcome in study	Relapse definition
MSCRG	96 weeks (reported as 104 weeks)	Annual exacerbation rates (per patient year) - all patients	Exacerbations: Appearance of new neurological symptoms or worsening of pre-existing neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days accompanied by objective change on neurological examination (worsening of 0.5 point on the EDSS or a worsening by $\geq$ 1 .0 point on the pyramidal, cerebellar, brainstem, or visual functional system scores).
OPERA I	96 weeks	Annualized relapse rate - The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment. Adjusted by Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. ROW). Log-transformed exposure time is included as an offset variable.	Occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of least 30 days. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, or adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS score, or 2 points on one of the appropriate FSS, or 1 point on two or more of the appropriate FSS.
OPERA II	96 weeks	Annualized relapse rate - The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment. Adjusted by Baseline EDSS (<4.0 vs. >=4.0) and Geographical Region (US vs. ROW). Log-transformed exposure time is included as an offset variable.	Occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of least 30 days. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, or adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS score, or 2 points on one of the appropriate FSS, or 1 point on two or more of the appropriate FSS.
REGARD	96 weeks	Annualized relapse rate	New or worsening neurological symptoms, without fever, that lasted for 48 h or more and was accompanied by a change in EDSS, KFSS (Non-qualifying relapses met the same criteria but were not accompanied by a change in the

Study ID	Time point	Definition of outcome in study	Relapse definition
			KFSS). For relapse outcomes, all relapses (qualifying and non-qualifying) were counted.
SELECT	52 weeks	Annualized relapse rate	New or recurrent neurological symptoms (not associated with fever or infection) lasting 24 h or more, accompanied by new neurological findings at assessment by the examining neurologist.
Stepien (2013)	144 weeks (reported as 3 years)	Annual rate of relapses for the 3-year therapy period	Emergence of a 'new' neurological symptom or a worsening of a pre-existing symptom for at least 24 h that could be attributed to MS and was preceded by improvement or no change in neurological status lasting for at least 30 days.
TEMSO	96 weeks (reported as 108 weeks)	Adjusted annualized rate	Appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of fever. Confirmed relapses required an increase of 1 point in each of two EDSS functional-system scores or of 2 points in one EDSS functional-system score (excluding bowel and bladder function and cerebral function) or an increase of 0.5 points in the EDSS score from the previous clinically stable assessment.
TENERE	96 weeks	Adjusted annualized rate - number of confirmed relapses during the treatment period per patient-year, adjusted for treatment duration, treatment group, region of enrolment and baseline EDSS stratum as covariates.	A 1-point increase in each of two Functional Systems, a 2-point increase in at least one Functional System (excluding bowel/bladder and cerebral) or an increase of ≥0.5 points in EDSS score from the previous stable assessment.
TOWER	up to 152 weeks	Annualized relapse rate.	New or worsening clinical signs or symptoms lasting at least 24 h without fever. Protocol-defined relapses constituted an increase of either 1 point in at least two EDSS functional system scores, or 2 points in one EDSS functional system

Study ID	Time point	Definition of outcome in study	Relapse definition
			score, or 0·5 points in total EDSS score from a previous clinically stable assessment.
TRANSFORMS	48 weeks (reported as 12 months)	Annualized relapse rate - defined as the number of confirmed relapses during a 12-month period.	New, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and that were accompanied by an increase of at least half a point on the EDSS or an increase of at least one point in two functional-systems scores or of at least two points in one functional-system score (excluding changes in bowel or bladder function and cognition). Potential relapses triggered an unscheduled visit and were confirmed by the treating neurologist on the basis of blinded examination by the examining neurologist.

Related to Question A18

Table 41 Summary table for CDP-12: definition of outcome and time point of assessment in trials reporting CDP-12

Study ID	Time point	Definition of CDP
ADVANCE	48 weeks	≥ 1.0 point increase of EDSS from a baseline score of 1.0 or more for 12 weeks, or an increase of at least 1.5 points for patients with a baseline score of 0, sustained for 12 weeks
AFFIRM	96 weeks (reported as 2 years)	Cumulative probability of progression. Sustained disability progression was defined as an increase of 1.0 point or more in scores on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 points or more from a baseline score of 0 that was sustained for 12 weeks.
BEYOND	96 weeks (assumed 2 years)	Confirmed EDSS progression (year 2), measured as a 1-point change in the score that was sustained for 3 months (Kaplan Meier estimate)
Bornstein (1987)	96 weeks	Based on Kurtzke scale, progression defined as an increase of at least one unit in the Kurtzke score and had to be maintained for at least three months
BRAVO	96 weeks (reported as 24 months)	EDSS progression confirmed at 3 months. Disability progression was defined as a 1.0 point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5 point increase if baseline score was 5.5, sustained for 3 months.
CAMMS223	144 weeks	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more for 3 months
CLARITY	96 weeks	Inverse of patients without a 3-mo sustained change in EDSS score (sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0). HR is the time to 3-mo sustained change in EDSS
CONFIRM	96 weeks	Disability progression was defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later
Copolymer 1 MS trial	96 weeks (reported as 24 months)	Defined as an increase of at least one EDSS steps maintained for more than 90 days.
DECIDE	144 weeks	Defined as an increase of at least 1.0 point from a baseline score of at least 1.0 or an increase of at least 1.5 points

Study ID	Time point	Definition of CDP
		from a baseline score of 0 on the EDSS that was confirmed at 12 weeks. Estimated percent
DEFINE	96 weeks	Disability progression was defined as at least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks.
EVIDENCE	48 weeks	EDSS progression by one point on the EDSS scale at 2 consecutive visits 3 months apart
FREEDOMS	96 weeks (reported at 24 months)	Confirmed disability progression, defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression. Inverse calculated from the reported absence of disability progression
FREEDOMS II	96 weeks (reported as 24 months)	Percentage of patients without disability progression confirmed at 3 months. (1 point EDSS change [0·5 point if baseline EDSS was >5·0]) confirmed at 3 months for up to 24 months. Inverse calculated from the reported percentage of patients without disability progression
IFNB MS	144 and 240 weeks	A persistent increase of one or more EDSS points confirmed on two consecutive evaluations separated by at least three months
OPERA I	96 weeks	Disability progression was defined as an increase in the EDSS score of: ≥ 1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5 or ≥ 0.5 point from the baseline EDSS score when the baseline score was > 5.5. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening. The initial event of neurological worsening had to occur during the 96-week, double-blind, double-dummy treatment period.
OPERA II	96 weeks	Disability progression was defined as an increase in the EDSS score of: ≥ 1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5 or ≥ 0.5 point from the baseline EDSS score when the baseline score was > 5.5. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening. The initial event of neurological worsening had to occur during the 96-week, double-blind, double-dummy treatment period.

Study ID	Time point	Definition of CDP
PRISMS	96 weeks	Time to confirmed progression. Progression in disability defined as an increase in EDSS of at least one point sustained over at least three months
SELECT	52 weeks	A 1.0 point increase in EDSS for a baseline EDSS score of 1.0, or a 1.5 point increase for a baseline score of 0 that was sustained for 12 weeks
TEMSO	96 weeks (reported as 108 weeks)	Sustained disability progression > 12 weeks - defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks.
TOWER	96 weeks (reported as 108 weeks)	Proportion of patients with sustained disability, defined as an EDSS score increase of at least 1 EDSS point sustained for a minimum of 12 weeks
TRANSFORMS	48 weeks (reported as 12 months)	Patients with confirmed disability progression calculated from the inverse of the percentage of patients with no confirmed disability progression. Progression of disability was defined as a one-point increase in the EDSS score (or a half-point increase for patients with a baseline score ≥5.5) that was confirmed 3 months later in the absence of relapse.

Table 42 Summary table for CDP-24: definition of outcome and time point of assessment in trials reporting CDP-24

Study ID	Time point	Definition of CDP
ADVANCE	48 weeks	Sustained 24-week confirmed disability progression (disability progression measured by ≥1.0-point increase in EDSS from baseline EDSS ≥1.0,or a ≥1.5-point increase from baseline EDSS=0, that is sustained for ≥24 weeks)
AFFIRM	96 weeks (reported as 2 years)	The sensitivity analysis of progression of disability that was sustained for 24 weeks
BRAVO	96 weeks (reported as 24 months)	Confirmed worsening of EDSS scores sustained for 6 months
CAMMS223	96 and 144 weeks	Sustained accumulation of disability was defined as a one-point increase in EDSS score if baseline EDSS was greater than 0 (or a 1·5 point increase if baseline EDSS was 0) sustained for a continuous 6-month period.
CARE-MS I	96 weeks (reported as 24 months)	Sustained accumulation of disability was defined as an increase from baseline of at least one EDSS point (or >=1.5 points if baseline EDSS score was 0) confirmed over 6 months

Study ID	Time point	Definition of CDP
CARE-MS II	96 weeks (reported as 24 months)	Sustained accumulation of disability was defined as a decrease from baseline by at least one EDSS point confirmed over 6 months for patients with baseline EDSS scores of at least 2·0.
CLARITY	96 weeks	Time to 6 month confirmed EDSS progression (sustained increase of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0)
CombiRx	144 weeks (results refer to 36 months)	Confirmed progression in a participant was defined as a 1.0 increase in the EDSS from baseline, when baseline <= 5.0; or an increase of 0.5 from baseline, when baseline >= 5.5, sustained for 6 months (2 successive quarterly visits).
CONFIRM	96 weeks	24-week confirmed disability progression
DECIDE	144 weeks	6-Month Confirmed Disability progression as measured by EDSS -Defined as an increase of at least 1.0 point from a baseline score of at least 1.0 or an increase of at least 1.5 points from a baseline score of 0 on the EDSS that was confirmed at 12 weeks. Estimated percent
DEFINE	96 weeks	Time to confirmed (24-week) disability progression
EVIDENCE	48 weeks	Disability was defined as progression by one point on the EDSS scale confirmed at a visit 6 months later without an intervening EDSS value that would not meet the criteria for progression
FREEDOMS	96 weeks (reported at 24 months)	Confirmed disability progression, defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 6 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression. Inverse calculated from the reported absence of disability progression
FREEDOMS II	96 weeks (reported at 24 months)	Percentage of patients without disability progression confirmed at 3 months. (1 point EDSS change [0·5 point if baseline EDSS was >5·0]) confirmed at 6 months for up to 24 months. Inverse calculated from percentage of patients without disability progression
INCOMIN	96 weeks	An increase in EDSS of at least one point sustained for at least 6 months and confirmed at the end of follow-up
MSCRG	96 weeks (reported as 104 weeks)	Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months.
OPERA I	96 weeks	Disability progression was defined as an increase in the EDSS score of: ≥ 1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5 or ≥ 0.5 point from the baseline EDSS score when the baseline score was > 5.5. Disability progression was considered confirmed when the increase in the EDSS was

Study ID	Time point	Definition of CDP
		confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening. The initial event of neurological worsening had to occur during the 96-week, double-blind, double-dummy treatment period.
OPERA II	96 weeks	Disability progression was defined as an increase in the EDSS score of: ≥ 1.0 point from the baseline EDSS score when the baseline score was ≤ 5.5 or ≥ 0.5 point from the baseline EDSS score when the baseline score was > 5.5. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening. The initial event of neurological worsening had to occur during the 96-week, double-blind, double-dummy treatment period.
REGARD	96 weeks	Disability progression at the 6-month follow-up visit was confirmed as follows: if the EDSS score at baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5−4.5 at baseline, then a change of 1.0 point or more was required; and if the EDSS at baseline was 5 points or more, then the change required was 0.5 points or more
SELECT	52 weeks	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 52
TEMSO	96 weeks (reported as 108 weeks)	Time to disability progression (sustained for 24 weeks)-defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5)
TOWER	96 weeks (reported as 108 weeks)	Time to disability progression (sustained for 24 weeks)-defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5)

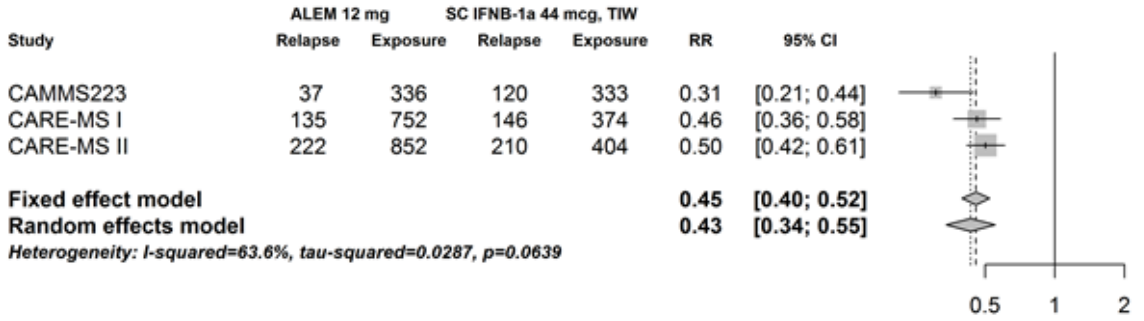
Related to Question A20 (a)

For the ARR network, there were 13 pairwise comparisons that were informed by at least two trials. Forest plots for these comparisons are illustrated below. Heterogeneity could not be evaluated for the 14 comparisons that were only informed by one trial and there were 109 comparisons that were not informed by any trials.

Based on the I2 statistic, most of the comparisons had low or low to moderate heterogeneity. Four comparisons had moderate to high heterogeneity:

- alemtuzumab versus IFNB-1a (Rebif),
- glatiramer acetate versus IFNB-1a (Avonex),
- IFNB-1b versus IFNB-1a (Avonex), and
- teriflunomide 14 mg versus teriflunomide 7 mg.

Heterogeneity assessment for ARR: alemtuzumab vs IFNB-1a (Rebif)

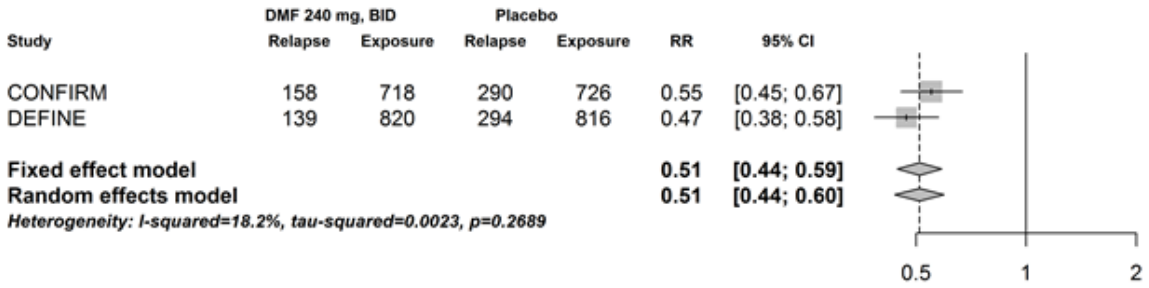


Potential sources of heterogeneity - alemtuzumab vs IFNB-1a (Rebif)

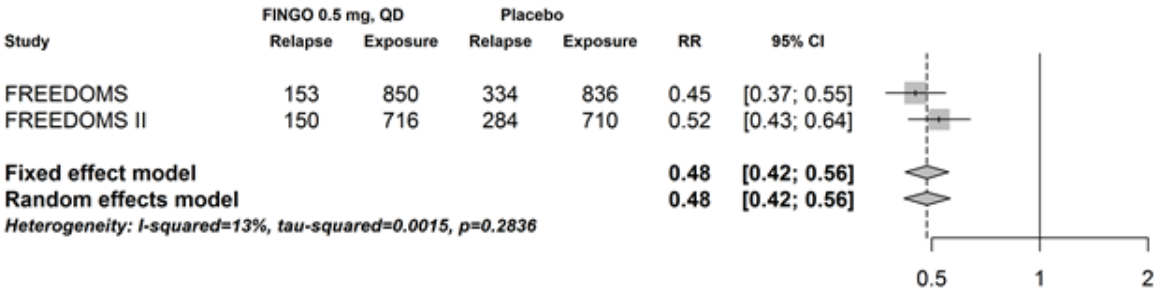
The rate ratios from CARE-MS I and CARE-MS II are similar. CAMMS223 suggested a lower rate ratio.

For CARE-MS I and CARE-MS II ARR was measured over 2 years. For CAMMS223, ARR was measured over 3 years.

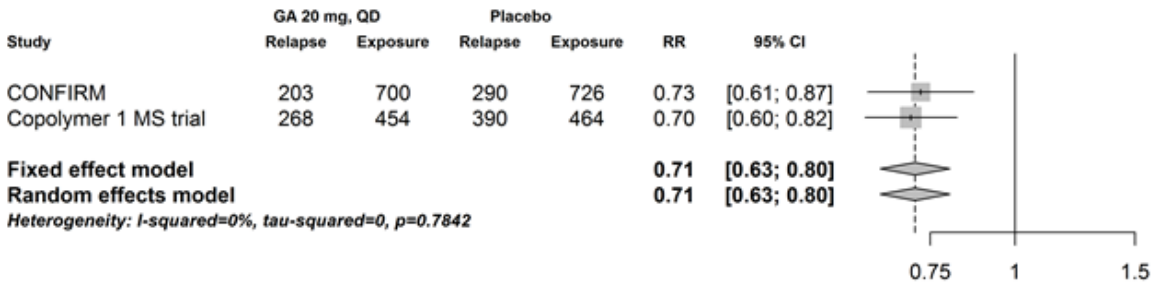
Heterogeneity assessment for ARR: dimethyl fumarate vs placebo



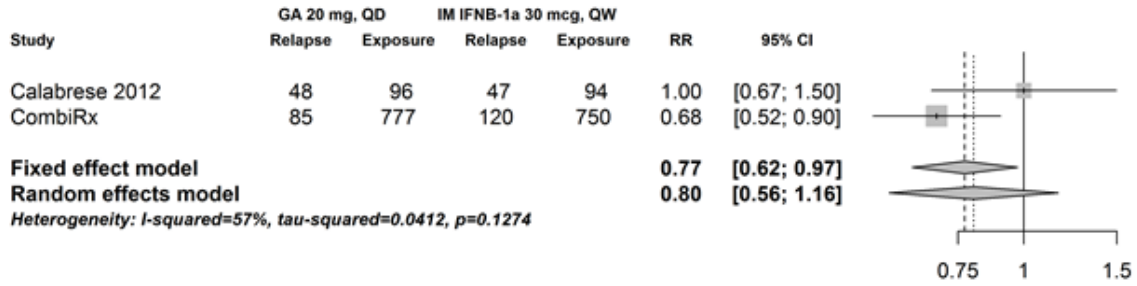
Heterogeneity assessment for ARR: fingolimod vs placebo



Heterogeneity assessment for ARR: glatiramer acetate vs placebo



Heterogeneity assessment for ARR: glatiramer acetate) vs IFNB-1a (Avonex)

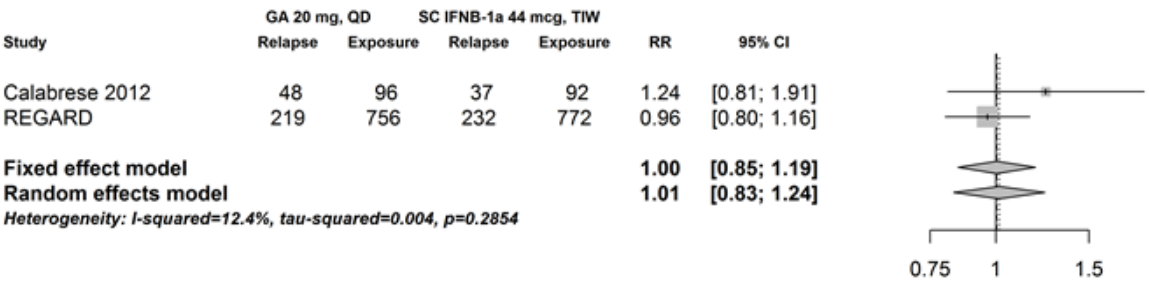


<u>Potential sources of heterogeneity - glatiramer acetate vs IFNB-1a (Avonex)</u>
CombiRx suggested that patients who receive glatiramer acetate 20 mg (QD) have fewer relapses than patients who receive Avonex 30 mcg (QW). However Calabrese 2012 suggested no evidence of a difference between the treatments.

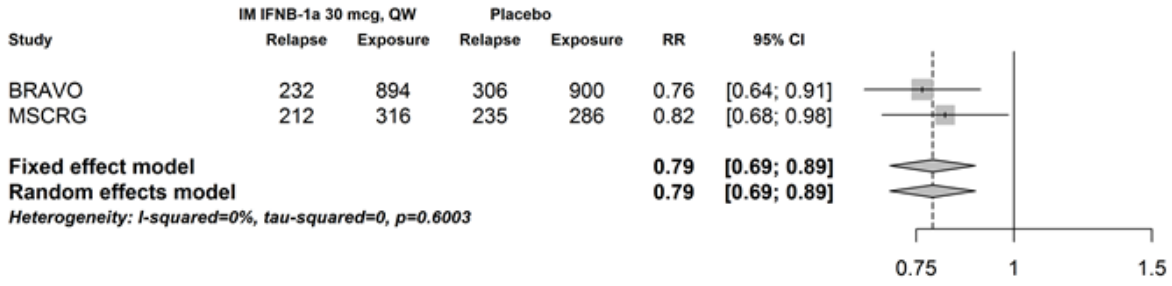
CombiRx measured ARR over 3 years, whereas Calabrese 2012 only evaluated ARR over 2 years.

Calabrese 2012 did not report the criteria they used to define a relapse.

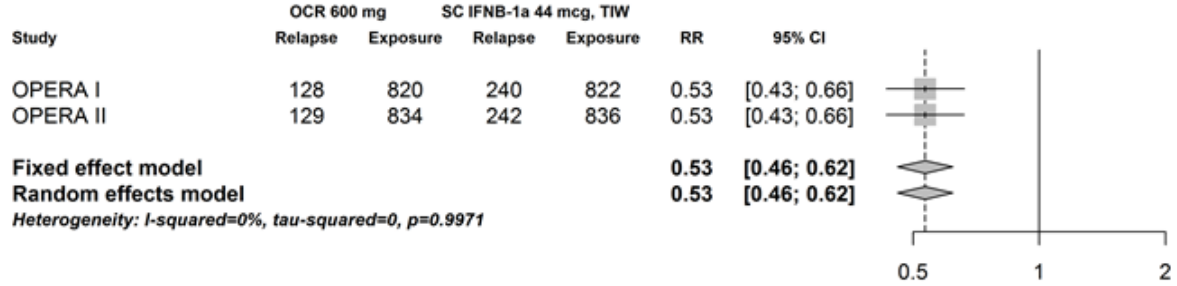
Heterogeneity assessment for ARR: glatiramer acetate vs IFNB-1a (Rebif)



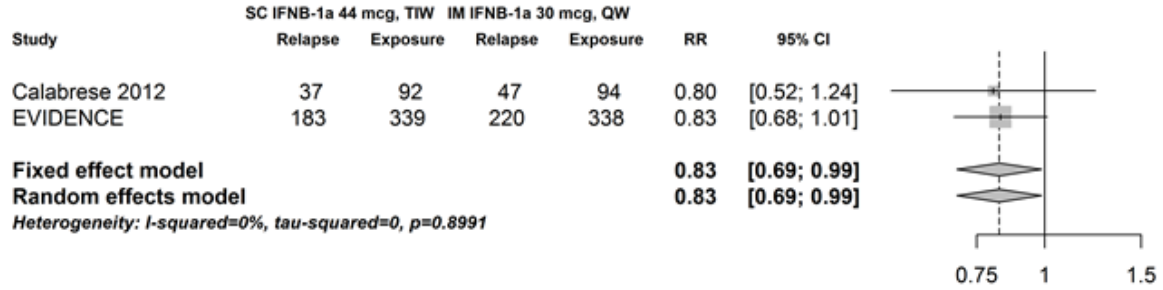
Heterogeneity assessment for ARR: IFNB-1a (Avonex) vs placebo



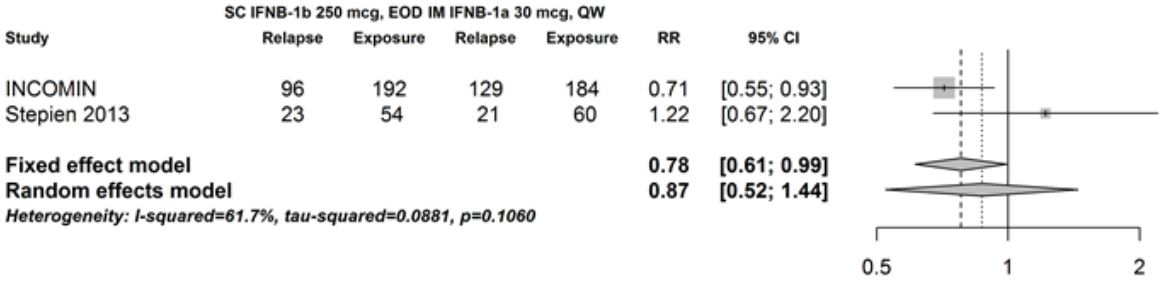
Heterogeneity assessment for ARR: ocrelizumab vs IFNB-1a (Rebif)



Heterogeneity assessment for ARR: IFNB-1a (Rebif) vs IFNB-1a (Avonex)



Heterogeneity assessment for ARR: IFNB-1b vs IFNB-1a (Avonex)



Potential sources of heterogeneity - IFNB-1b vs IFNB-1a (Avonex)

INCOMIN suggested that patients who receive subcutaneous interferon beta-1b 250 mcg (EOD) have fewer relapses than patients who receive Avonex 30 mcg (QW). Stepien 2013 suggested no evidence of a difference between the treatments.

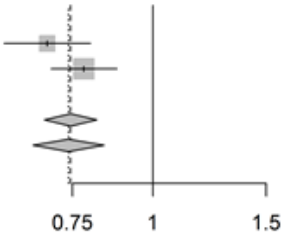
INCOMIN measured ARR over 96 weeks whilst Stepien 2013 measured it over 144 weeks. The studies used different definitions of relapse.

For CDP at 24 weeks, the INCOMIN trial results are widely considered outlier results by most clinical experts.

Heterogeneity assessment for ARR: teriflunomide 7 mg vs placebo

Study	TERI 7 mg, QD Relapse	TERI 7 mg, QD Exposure	Placebo Relapse	Placebo Exposure	RR	95% CI
TEMSO	270	730	392	726	0.69	[0.59; 0.80]
TOWER	503	1289	614	1229	0.78	[0.69; 0.88]
Fixed effect model					**0.74**	**[0.68; 0.82]**
Random effects model					**0.74**	**[0.65; 0.84]**

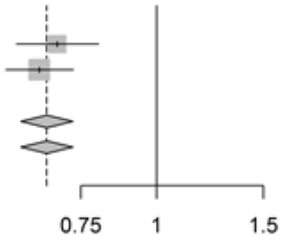
Heterogeneity: I-squared=42.7%, tau-squared=0.0037, p=0.1864



Heterogeneity assessment for ARR: teriflunomide 14 mg vs placebo

Study	TERI 14 mg, QD Relapse	TERI 14 mg, QD Exposure	Placebo Relapse	Placebo Exposure	RR	95% CI
TEMSO	265	716	392	726	0.69	[0.59; 0.80]
TOWER	375	1172	614	1229	0.64	[0.56; 0.73]
Fixed effect model					**0.66**	**[0.60; 0.73]**
Random effects model					**0.66**	**[0.60; 0.73]**

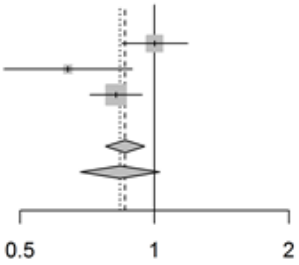
Heterogeneity: I-squared=0%, tau-squared=0, p=0.5099



Heterogeneity assessment for ARR: teriflunomide 14 mg vs teriflunomide 7 mg

Study	TERI 14 mg, QD Relapse	TERI 14 mg, QD Exposure	TERI 7 mg, QD Relapse	TERI 7 mg, QD Exposure	RR	95% CI
TEMSO	265	716	270	730	1.00	[0.84; 1.19]
TENERE	58	222	89	218	0.64	[0.46; 0.89]
TOWER	375	1172	503	1289	0.82	[0.72; 0.94]
Fixed effect model					**0.86**	**[0.78; 0.95]**
Random effects model					**0.84**	**[0.68; 1.03]**

Heterogeneity: I-squared=69.8%, tau-squared=0.0217, p=0.0364



<u>*Potential sources of heterogeneity - teriflunomide 14 mg vs teriflunomide 7 mg*</u>

TENERE and TOWER suggested that patients who receive teriflunomide 14 mg (QD) experience fewer relapses than patient who receive teriflunomide 7 mg (QD). TEMSO found no evidence of a difference between the treatments.

It is unclear what factors may have contributed to the heterogeneity in this comparison. Neither the definition of relapse nor the time period appeared to explain the heterogeneity. The studies used similar definitions of relapse. ARR was measured over a longer period for TOWER (152 weeks) compared to TEMSO (108 weeks) and TENERE (96 weeks), however the rate ratio result from TOWER is intermediate to the other results.

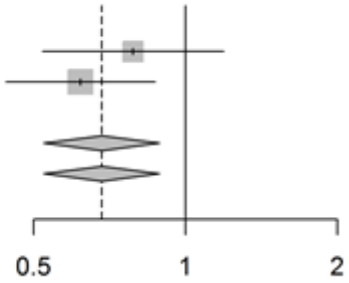
For the CDP-12 network, there were 7 pairwise comparisons that were informed by at least two trials. Forest plots for these comparisons are illustrated below. Heterogeneity could not be evaluated for the 17 comparisons that were only informed by one trial and there were 112 comparisons that were not informed by any trials.

Based on the I2 statistic, all of the comparisons had low, or low to moderate heterogeneity.

Heterogeneity assessment for CDP-12: dimethyl fumarate vs placebo

Study	log(HR)	Std. Error	HR	95% CI
CONFIRM	-0.24	0.2112	0.79	[0.52; 1.19]
DEFINE	-0.48	0.1739	0.62	[0.44; 0.87]
Fixed effect model			**0.68**	**[0.52; 0.89]**
Random effects model			**0.68**	**[0.52; 0.89]**

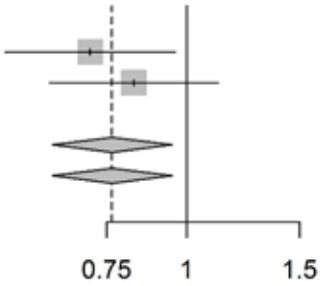
Heterogeneity: I-squared=0%, tau-squared=0, p=0.3801



Heterogeneity assessment for CDP-12: fingolimod vs placebo

Study	log(HR)	Std. Error	HR	95% CI
FREEDOMS	-0.35	0.1564	0.70	[0.52; 0.96]
FREEDOMS II	-0.19	0.1550	0.83	[0.61; 1.12]
Fixed effect model			**0.76**	**[0.62; 0.95]**
Random effects model			**0.76**	**[0.62; 0.95]**

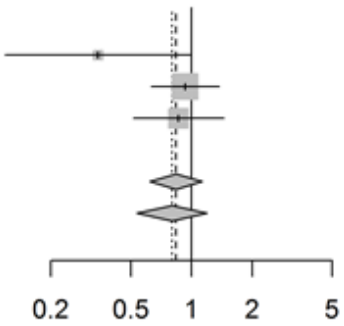
Heterogeneity: I-squared=0%, tau-squared=0, p=0.4762



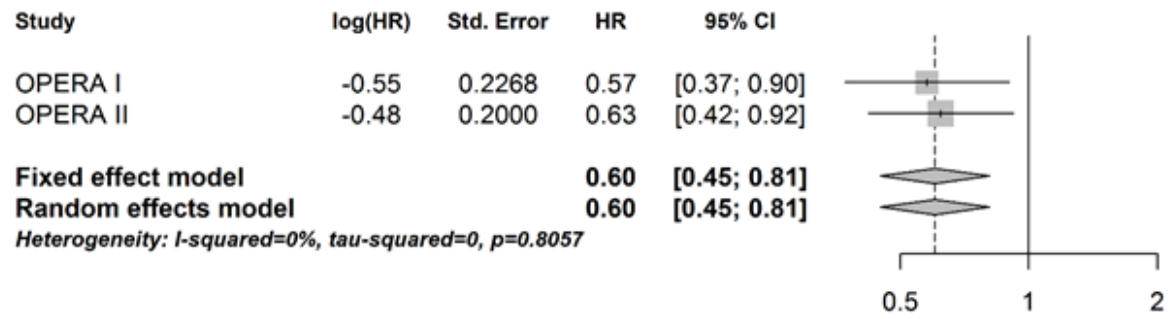
Heterogeneity assessment for CDP-12: glatiramer acetate vs placebo

Study	log(HR)	Std. Error	HR	95% CI
Bornstein 1987	-1.07	0.5431	0.34	[0.12; 0.99]
CONFIRM	-0.07	0.1982	0.93	[0.63; 1.37]
Copolymer 1 MS trial	-0.15	0.2640	0.86	[0.51; 1.45]
Fixed effect model			**0.84**	**[0.62; 1.13]**
Random effects model			**0.80**	**[0.54; 1.19]**

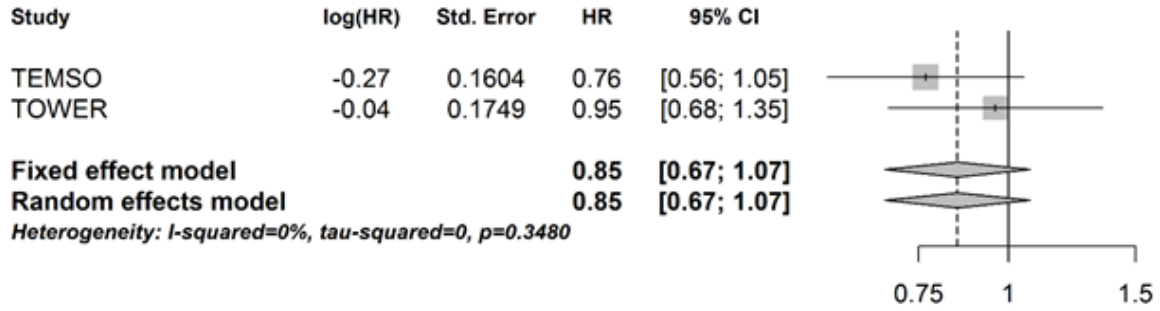
Heterogeneity: I-squared=33.1%, tau-squared=0.0426, p=0.2246



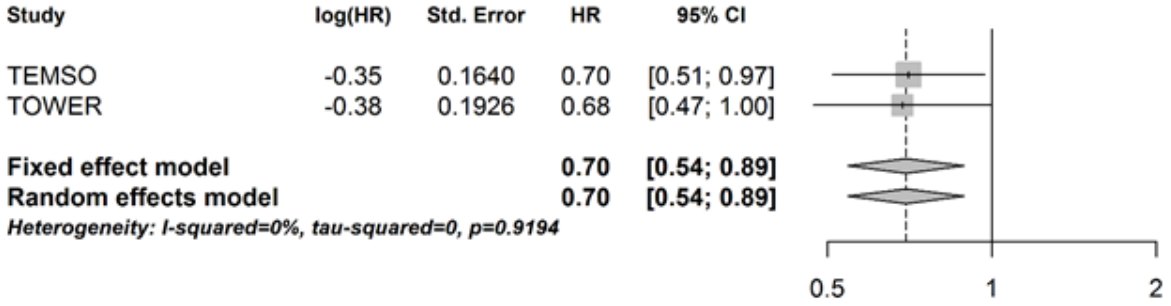
Heterogeneity assessment for CDP-12: ocrelizumab vs IFNB-1a (Rebif)



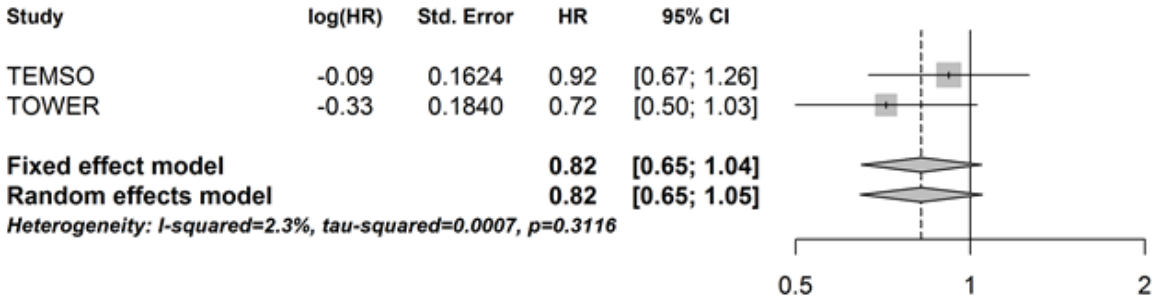
Heterogeneity assessment for CDP-12: teriflunomide 7 mg vs placebo



Heterogeneity assessment for CDP-12: teriflunomide 14 mg vs placebo



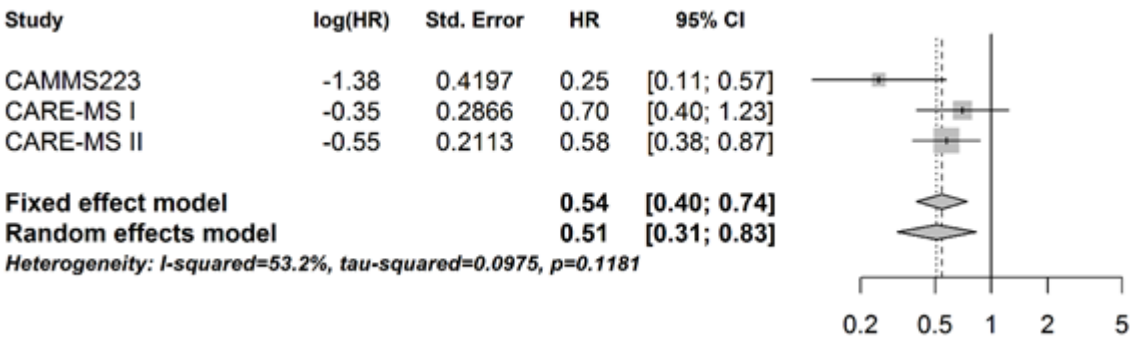
Heterogeneity assessment for CDP-12: teriflunomide 14 mg vs teriflunomide 7 mg



For the CDP-24 network, there were 6 pairwise comparisons that were informed by at least two trials. Forest plots for these comparisons are illustrated below. Heterogeneity could not be evaluated for the 12 comparisons that were only informed by one trial and there were 73 comparisons that were not informed by any trials.

Based on the I2 statistic, most of the comparisons had low heterogeneity. The comparison of alemtuzumab versus IFNB-1a (Rebif) had moderate to high heterogeneity.

Heterogeneity assessment for CDP-24: alemtuzumab 12 mg vs IFNB-1a (Rebif)

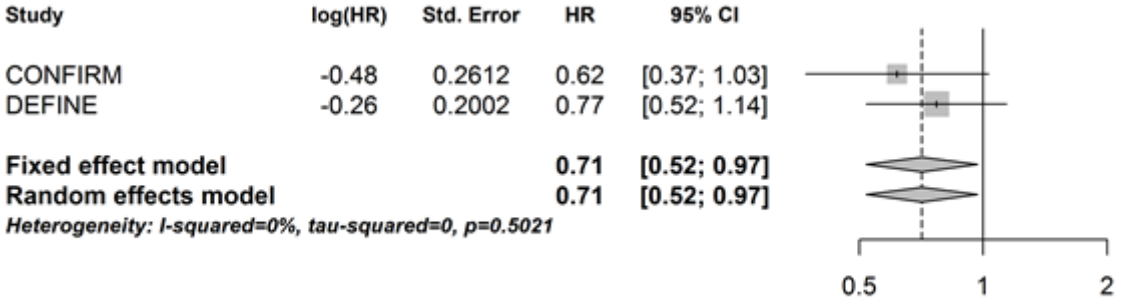


Potential sources of heterogeneity - alemtuzumab vs IFNB-1a (Rebif)

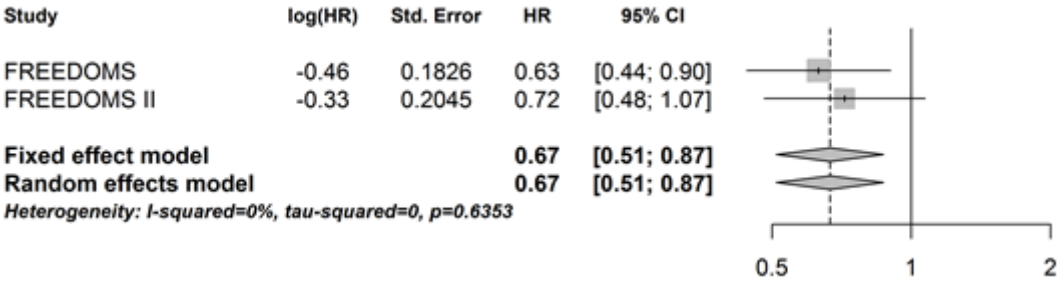
The hazard ratios from CARE-MS I and CARE-MS II are similar. CAMMS223 suggested a lower hazard ratio. Note that a similar pattern was also observed for ARR.

For CARE-MS I and CARE-MS II progression was followed up for up to 2 years. For CAMMS223, progression was followed up for up to 3 years.

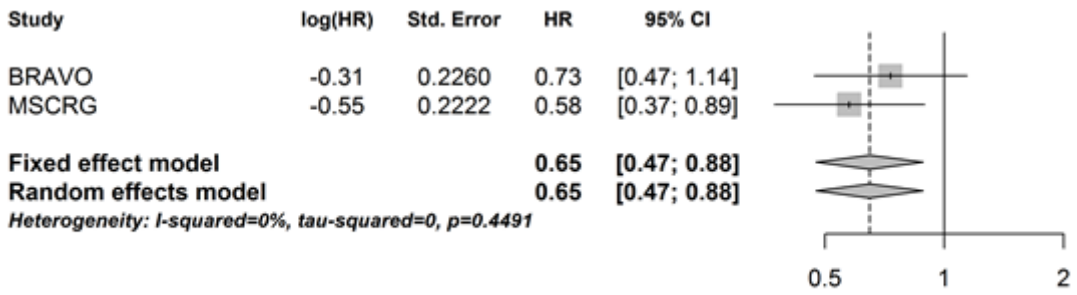
Heterogeneity assessment for CDP-24: dimethyl fumarate vs placebo



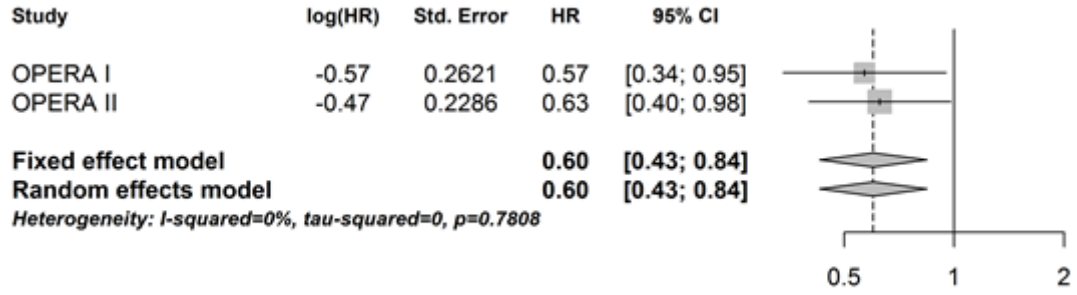
Heterogeneity assessment for CDP-24: fingolimod vs placebo



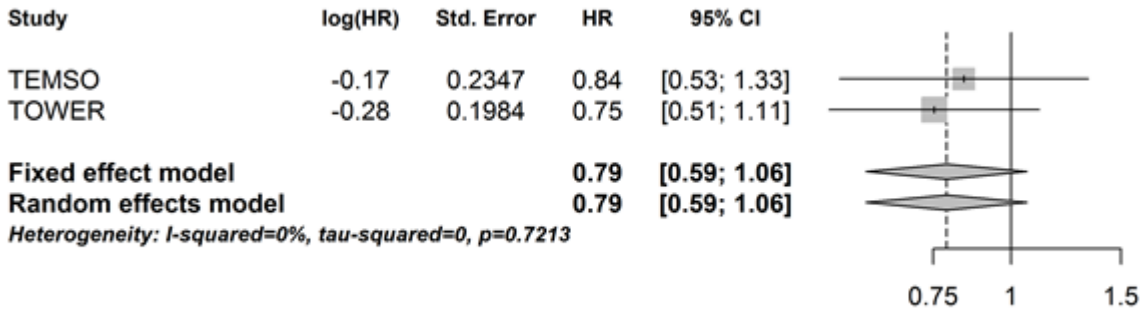
Heterogeneity assessment for CDP-24: IFNB-1a (Avonex) vs placebo



Heterogeneity assessment for CDP-24: ocrelizumab vs IFNB-1a (Rebif)

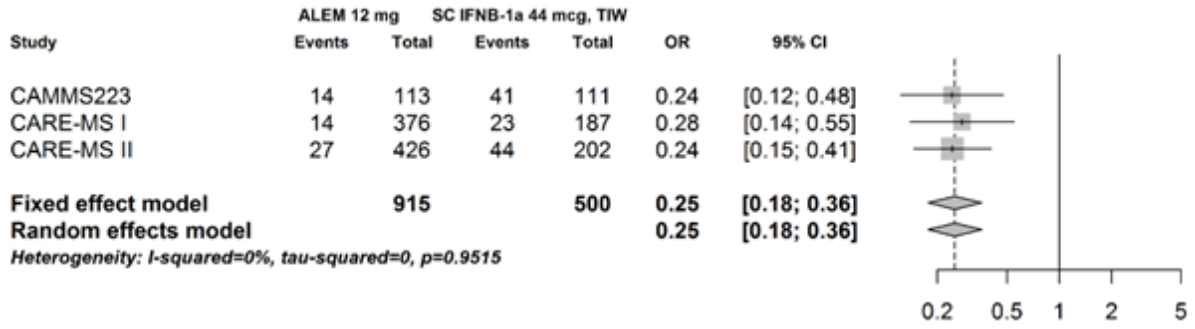


Heterogeneity assessment for CDP-24s: teriflunomide 14 mg vs placebo

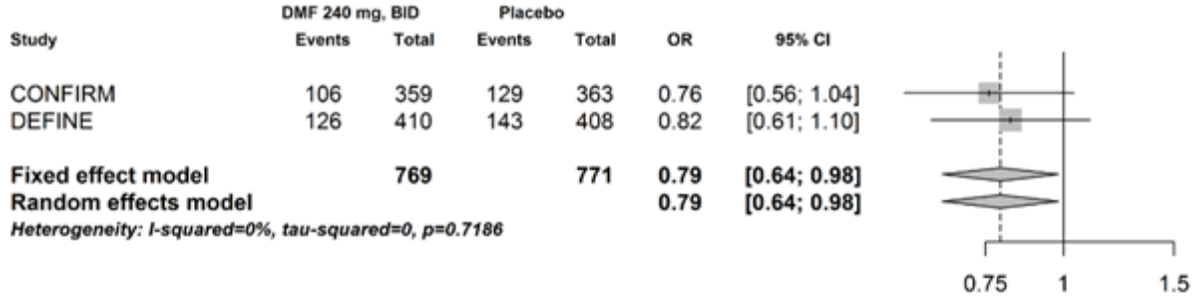


For the all-cause discontinuation network, there were 8 pairwise comparisons that were informed by at least two trials. Forest plots for these comparisons are illustrated below. Heterogeneity could not be evaluated the 20 comparisons that were only informed by one trial and there were 108 comparisons that were not informed by any trials.
Based on the I2 statistic, all-bar-two of the comparisons had low heterogeneity or low to moderate heterogeneity. The comparisons of fingolimod versus placebo and glatiramer acetate vs placebo had moderate to high heterogeneity.

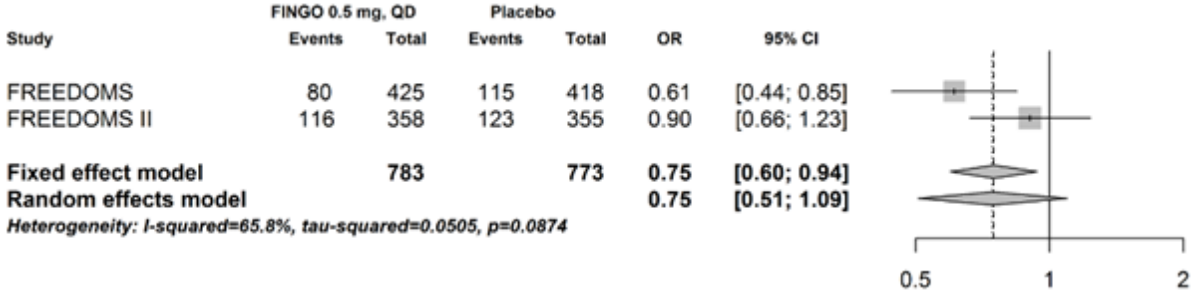
Heterogeneity assessment for all-cause discontinuation: alemtuzumab vs IFNB-1a (Rebif)



Heterogeneity assessment for all-cause discontinuation: dimethyl fumarate vs placebo



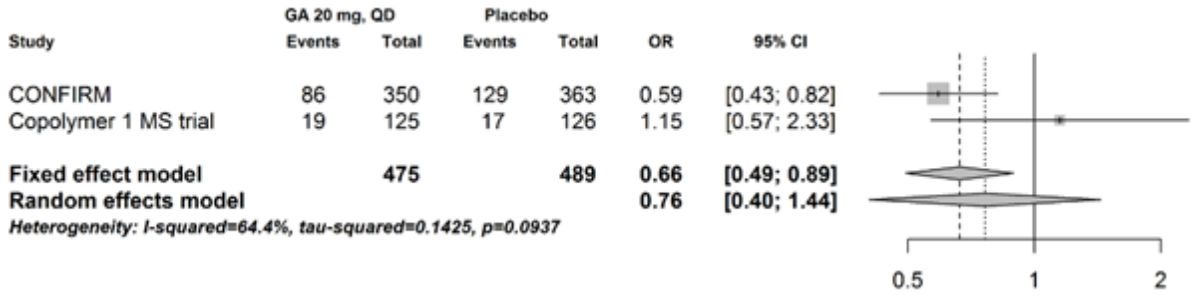
Heterogeneity assessment for all-cause discontinuation: fingolimod vs placebo



Potential sources of heterogeneity - fingolimod vs placebo

Both studies reported all-cause discontinuation over 96 weeks. Note that overall rates of discontinuation were higher in FREEDOM MS II (32.4% for fingolimod 0.5 mg (QD), 34.6% for placebo) compared with FREEDOM MS (18.8% for fingolimod 0.5 mg (QD), 27.5% for placebo).

Heterogeneity assessment for all-cause discontinuation: glatiramer acetate vs placebo



Potential sources of heterogeneity - glatiramer acetate vs placebo

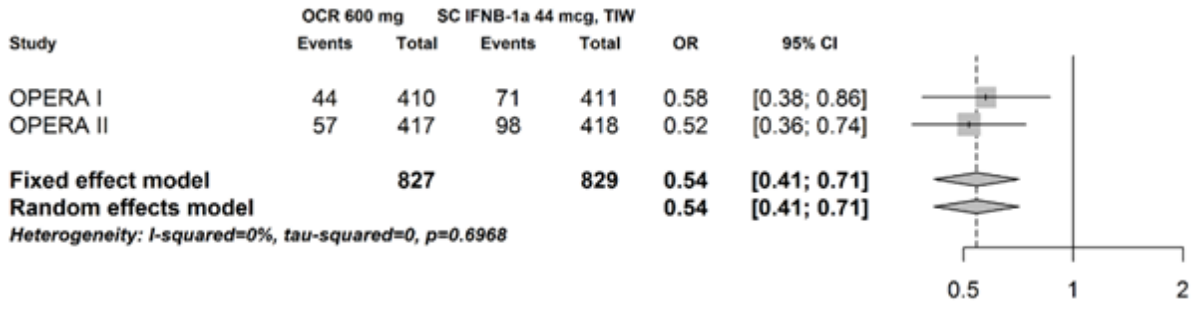
In the Copolymer 1 MS trial, patients receiving glatiramer acetate 20 mg (QD) and placebo had similar rates of discontinuation. In CONFIRM there was a higher rate of discontinuation for patients in the placebo arm.

The Copolymer 1 MS trial is one of the older trials in the network. It was conducted between 1991 and 1994. CONFIRM was conducted between 2007 and 2011. Hence the results from CONFIRM may be more relevant to current practice than the results from the Copolymer 1 MS trial.

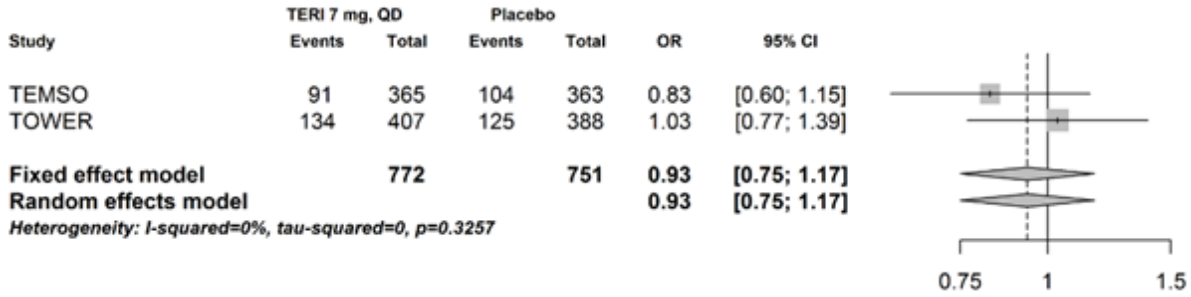
In CONFIRM, the most common reasons for discontinuing glatiramer acetate 20 mg (QD) were adverse events (27 patients, 31.4% of discontinuations due to treatment on this arm) and withdrawal of consent (10 patients, 11.6% of discontinuations). The most common reasons for discontinuing placebo were adverse events (21 patients, 16.3% of discontinuations) and MS relapse (18 patients, 14.0% of discontinuations). Other reasons for discontinuation of treatment in CONFIRM included MS progression, lost to follow-up, investigator decision, subject non-compliance, death and having previously met the protocol-defined relapse criteria for alternative MS medication.

In the Copolymer 1 MS trial, reasons for discontinuing glatiramer acetate 20 mg (QD) included pregnancy (3 patients, 15.8% of discontinuations), serious adverse events (2 patients, 10.5% of discontinuations), disease progression (1 patient, 5.3% of discontinuations) and transient self-limited systemic reactions that were brief and not considered serious (3 patients, 15.8% of discontinuations). Reasons for discontinuing placebo included failure to comply with the protocol (2 patients, 11.8% of discontinuations) and a transient self-limited systemic reaction that was brief and not considered serious (1 patient, 5.9% of discontinuations). Other reasons for discontinuation were not specified and it is not clear if the Copolymer 1 MS trial included a protocol-defined relapse criteria for alternative MS medication.

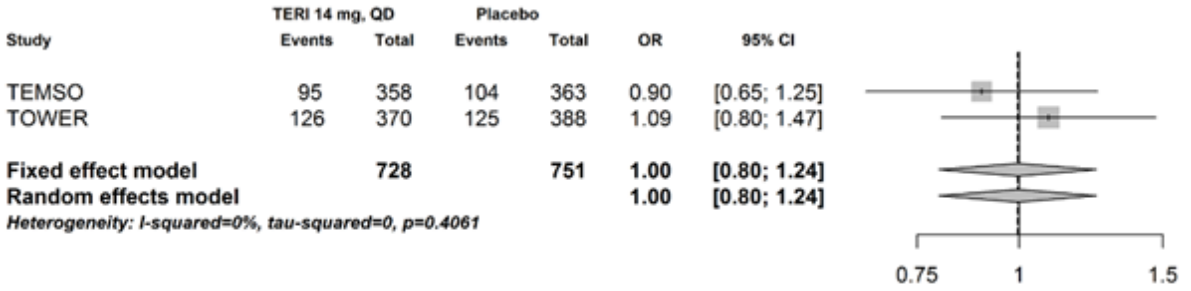
Heterogeneity assessment for all-cause discontinuation: ocrelizumab vs IFNB-1a (Rebif)



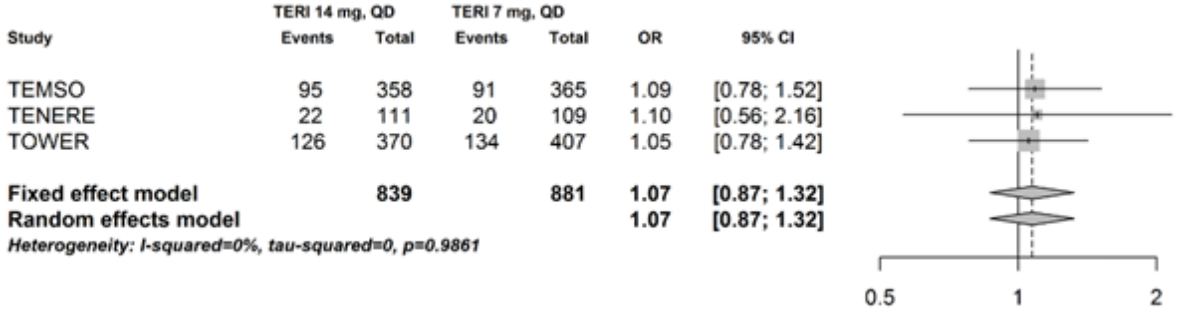
Heterogeneity assessment for all-cause discontinuation: teriflunomide 7 mg vs placebo



Heterogeneity assessment for all-cause discontinuation: teriflunomide 14 mg vs placebo



Heterogeneity assessment for all-cause discontinuation: teriflunomide 14 mg vs teriflunomide 7 mg



Related to Question A22

Table 43 Overview of studies with mixed populations, of studies reporting treatment history at baseline

Trial ID	Treatment arm	Total population at baseline (N)	Number pre-treated at baseline (n)	Proportion pre-treated at baseline (%)
ADVANCE	Peginterferon beta-1a 2W	512	87	17
	Peginterferon beta-1a 4W	500	85	17
	Placebo	500	85	17
BRAVO	IFNB-1a	447	42	9.4
	Placebo	450	27	6
CLARITY	Placebo	437	142	32.5
	Cladribine 3.5 mg/kg	433	113	26.1
	Cladribine 5.25 mg/kg	456	147	32.2
CONFIRM	Dimethyl fumarate	359	101	28
	Glatiramer acetate	350	100	29
	Placebo	363	111	31
DECIDE	Daclizumab HYP 150	919	380	41
	IFNB-1a	922	376	41
	Dimethyl fumarate	410	162	40

	Placebo	408	172	42
FREEDOMS	Fingolimod 0.5	425	181	42.6
	Placebo	418	169	40.4
FREEDOMS II	Fingolimod 0.5	358	264	74
	Placebo	355	259	73
Kappos, 2012	Ocrelizumab 2000mg	55		51
	Ocrelizumab 600mg	55		53
	IFNB-1a	54		69
	Placebo	54		30
Polman, 2003	IFNB-1a	44		2.3
	Placebo	42		2.4
TEMSO	Teriflunomide 7	366	102	27.9
	Teriflunomide 14	359	102	28.4
	Placebo	363	90	24.8
TENERE	Teriflunomide 7	109	23	21.1
	Teriflunomide 14	111	13	11.7
	IFNB-1a	104	25	24
TOWER	Teriflunomide 7	408	123	30
	Teriflunomide 14	372	126	34
	Placebo	389	135	35
TRANSFORMS	Fingolimod 0.5	432	238	55.2
	IFNB-1a	435	245	56.3
OPERA I	IFNB-1a 44	409	117	28.6
	Ocrelizumab 600mg	408	107	26.2
OPERA II	IFNB-1a 44	417	103	24.7
	Ocrelizumab 600mg	417	113	27.1

References

1. Hawkins N, Scott DA, Woods B. 'Arm-based' parameterization for network meta-analysis. Res Synth Methods. 2016;7(3):306-13.

2. European Medicines Agency. NOTE FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS. 1998.

3. Healy BC, Engler D, Glanz BI, Musallam A, Chitnis T. Assessment of Definitions of Sustained Disease Progression in Relapsing-Remitting Multiple Sclerosis. Multiple Sclerosis International. 2013;2013.

4. European Medicines Agency. Guideline on adjustment for baseline covariates in clinical trials. 2015.

5. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Med Decis Making. 2013;33(5):618–40.

6. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades A. NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials. NICE Decision Support Unit. 2011.

7. National Institute for Clinical Excellence. Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809] - Committee Papers. 2016.

8. Hauser S, Kappos L, Montalban X, Guittari CJ, Koendgen H, Li C, et al., editors. Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients With Relapsing and Primary Progressive Multiple Sclerosis. ECTRIMS/ACTRIMS; 2017.

9. Hauser SL, Kappos L, Montalban X, Chin P, Green MC, Koendgen H, et al., editors. Incidence Rates of Malignancies in Patients With Multiple Sclerosis in Clinical Trials and Epidemiological Studies. ECTRIMS/ACTRIMS; 2017.

10. Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer. 2006;118(4):979-84.

11. Johnson KP, Brooks BR, Cohen JA, Ford C, Goldstein J, Lisak RP, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Neurology. 1998;50(3):701-8.

12. Duquette P, Girard M, Despault L, DuBois R, Knobler RL, Lublin FD, et al. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial. Neurology. 1993;43(4 I):655-61.

13. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20(6):705-16.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Multiple Sclerosis (relapsing) – ocrelizumab (937)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We're the MS Society. Our community is here for people with MS through the highs, lows and everything in between. We understand what life's like with MS. Together, we are strong enough to stop MS. We have over 32,000 members and the vast majority of our income comes from voluntary donations and legacies.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have expertise from years of experience working alongside people with MS and their carers. For this submission we have engaged directly with people with MS, asking them to get in touch with us via an online blog and social media platforms as well as contacting neurologists who have been involved in the ocrelizumab clinical trials to ask them to put us in touch with people who are currently taking it. We specifically asked people who have experience of taking ocrelizumab or feel that ocrelizumab would benefit their MS to contact us and tell us about what it is like to live with MS and their experiences of MS treatments.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is one of the most common disabling neurological conditions affecting young adults. Around 100,000 people in the UK have MS, 93,000 of whom live in England and Wales, and 5000 people are newly diagnosed each year.[1] MS attacks at random with many of the symptoms invisible to others. It affects almost three times as many women as men with people usually experiencing their first symptoms in their 20s or 30s. Although much progress has been made in developing disease modifying treatments (DMTs), these are not curative and even the most effective carry significant risks for people with MS. Living with a chronic, disabling and degenerative condition such as MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week[2]. Around 85% of people with MS are first diagnosed with relapsing MS. A relapse is defined as an episode of neurological symptoms, which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. In relapses, symptoms usually come on over a short period of time but often remain for a number of weeks – usually three to four – and can sometimes last for months. Our understanding of how MS attacks the body is changing. MS specialists used to think that once a relapse was over, the damage to the brain and spinal cord stops and no new damage was happening. However we now understand that even when people with MS are not having relapses, their MS can still cause damage and neurodegeneration.[3] This damage can be happening from onset and even if there are no clinical signs of MS, such as a relapse. As a result early treatment with a DMT is now considered to be the best method of slowing the disability progression by preventing unnecessary neurodegeneration.

[1] MS Society estimate based on 2010 incidence and prevalence rates (Mackenzie et al. 2013) adjusted for accuracy based on the assumption that 82% of cases from this study can be validated (estimate based on Alonso et al. 2007). These adjusted rates have been applied to 2014 population estimates (Office of National Statistics

[2]Extra Costs Commission, Driving down the costs disabled people face : Final report, June 2015, pp. 13

[3] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015

	People with MS can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. Relapses can vary from mild to severe, with 95% of people with MS feeling relapses left them unable to do the things they wanted to do.[4] At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a GP, MS specialist nurse and other healthcare professionals. Around half of all relapses can leave a range of residual problems. New evidence has highlighted that disability also progresses regardless of whether a person experiences relapses regularly.[5] These are further important reasons to reduce the frequency and severity of relapses through ensuring that those who are eligible find the best treatment for them as soon as possible. Due to the varied and unpredictable nature of MS, determining an 'average' relapse rate is not straight forward. Relapses can have a resonating emotional impact on a person. The loss of independence that can often come with a relapse mean that people can often feel a burden on their family (93%). Relapses are often unpredictable and distressing, leaving most people feeling frustrated (80%) and anxious (67%) and causing a disruption to everyday life.[6] The majority of people with MS experience a progression of disability over the course of the condition. It is estimated that approximately 65% of people with relapsing MS will eventually go on to develop secondary progressive MS 15 years after being diagnosed and 10-15% are affected by primary progressive MS. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. This progression occurs at varying rates and can lead to a worsening of symptoms resulting in a permanent loss of mobility and the need to use a wheelchair, cognitive damage and permanent sight loss. There is also a real risk of accumulating disability for those with relapsing MS who are refractory to first line treatment. Tackling disability progression is a major issue for people with MS and there are currently insufficient treatment options for slowing progression. Our Research Strategy (2013-17) highlights research into progression as a major priority for the MS Society going forward. The strategy was formed in consultation

[4] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010.
[5] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015
[6] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010.

	with people affected by MS and the MS research community. It was approved by our Board of Trustees - the majority of whom are people affected by MS. Proving DMTs slow disability progression is notoriously difficult; but without at all minimising the difficulty of living with relapses, a product that has shown significant benefit over existing treatments (where benefit is less certain) here would be greatly valued by people affected by MS. The potential to maintain function and have a greater quality of life is of critical importance, especially for a chronic, long-term and potentially debilitating condition such as MS that so often evolves from relapsing remitting MS to the secondary progressive phase. People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely normal life. As each person's response to DMTs is different the more effective options available on the NHS will result in more people finding a treatment which best suits them. **Impact on Carers** The progressive, fluctuating nature of MS presents particular challenges to families and carers. It can make balancing work, education and taking care of one's own health and wellbeing difficult. 15% of people with MS consider a family member or carer their main contact for health care support[7]. Our research also shows that 85% of people with MS who need care and support receive unpaid care, support or assistance from a friend or family member. This has increased from 71% in 2013, suggesting carers are taking on more of a role supporting people with MS relative to the state or paid support. In addition, 36% of people who need support told us they rely solely on unpaid care (2016). Based on the latest prevalence data and our research, there could be more than 54,000 people with MS in England who need care and support, indicating there are tens of thousands of carers supporting them. Carers support people with MS with a wide variety of essential activities. Our research found 63% of people with MS who need support require help carrying out essential activities of daily living such as getting up in the morning, washing and eating. We found that severity of needs increase with age, as the

[7] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	disease progresses. Treatment's that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too. But too many carers tell us they don't get the support they need to continue caring, from respite care to social care for the person they care for, financial support and emotion support. Carers also often act as care coordinators for the person they support, overseeing complex treatment regimens and navigating disjointed health, care and welfare systems. In our survey of over 11,000 people with MS last year, 15% of respondents said a carer or member of their family was their key contact for health care and support. One carer described just how complex this support network can be: "*Between the nurse, the speech and language therapist, the neurologist and various other specialists, there is roughly a team of twenty involved in my wife's care. She relies on me as a part of this team and to co-ordinate them. It's becomes a big 'project' to manage".*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	People often experience long delays in being diagnosed with MS. Timely referral or diagnosis for people with suspected MS is hugely important, yet we know this is not always achieved. In a recent survey of people with MS, 37% of respondents waited six months or more to be diagnosed with the condition, and 17% reported waiting more than 12 months to have a consultation with a neurological specialist. [8] There are currently 12 DMTs available on the NHS in the UK (with a 13th just approved by NICE for England and Wales), offering people with relapsing MS a variety in treatments, that, until recently did not exist. In research carried out by the MS Society in 2014, those who responded identified stopping further relapses as the most important reason to start taking DMTs (93%), followed by 84% who hoped it would reduce the severity of their relapses, and 84% who hoped it would result in less disability over the long

[8] Neurological Alliance, 2017, *Falling Short – How has neurology patient experience changed since 2014?* http://neural.org.uk/updates/278-New-Neurological-Alliance-patient-experience-report-2017

	term.[9] While many people have had positive experiences with DMTs, others experience negative experiences such as side effects, no treatment effect, and many people simply are not eligible for the DMTs available on the NHS. Remaining in work and engaged in wider society is an important outcome which is not always captured when evaluating a treatments cost effectiveness but is incredibly important for people with MS. For those taking first line injectable treatments that involve daily or weekly injections and those undergoing regular treatment infusions within hospital, there is a substantial impact on their lives. Planning around administering these treatments, the side effects and storage needs are too great for many which is why the adherence rates are higher for DMTs which require less frequent administration.[10] Of the 13 DMTs available, alemtuzumab and natalizumab are classified as 'high efficacy' by the Association of British Neurologists (ABN). Beta interferons, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod, are regarded as having moderate efficacy. With the latter two drugs considered the more effective within this category. Cladribine, recently approved by NICE offers another option of good efficacy for people with highly active relapsing MS. Decisions on which DMT to take are determined by a variety of factors including the eligibility, efficacy, related side effects, the method and frequency of taking, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. Choosing which option to take requires access to evidence-based information, and support and advice from specialist health professionals. In 2014, the MS Society found that there is a lack of understanding and communication about what treatment options are currently available, with one in five people not having heard of any DMTs, or only heard of just one.[11] While MS nurses and neurologists are reported to be the most useful sources of evidence in aiding people to make a DMT decision, our research from last year showed that, of the people

[9] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014
[10] Halpern et al, 'Comparison of adherence and persistence among multiple sclerosis patients treated with disease-modifying therapies: a retrospective administrative claims analysis', Patient Prefer Adherence, 2011
[11] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014

	who are taking or are eligible for taking a DMTs, 13% had not met with a neurologist despite needing to and 14% had not met with an MS nurse despite needing to.[12] The MS Trust has found that the increased number of DMTs has led to inefficiencies in the necessary services needed alongside them. MS nurses have to deal with increasingly stretched workloads where they are responsible for fulfilling a range of non-clinical tasks such as scheduling monitoring appointments and booking chairs for IV infusions, which could be covered by an administrator. They have also found that there are a lack of information services to assist with the planning and monitoring of care for people undergoing treatments, a lack of integration between different providers of care and substantial difficulties with the home care delivery systems needed for many of the treatments.[13]
8. Is there an unmet need for patients with this condition?	There are several unmet treatment needs for people with MS. Currently there are no treatment options which have been proven to reverse disability and repair the damage that MS does to the myelin sheath. Within the drugs pathway for relapsing MS there are unmet needs which are more specific to individuals. Many people feel that the side effects from the frequent administration of the less effective treatments are too great for them, while others are risk averse or unable to tolerate the greater risks which come with the more effective treatments. An effective treatment taken infrequently which carries minimal side effects would be welcomed by many people with relapsing MS.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Trial results indicate that ocrelizumab is as effective as the most effective of the currently available treatments while carrying fewer side effects. This would make it an attractive option to many people who are risk averse to other available treatments. People with relapsing MS who have taken part in the clinical trials have commented that since taking ocrelizumab they have seen a significant improvement, with

[12] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report
[13] Mynors, G., Roberts, M. and Bowen, A. (2016) Improving the efficiency of disease modifying drug provision

	symptoms subsiding and commenting that they 'no longer feel that my MS is a daily challenge'. *"From the day after the first Ocrelizumab infusion, the brain fog I had experienced for 6 years without remission has gone. It only returned three weeks before my next infusion date and disappeared again after my repeat infusion."* **Reduction in relapses** The results from two phase 3 trials (OPERA I and OPERA II) involving over 1,600 people with relapsing MS found that ocrelizumab significantly reduces relapses. Compared to beta interferon relapse rates for people taking ocrelizumab dropped by 46%, and overall 81% of people who took ocrelizumab remained relapse free over two years, compared to 68% who took beta interferon. *"Numbness in my toes which developed after a relapse four years ago has disappeared. Numbness in the fingers of my left hand which developed after my first relapse seven years ago has disappeared except for my little finger. I can now discern between wet and cold sensations which had not been possible since the first relapse."* **Reduction in disability progression** The trials also found that disability progression was slowed down by 43% for people taking ocrelizumab compared to people taking beta interferon. This meant that over two years 91% of people who took ocrelizumab did not experience a progression in disability compared to 84% of people who took beta interferon. The trial also found that around 50% of people taking ocrelizumab saw no evidence of disease activity (NEDA) in both OPERA I and OPERA II. This was compared with 25-30% of people taking beta interferon. **Brain atrophy**

	Compared to beta interferon, ocrelizumab showed an 18.8% reduction in brain atrophy. **Impact on quality of life compared to alternative treatments** There are a number of factors that influence a person's decision to choose one treatment over another that are not easily addressed in cost effectiveness models. A highly effective treatment with minimal side effects and recently granted a broad licence to treat relapsing MS by the EMA, ocrelizumab could well be the treatment of choice for many people with MS. The side effects that come with the currently available first line injectable treatments are often cited as a reason people move onto other drugs. The most common side effects of the first line injectable treatments include flu like symptoms, and injection site reactions. As beta interferons and glatiramer acetate are all taken relatively frequently (ranging from every other day, to every two weeks), the side effects are unsurmountable for some. For some, the storage and planning involved around these treatments is also difficult to fit around their life. *"I am currently on, or meant to be on, Copaxone injections. I find it really sore, my injections sites flame up and swell for days at a time, I've actually stopped taking it now"* It also offers another highly effective option which is less disruptive to day to day life. Taken through infusion every six months, people would not have to organise their life around more frequent hospital visits that are involved with some of the other treatments such as natalizumab. For many people with more severe relapsing MS, alemtuzumab is seen as undesirable due to the common side effect of developing thyroid problems. This affects as many as 40% of people and in turn requires lifelong medication to treat.[14] Understandably, this puts off many despite alemtuzumab's proven effectiveness at treating relapsing MS. A new treatment with a similarly broad licence to alemtuzumab would mean more people find a treatment which is right for them.

[14] Udiawar, M, & Bolusani, H. Alemtuzumab and thyroid dysfunction in patients with multiple sclerosis: experience in a university hospital, Society for Endocrinology BES 2014

Helping people with MS to remain in work

In an MS Society survey we found that, at some point, a relapse had prevented 82% of people with MS from carrying out their work duties (paid employment) and that a further 89% were unable to fulfil their usual roles and responsibilities during a relapse. Over half of the respondents reported that a relapse often or always has an impact on their ability to carry out their work duties.[15]

A positive appraisal of ocrelizumab would increase the number of treatments available for people with MS and therefore increase the likelihood that more people identify DMTs which best suit their MS. This would result in more people effectively slowing the progression of disability and enjoying a fulfilling work life for longer.

Positive impact on lifestyle and carers

People with MS often need support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting out and about. At times of relapses and as disability progresses the need for this support increases and the impact on carers can be greater. Recent research by the MS Society on the needs of people with MS who received care, support or assistance from a friend or family member had increased from 71% to 85% from 2013 to 2016.[16] The effect MS has, not only on the person's life that has the condition, but also on those close to them is significant. As ocrelizumab could potentially represent a new highly effective treatment it would increase the chance of people finding a DMT which works for them and lead to a reduction on the reliance on carers as more people are treated.

[15] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010.
[16] Wallace, L., Cavander- Attwood, F., Redfern-Todts, D. Social care and the MS community in England 2016

	"Whilst on Rebif, I would have to sleep 12 hours a night on injection days so as not to feel woozy. Sleep was disturbed and often punctuated by bathroom visits. (My sleep now is more settled and never necessitating bathroom visits) This routine on Rebif was inconvenient and problematic to work around family and social commitments. The convenience of giving up one day every six months cannot be underestimated after over six years of being unavailable for half the week."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None of the phase 3 trials reported any unexpected adverse side effects. In the phase 2 relapsing trial, serious side effects were rare and were comparable for all groups. One patient died in the high dose ocrelizumab group but it was unclear as to whether this was connected to ocrelizumab. However, we it is true that longer term studies are needed to understand the full safety profile of ocrelizumab. There are two areas in particular where, if further data confirmed higher risks, patients or carers could become more worried about disadvantages: • Weakening the immune system increases the risk of infection and of cancer emerging, and doctors have been advised to "stay vigilant". • In May 2017 Roche reported that a person had contracted progressive multifocal leukoencephalopathy (PML) after switching from natalizumab (Tysabri) to ocrelizumab in April. Right now it is unclear whether PML was linked to use of ocrelizumab, Roche are investigating further. Tysabri has previously been linked to an increased risk of PML.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Ocrelizumab has shown to be highly effective at reducing relapses, brain atrophy and disability progression in clinical trials and follow up studies.
- Ocrelizumab carries less side effects than other highly effective DMTs and so it seems reasonable to conclude that it will be of interest to a significant portion of people who could benefit who are not currently taking a DMT, as well as working better for some people who are taking a different one.
- 44% of people who could potentially benefit from a DMT are not taking one currently, so more DMT options mean it is more likely that people are able to find a treatment that works for them, improving adherence and efficacy overall. This has been witnessed with the uptake of DMTs increasing in recent years with the increase of available options.
- Evidence shows the importance of treating early with a DMT in reducing relapses and slowing disability progression.
- DMTs enable people with MS to take control of their lives and maintain their independence, thereby reducing productivity and societal costs associated with living with MS.

Thank you for your time.

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Patient organisation submission

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding and rely on donations, fundraising and gifts in wills to fund our services.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to relapsing remitting MS: coping with the impact of diagnosis, choosing which treatment to take, understanding and balancing risk/benefit profiles, concern about switching to a new disease modifying drug (DMD), dealing with difficulties of self-injection or side effects, and coping with physical and financial consequences of relapses. We have also gathered feedback from a number of people who are currently taking ocrelizumab. Their experiences provide a valuable personal perspective on ocrelizumab, the impact it has had on their quality of life and how it compares with other DMDs they have taken.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well and not taken account of in cost effectiveness calculations. MS is sometimes mild, frequently relapsing remitting, but often progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity. Good management of MS can be a huge challenge to health professionals because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers. Approximately 80% of people with MS will have relapsing remitting MS (RRMS). MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms. Many of these invisible symptoms are sensitive areas and can be difficult to recognise or talk about, putting an extra burden on a person with MS to deal with on their own. Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect

	financial burden, both for the individual, their family and the state. They can have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends. In a cash-strapped NHS, the reality is that services to support people coping with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. For example, a caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS. Research evidence supports the treatment of people with relapsing remitting MS with disease modifying drugs (DMDs) early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that if people with MS continue to have relapses while on therapy, this should prompt a discussion about switching treatments. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; signs of MS activity trigger a treatment review and escalation to an alternative disease modifying drug is considered. A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing forms of MS.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	MS care involves a mix of clinical management of symptoms, responsive services to manage relapses and other acute deteriorations, therapies including physiotherapy and occupational therapy, tailored, evidence based information, support for effective self-management and, for those with RRMS, access to the range of DMDs and support to make the choice that is right for their condition, their lifestyle and their treatment goals. The majority of people with RRMS are eager to start treatment with one of the DMDs and

	aware of the importance of starting treatment soon after diagnosis. A number of DMDs are available for relapsing remitting MS: • beta interferons • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • daclizumab • cladribine • natalizumab • alemtuzumab It is not possible to say which of these treatments are preferred; the widening range of DMDs gives greater scope for personalised treatments. If MS remains active despite taking one of the DMDs there is more potential to switch to a treatment with a different mechanism of action. Different responses to DMDs from one person to another are not easily captured in clinical trial data but are important to address in clinical practice. Through different aspects of our work with people affected by MS, we are aware that a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, as is evidence of their effect on the underlying course of the condition and their impact on disease progression. Other issues will also be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD. People with MS rely heavily on their MS specialist team to provide information and guidance to help with

	treatment choices. MS teams are skilled and experienced in helping an individual make the choice that is the best match for their level of disease activity, their personal circumstances, their attitude to risk and their treatment goals.
8. Is there an unmet need for patients with this condition?	Clearly, the most significant unmet need for people with MS is a cure. In the absence of a cure, people with MS want to live a life free from the impact of their disease. For many people, the ultimate goal of taking one of the DMDs is to reduce their risk of disease progression and future disability. Inevitably, the frequency and severity of relapses rank highly for those with RRMS, not just for the disruption and distress that relapses cause, but also because of the risk of residual disability and increased chances of conversion to secondary progressive MS. Ranking the impact of individual symptoms is difficult and ultimately inadequate as the condition varies so widely between individuals. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to DMDs. For those people with very active relapsing MS - either rapidly evolving severe or highly active despite treatment - the side effects associated with the current, more effective DMDs is a cause for concern, for example the risk of PML with natalizumab and secondary autoimmune conditions with alemtuzumab. For people with very active relapsing MS, the option to switch to a more effective DMD with minimal or reversible side effects would be a major benefit. Remaining in employment is of critical importance to people with MS. Within 10 years of diagnosis, around 50% of people with MS will have left employment, with all the associated financial, social and psychological consequences. Cost effectiveness calculations do not take account of the burden of loss of work on the individual, their family and society.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The clinical trial data have demonstrated the effectiveness of ocrelizumab: • Highly effective at reducing the risk of relapses • Highly effective at reducing invisible MS activity • More effective at reducing 3 and 6 month disability progression compared to beta interferon • No evidence of disease activity more likely for those taking ocrelizumab • Low level of side effects - resulting in minimal requirements for routine blood and urine tests • Innovative mechanism of action - depletes B cells. The personal experiences of people who have been taking ocrelizumab in a clinical trial highlight additional benefits of ocrelizumab: • **Novel treatment schedule** Ocrelizumab is taken as an infusion, the first dose is given as two separate infusions, two weeks apart. Further doses are given as one infusion every six months. The novel treatment regime of ocrelizumab was a significant benefit compared to taking pills once or twice daily or self-injecting every other day. As one person stated: "I can't understate the psychological effect of coming off the treadmill of doing those injections". • **Relief from side effects** Side effects were limited to a day or two following an infusion (and became milder after the first infusion), compared to the constant presence of side effects associated with more frequent pills or self-injections. One person described the realities of disrupted daily life caused by side effects of her previous DMD, and the need to minimise these by taking the medicine after meals, at the same time as dealing with work commitments and looking after small children. • **Quality of life** One person we spoke to was frustrated by the lack of detail he was able to record when asked to complete questionnaires on quality of life and fatigue levels in clinical trials. Simply selecting a number on a scale of 1-5 did not allow him to express the pleasure of once again being able to go on long country walks with his dog and family and attending an international rugby match at Twickenham with his son and

	wife. A young mum with small children spoke of the relief at not having to deal, every month, with unpredictable home delivery of her medication, a particular problem when balancing work commitments and collecting children from school. "Switching to ocrelizumab has been 150% better for me, my husband, my children and my work".
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There will always be individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines. Overall, the potential risk of side effects from individual drugs tends to be the biggest barrier to starting a treatment. Across all the clinical trials, infusion-related reactions (which become milder after the first infusion), chest infections and herpes (oral herpes and shingles) were more frequent in those taking ocrelizumab. Neoplasms, including several cases of breast cancer, were reported more frequently in those taking ocrelizumab. One case of the serious brain infection, progressive multifocal leukoencephalopathy, has been reported in one person who had switched to ocrelizumab after taking natalizumab for three years; further investigations are being carried out into this case. Ocrelizumab has previously been investigated as a treatment for rheumatoid arthritis but studies were discontinued because of a high incidence of opportunistic infections in participants. To date, opportunistic infections have not been reported in ocrelizumab MS trials.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that we are aware of. Ocrelizumab has been licensed for people with relapsing MS with active disease defined by clinical and imaging features - this covers the full range from those recently diagnosed through to those with very active relapsing MS and those whose MS remains active despite previous treatment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Ocrelizumab has a different mechanism of action to other DMDs. Given the heterogeneous nature of MS, both in disease course and in response to treatments, a broadening range of drugs which work in different ways increases the potential for personalisation of treatment. The dosing schedule consisting of two initial infusions, followed by six monthly infusions offers an alternative dosing schedule to other DMDs, increasing scope to tailor treatment to individual needs.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- ocrelizumab offers a novel treatment schedule, aiding adherence and minimising service usage
- a combination of high efficacy and low level of serious side effects makes ocrelizumab an attractive alternative to other highly effective disease modifying drugs
- MS is a complex and unpredictable condition which has an impact on all aspects of life; early proactive treatment is essential to prevent future disability
- as with other DMDs, an individual and their MS team will need to consider the risks and benefits of ocrelizumab
- adding ocrelizumab to the range of DMDs gives greater scope for personalisation of treatments

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Professional organisation submission

Multiple sclerosis (Relapsing Remitting) – ocrelizumab

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists (ABN)**

3. Job title or position	**Consultant Neurologist** [redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Association of British Neurologists is the professional society for neurologists and clinical neurology researchers in the United Kingdom; it has 800 members. The aim of the Association of British Neurologists is to promote excellent standards of care and champion high-quality education and world-class research in neurology. It is funded by member subscription.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No.**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	**The aim of ocrelizumab is to reduce the frequency and severity of relapses in people with relapsing remitting multiple sclerosis (RRMS). It may also reduce disability progression.** **There is evidence of efficacy in RRMS from two large phase III randomised controlled trials. OPERA I and OPERA II. Also ~~showing~~ reduction in disability progression in primary progressive MS- the first drug to do so, in the ORATORIO phase III trial.**

or prevent progression or disability.)	**Participants in the trials were aged 18-55 and had either 2 relapses within previous 2 years or 1 within last year. Were stable for 30 days prior to screening and included some with relapsing secondary progressive MS. EDDS was 0- 5.5 that is walking >/= to 100meters independently.** **It is a humanised monoclonal antibody that depletes CD20 expressing B cells. This is expressed on pre-B, mature B and memory B cells but not lymphoid stem cells or plasma cells. The capacity of B-Cell reconstitution and humoral immunity is thus preserved. This a new mechanism in drugs licensed for MS. It is thought to effect antigen presentation and T cell activation and alter the cytokine signalling. It may be effecting more antibody mediated pathology, meningeal follicle formation and microglial activation.**
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**A reduction in the number of relapses and the severity of relapse are both significant, although the former is easier to measure. The OPERA I trial reduced relapses by 46% (0.16 v0.29) p<0.001 versus Rebif 44 (high dose beta interferon 1a) and OPERA II by 47% versus Rebif 44 (0.16 v0.29) p<0.001. Although patient populations are not identical the pivotal studies showed that Rebif reduced annual relapse rate by about one third. Although in theory more infections would be expected with a B cell depleting drug, adverse events including infections were similar. Most frequent adverse effects were infusion reactions and infections. It therefore falls into the more highly effective disease modifying treatment group, along with drugs such as Natalizumab, Alemtuzumab and Cladribine.** **The phase III studies also showed significant improvements in secondary endpoints. A 40% risk reduction in both 12 and 24 week confirmed disability progression, 9.1%v 13.6% and 6.9% v10,5% respectively.** **An increase in disease free interval with 81% relative increase in patients with no evidence of disease activity (NEDA) p<0.0001.** **A 94% relative reduction in total number of Gadolinium enhancing lesions on MRI.,** **A 82.9% relative reduction in new or enlarging T2 lesions on MRI**

	A 64.3% relative reduction in total new T1 hypointense lesions on MRI **A 14.9% relative reduction in mean percent brain volume loss.**
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**Although there are other disease modifying drugs for RRMS available Ocrelizumab falls into the more highly effective group of drugs. Multiple sclerosis is a highly heterogeneous disease with some people responding or not responding to different drugs, particularly the less efficacious drugs. Given the novel mechanism of action people who have not responded to other drugs may respond to this one. It also may have advantages in the form of fewer infusions per year and a much reduced risk of progressive multifocal leukoencephalopathy (PML) that Natalizumab. Less long term autoimmune complications that Alemtuzumab.** **The efficacy of this drug in reducing disability progression in primary progressive MS suggests it may also have an effect on disability progression separate to its efficacy on relapse reduction.**
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	**There are other available disease modifying drugs for RRMS available under the NHS in England. A treatment algorithm developed by the ABN together with NHS England is currently out for consultation. It summarises how we recommend their use. These drugs are usually prescribed by a consultant neurologist, with the more complex drugs used at major centres by MS subspecialists and often with MDT input. They are monitored by MS nurses and consultants. Facilities for infusion of monoclonal antibodies are already available. Safe systems for blood and MRI monitoring need to be in place.** **Different drugs are targeted according to their efficacy and safety profile to treat people with very early MS (Clinically isolated syndrome with active scan), mobile individuals with 2 or more relapses in 2 years. People with aggressive multiple sclerosis- divided into Rapidly Evolving Severe (RES) MS (2 disabling relapses and activity or progression on MRI) or Highly active MS – variously defined but usually having breakthrough relapses on a first line drug plus or minus MRI criteria. These drugs include the Beta interferons 1a and 1b (Avonex, Plegridy, Rebif, Betaferon and Extavia), Glatiamer acetate(Copaxone in two regimens). Teriflunomide, Dimethylfumurate**

	(conventional first line for milder disease) but Alemtuzumab approved, Fingolimod, Cladribine and Alemtuzumab and occasionally daclizumab for highly active MS and Natalizumab, Cladribine , alemtuzumab for RES MS with autologous bone marrow transplant considered for the most aggressive cases.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**Multiple sclerosis. Management of multiple sclerosis in primary and secondary care** **Issued: November 2003, NICE clinical guideline 8** **Clinical Guideline CG186 Multiple Sclerosis in Adults – management 2014** **NICE Clinical Guidelines on Natalizumab, Alemtuzumab, Fingolimod, Dimethy fumurate, Teriflunoimide, Cladribine and Daclizumab.** **NHS HSC circular 2002/4** **NHS England Guidelines for the use of Disease modifying treatments in Multiple sclerosis 2016 and the Scottish and Welsh equivalents.** **ABN prescribing guidelines for disease modifying drugs in MS** **New ABN NHS algorithm.** **For patients with relapsing remitting MS and for symptoms management:** **http://pathways.nice.org.uk/pathways/multiple-sclerosis** **NICE Pathway last updated: 05 December 2017**
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**The pathway for assessing and Managing RRMS in adults is well established. There are variations in whether all Neurologists or just subspecialists manage disease modifying treatments outside of regional centres. Under the proposed NHS England guidelines, high-efficacy medications like ocrelizumab should be managed by multi-disciplinary teams. Some neurologists and some people with MS prefer an induction (strongest treatment available first) model and others a model of escalation from weaker safer drugs to the stronger. Ocrelizumab should be available as a first-line**

	"induction" drug, and a second-line treatment to be escalate to, if less potent therapies are not effective.
• What impact would the technology have on the current pathway of care?	**Although the majority of the 100,000 or so people with MS in the UK have started with relapsing disease (85-90%), some will have progressed to a disability level beyond which most disease modifying drugs are ineffective. The current stopping criteria, for most drugs, are an EDSS of 7 or more. Many people with relapse onset disease will be stable on other drugs.** **We therefore anticipate only a modest effect on the current treatment pathway for RRMS. The ABN anticipate that ocrelizumab is most likely to be used in people with highly active or RES MS unless the cost per QALY is very low and permits more widespread use.** **Ocrelizumab is most likely to be considered where Fingolimod, Natalizumab, Alemtuzumab, Cladribine or occasionally daclizumab would be used. That is for highly active or RES MS.** **The risk of PML is likely less than with Natalizumab (one case in a patient previously on natalizumab). About 2/3 of UK population carry JC Virus so are at increased risk of PML. Thus the reduction in number of infusions from 4 weekly to 6 monthly and lower risk will mean many may choose ocrelizumab over natalizumab, especially if JCV positive. Although on the non-humanised antibody Ritixumab cases of PML have occured, it seems infrequent in neurological diseases such as neuromyelitis optica as well as non-neurological ones like rheumatoid arthritis.** **It does not share the risk of auto immune disease with Alemtuzumab and does not have such a broad suppression of T and B lymphocytes as Alemtuzumab and Cladribine. It does not share the cardiac risks of fingolimod. It is more effective and safer than Daclizumab.** **MS centres are used to managing monoclonal antibody infusions, monitoring for immunosuppression and infections. However it will take time to set up protocols and may require more MS nurse specialist input and MRI availability. Plus additional monitoring of immunoglobulins.** **Whether or not it would increase or decrease need for infusion facilities would depend on its position in the treatment algorithm**

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**There is no current care for the use of ocrelizumab, but its parent molecule, rituximab, is in wide use throughout secondary healthcare (although not in multiple sclerosis in UK, there is off licence use elsewhere e.g. Sweden).**
• How does healthcare resource use differ between the technology and current care?	**The use of ocrelizumab will:** • **Marginally increase the number of patients needing to access specialist disease-modifying therapy clinics** • **Increase the requests for MRI scans with (and without) gadolinium** • **Could decrease or increase the workload on infusion centres, depending on where it is positioned in treatment algorithms** • **May increase primary and secondary care workload managing adverse effects** • **Increase the workload on MS specialist Nurses and monitoring systems.**
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**We recommend ocrelizumab is used in the same settings as other high-efficacy multiple sclerosis therapies, namely managed by specialist multiple sclerosis neurologists and nurses in secondary care, supported by multidisciplinary teams.**
• What investment is needed to introduce the technology? (For	**Investment would be required to increase the capacity of specialist neurology and nursing time, disease-modifying therapy clinics, MRI units and infusion centres. If MDT working is recommended that may need some technological and administrative support to allow Neurologists working outside of major centres to access them.**

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**Ocrelizumab is an effective drug for relapsing MS. It may have both safety and convenience advantages over other drugs for aggressive multiple sclerosis. It has a mechanism of action that differs from our other drugs, so provides another option for those who have had continued disease activity on other drugs.** **Although one cannot directly extrapolate, ocrelizumab also provides statistically significant benefits to the progression of disability for people with primary progressive multiple sclerosis. We are therefore hopeful it will benefit this aspect of disability accrual in relapse onset disease too.**
• Do you expect the technology to increase length of life more than current care?	**No, because we have no trial data to support this. Someone with MS onset in their 20's may have life expectancy reduced by a few years compared to general population but no trial has followed interventions out for 60 plus years. However some data shows mortality rate among patients treated with beta interferon 1b in the first 5 years of MS had a lower mortality from all causes compared to placebo group (Goodwin 2009)**
• Do you expect the technology to increase health-related quality of life more than current care?	**Yes, as provides advantage of lower PML risk and less frequent infusion or better side effect profile than other highly active treatments.**
12. Are there any groups of people for whom the technology would be more or	**Patients aged less than 40 had a greater reduction in annualised relapse rate (adjusted ARR ratio 0.423 v 0.692) compared to Beta interferon.** **Patients with 1 or more gadolinium enhancing lesion also had a greater reduction in annualised relapse rate (0.313) compared to those with none (0.787) compared to beta interferon** **However there was a significant treatment effect in all groups.**

less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	**Ocrelizumab is another infused monoclonal antibody treatment for multiple sclerosis, is no more difficult to use than rituximab or any of the infusions already licensed for relapsing-remitting multiple sclerosis, such as Natalizumab or Alemtuzumab..** **Testing eligibility for ocrelizumab requires visits in specialist clinics for disability assessment and additional MRI scans with (and without) gadolinium. Screening blood tests, for instance for blood borne viruses like hepatitis B serology, are required before treatment.** **To manage infusion reactions, all people receiving ocrelizumab should have intravenous methylprednisolone (100 mg) before infusion and, optionally, prophylaxis with analgesics or antipyretics and antihistamine.**

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**We recommend that starting rules are discussed to identify the people with relapsing remitting MS who are likely to benefit. A discussion about whether it will be confined to highly active or RES MS or offered to all who have relapsing disease as used in the phase III trials needs to be undertaken.** **Stopping rules are more difficult. The NHS England stopping rules for current disease-modifying therapies in relapsing-remitting disease include a persistent inability to walk more than a few steps (corresponding to a disability score of EDSS 7.0 or greater). However, many ABN members argue for continued dosing in progressive multiple sclerosis beyond this disability score, in order to preserve upper limb function. In favour of this argument, ocrelizumab reduce the worsening of scores for the "nine hole peg test" (a test of arm and hand coordination) in the ORATORIO trial (supplementary appendix). Against this view is the fact that patients with an EDSS of greater than 5.5 were not included in the relapsing remitting trials (OPERA I and II) and therefore trial results cannot be extrapolated to them.** **Less controversial stopping criteria are: Intolerable adverse effects of the drug or plans for pregnancy or breastfeeding.**
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	**No. We consider that QALYs should appropriately capture health-related benefit.** **However, we anticipate that there will be discussion at the appraisal meeting on how to appropriately derive QALYs from current models of disability progression in multiple sclerosis.** **For instance, we are aware of one view that there should be an emphasis on preserving upper-limb function in multiple sclerosis.** **.**
16. Do you consider the technology to be innovative in	**This technology has a differing mechanism of action and is highly effective at reducing relapse, MRI progression and has effects on disability progression. It has some advantages over some of**

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	**our other highly active drugs with fewer infusions, less risk of PML and less risk of autoimmune sequelae than our other monoclonal antibody drugs.**
• Is the technology a 'step-change' in the management of the condition?	**No, only a moderate effect in the context of relapsing disease but its effect in primary progressive disease would be a step change.**
• Does the use of the technology address any particular unmet need of the patient population?	**Yes the group of people who have failed on other drugs or who are JC virus carriers have a safer option for treatment.**
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	**The infusion-related side effects of ocrelizumab are common, mild and not significant in the long-term, occiring in about one third of patients.** **Number of serious infections was slightly higher in RRMS trials than with beta interferon (84% v 67.8 % per 100 patient years). Although trials quote 1,3% for ocrelizumab and 2.9% for Rebif. Hepes group viral infections being more common on ocrelizumab.**

	No concerning adverse events emerged from the phase 3 trials of ocrelizumab in multiple sclerosis. There was a slight excess of malignancies (0.28 v0.14 per 100PY on interferon (4 (0.5%) and 2(().2%) patients, confidence intervals overlapped). **From our experience of the long-term use of rituximab in the treatment of neuromyelitis optica, we anticipate that a significant proportion of people treated with ocrelizumab will develop hypogammaglobulinaemia and a few of these would experience opportunistic infections.** **One case of progressive multifocal leukoencephalopathy (PML) was described in a patient with relapsing remitting multiple sclerosis (MS) after treatment with ocrelizumab which was considered to be a "carryover" from treatment with natalizumab. Cases of PML have been described in association with rituximab in disorders other than MS. The SmPC for ocrelizumab states that PML has been observed in patients treated with anti-CD20 antibodies, so physicians should be vigilant For the early signs and symptoms of PML.**
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	**Yes.**
• If not, how could the results be extrapolated to the UK setting?	**N/A**
• What, in your view, are the most important outcomes, and were they measured in the trials?	**The most important outcomes for people with relapsing remitting multiple sclerosis are reduction in number and severity of relapses and the accumulation of disability. Also the number who achieve no evidence of disease progression (NEDA) clinically – no relapses and no progression, plus**

	stability on MRI. The OPERA I and II trials captured this by documentation of relapse, measurement of the Kurtzke EDSS -the "industry-standard" measure of disability. Plus MRI with gadolinium. **A reasonable criticism of the EDSS is that is biased towards ambulation and fails to sensitively capture hand and arm function.**
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	**Ocrelizumab reduced the number of Gadolinium enhancing lesions, new or enlarging T2 lesion and hypointense lesions as well as brain atrophy. MRI is currently our best biomarker for MS activity and progression. In relapsing disease MRI is more sensitive to disease activity than the clinical measurement of relapse.**
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	**Not that we are aware of.**
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**No**.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	**No**

appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	**Ocrelizumab is not in current use to compare. Ritixumab used off licence and in phase II trial has proved effective for MS.**
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	**No.**
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- **Ocrelizumab is the first licenced B cell depleting therapy to be licensed for relapsing multiple sclerosis. A different mechanism offers hope to those who have not responded to other drugs**
- **It reduces relapses by 46-47% compared to the moderately effective drug Beta interferon 1a.**
- **It requires fewer infusions and has less risk of PML than natalizumab and autoimmune disease than Alemtuzumab.**
- **It will require infusion facilities and will need systems for safe monitoring, so may need more investment in MRI, day care facilities and MS nurses**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the	A NICE Clinical Guideline on MS, several TA's on the use of medicines in MS and a NHS England policy on the use of several medicines in MS including beta interferon and glatiramer acetate. The policy can be

condition, and if so, which?	found at https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is current variation in the approach to the treatment of multiple sclerosis with some clinicians taking an incremental approach, starting with drugs of lower toxicity and efficacy and escalating to more potent/toxic therapies if disease breaks through. Alternatively, advocates of "induction therapy" suggest early treatment with more potent/toxic treatments is favourable such as alemtuzumab. NHS England has recently introduced a prior approval system for MS drugs which requires Trusts to register patients on treatment which overtime should identify the level of variation in practice. The key aim will be to agree a national algorithm based on NICE guidance and this clinical practice. The algorithm is due to be published shortly.
8. What impact would the technology have on the current pathway of care?	Relatively small as there are several treatments available for RRMS including oral options
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	It is not currently funded although some patients may be gaining access via eg clinical trials.
10. Will the technology be used (or is it already used) in	It would be delivered in the same way as other existing drugs such as natalizumab and alemtuzumab which are also intravenous drugs.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No different to other treatments such as natalizumab and daclizumab.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should only be prescribed in settings where there is an appropriately constructed MS MDT. As it is IV it will need to be delivered in secondary care day case clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities are already available. The main investment will be for the drug itself if it is more expensive than current treatments.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Unknown

11. What is the outcome of any evaluations or audits of the use of the technology?	There have been no audits on the use of this technology
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any
12b. Consider whether these issues are different from issues with current care and why.	n/a

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Helen Ford**
2. Name of organisation	**Leeds Teaching Hospitals**

3. Job title or position	**Consultant Neurologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.) I was nominated as a neutral clinical expert**.**
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to reduce the rate of relapses in people with relapsing remitting multiple sclerosis (MS). The primary end point in the two phase 3 trials was the annualised relapse rate. By reducing the number of relapses the treatment aims to reduce the accumulation of disability due to MS. This is referred to as disability progression in the clinical trials. A further aim is to reduce the number of active lesions and new or enlarged lesions seen on MRI of the brain.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant reduction in relapse rate for a treatment in MS would be a minimum reduction in relapses by a third compared to placebo. A higher reduction in relapse rate with an active comparator, e.g. licensed first line treatments such as interferon beta, would be expected in new treatments for MS.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need for people with relapsing remitting MS to have access to more effective treatments with a better safety profile than some of the currently approved treatments. There is also a need for treatments which have less impact on people living with MS in terms of frequency of treatment and intensity of monitoring.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England 2014 DMT policy. NICE TAs for natalizumab TA127, fingolimod TA254, teriflunomide TA 303, alemtuzumab TA312, dimethyl fumarate TA320, daclizumab TA441 . Previous DoH Risk Sharing Scheme for Beta-interferon and Copaxone.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not well-defined. There are differences of opinion between professionals across the NHS as to the best treatment approach for relapsing remitting MS (RRMS). There is a more defined pathway for people with rapidly evolving severe MS with highly effective treatments recommended first line. For RRMS with 2 relapses in the last 2 years the two main approaches are an escalation approach starting with a lower efficacy treatment and escalating if there is new clinical activity e.g. a new relapse of MS, or an induction approach starting with a highly effective treatment followed by a maintenance treatment.
• What impact would the technology have on the current pathway of care?	The new technology would provide a highly effective treatment choice with a better safety profile.
11. Will the technology be used (or is it already used) in	The technology can be delivered in the NHS in the same way as current care with infusions on a day-case unit.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The frequency of infusions is every 24 weeks, with the first infusion divided in to two doses on day 1 and day15. This is a reduced frequency compared to natalizumab which is 4 weekly and a higher frequency than alemtuzumab which is annual for at least 2 years.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should be used in MS specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The technology could be introduced in to existing MS specialist services. These services require adequate staffing with MS specialist neurologists, MS specialist nurses and infusion nurses. Adequate fully staffed day-case facilities need to be available to safely deliver intravenous infusions.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	I don’t expect an increase in overall life expectancy.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	I would expect an increase in quality of life compared to other less effective DMTs. The regime for the infusions is less burdensome than some of the other DMTs. This may have less impact on employment and time away from work for people with MS and less impact on home life and any caring responsibilities.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be appropriate for RRMS and Rapidly evolving severe (RES) MS.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The technology will be easier than some treatments as outlined above with a significantly lower frequency of infusions than e.g. natalizumab. However the technology will require infusions at an appropriate day-case unit, usually hospital based, every six months. This is less convenient than a daily oral medication. Concomitant treatment would usually include an antihistamine and an analgesic/antipyretic and a 100mg dose of intravenous methylprednisolone. Infusion related-reactions are common.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are defined starting and stopping or switching criteria for all DMTs in MS. These would apply to this technology.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I think the impact of reduced relapse rate on continued employment for people with MS should be considered. The short-term impact in terms of convenience and reduced time off work to attend hospital for either treatment or monitoring should also be considered.
17. Do you consider the technology to be innovative in	.

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The technology has similar efficacy to other approved treatments. However it may have a better safety profile.
• Does the use of the technology address any particular unmet need of the patient population?	There is an unmet need for people with MS to have access to a new effective treatment without a significant risk of PML, fulminant liver failure or life-long autoimmune conditions.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common adverse effects reported in the Phase 3 clinical trials were infusion-related reactions, nasopharyngitis, upper respiratory tract infection, headache and urinary tract infection. No cases of PML have been reported so far in the clinical studies. In the two Phase 3 trials four neoplasms were reported in the treatment groups Five further neoplasms were reported in the open label extension to 30 June 2016.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	The study population is similar to the population in other MS DMT trials and reflects current UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Annualised relapse rate was the primary end point which is the most important clinical outcome in RRMS. Reduction in sustained disability progression is less meaningful at 12 weeks. In this trial it was measured at 12 and 24 weeks.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MRI was used as a surrogate outcome. This was one of the secondary end points. It was used to assess disease activity by measuring the number of gadolinium -enhancing lesions i.e. currently active lesions and the number of new or enlarging lesions on T2 weighted imaging.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA32, TA127, TA254, TA303, TA312, TA441, TA475]?	TA 475 is for dimethyl fumarate for treating moderate to severe plaque psoriasis and not relevant to this technology. There has been a new Healthcare Professional letter dated 29 November 2017 with reference to daclizumab TA441 and discussed below (Question 24).
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be	Equitable access to MS Specialist Neurologists and MS Specialist Nurses across different regions of England.

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is daclizumab considered to be established clinical practice in the NHS for treating relapsing-remitting multiple sclerosis? How is this expected to change given that its licence has recently been restricted to people whose disease has responded inadequately to at least 2 disease modifying therapies? Approximately how many people have disease that	On 29 November 2017 Biogen in agreement with the EMA and the MHRA sent a Healthcare Professional letter to advise that Daclizumab can cause unpredictable and potentially fatal immune-mediated liver injury. The use of Daclizumab has been restricted only to those in whom treatment with any other DMT would be contraindicated or otherwise unsuitable. In view of this I think that the use of Daclizumab will be minimal in the NHS and can't be considered established clinical practice.

responds inadequately to at least 2 disease modifying therapies and would be eligible for treatment with daclizumab?	
25. Are glatiramer acetate, IFNB-1a (Avonex), IFNB-1a (Rebif), pegIFNB-1a and IFNB-1b routinely used in clinical practice and could they all collectively be displaced from NHS practice by ocrelizumab?	These injectable treatments are still routinely used in the NHS although their use has decreased with the wider availability of newer DMTs. I wouldn't expect that these treatments would be completely displaced from NHS practice by ocrelizumab although there may be further reduction in their use. People with MS have a range of views about acceptable risks of treatment and some people with MS and healthcare professionals may prefer an escalation treatment strategy.
26. In which cases would it not be suitable to recommend treatment with alemtuzumab due to immunosuppressive effects? How would these patients differ to other patients?	Alemtuzumab would not be suitable for people with pre-existing autoimmune disease, thyroid disease, anaemia, thrombocytopenia or renal disease. It would be contraindicated for people with TB, HIV, hepatitis B or C, HPV and other significant infections. Pre-existing or on-going malignancy would also be a contraindication. Alemtuzumab would not be suitable for people with MS who were unable to comply with the required monthly monitoring of blood tests. This may be due to various factors including employment and time required off work or caring responsibilities. Alemtuzumab is contraindicated in pregnancy and for 4 months following a course of treatment.

27. What is your opinion on the likely duration of treatment effect of Ocrelizumab and the possibility of a treatment waning effect?	I'm not aware of any data on a treatment waning effect. In the two phase 3 trials 0.4% developed anti-drug antibodies. This was lower than the comparator drug. However a consistent link between the presence of antibodies and reduced efficacy has not been reported with other anti-CD20 drugs.

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- Ocrelizumab is an effective new treatment for relapsing remitting MS.
- Two large phase 3 trials have shown a significant reduction in annualised relapse rate compared to an active comparator.
- There have been no cases of PML reported so far across all clinical studies. Long term safety monitoring is required to assess the risk of serious infection and malignancy.
- The treatment is given by intravenous infusion every 24 weeks which may be more convenient for some people with MS than other approved DMTs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Helen Goodman**
2. Are you (please tick all that apply):	**x**☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	MS Society
4. Did your nominating organisation submit a submission?	x☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	x☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with Relapsing Remitting MS in 2012 at the age 42. It came as a complete shock to me, I had had some strange pains in my legs and struggled to pick up my feet when walking. Other symptoms followed – 'pins and needles' sensation in my hand which lasted a number of months and made sleeping difficult; numbness around my face; my eyesight was affected with restrictions on vision and when walking my eyes focus did not keep up with my steps which left me very disorientated; extreme sensitivity on my side to the pressure of water spraying when taking a shower. Driving, working and caring for children became very difficult for unpredictable periods of time. The unpredictability of symptoms and their likely duration made me paranoid that every ache or pain was another bout of MS symptoms which coupled with fatigue made life very difficult for me and those around me.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	As part of the trial I did inject myself, (I think 3 times a week) into my stomach. I did not have any reaction to the injections themselves and this may have been because they were a placebo however the inconvenience of having to keep the drug in the fridge and make arrangements to transport the drug and needles when going on holiday was limiting.
10. Is there an unmet need for patients with this condition?	I do not have sufficient knowledge to comment
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	My Ocrelizumab infusions (twice a year) with a pre-visit for blood tests could be considered time consuming as each infusion usually takes up about 4-6 hours. However the results for me have been very positive in terms of no relapses and therefore fully justify these visits.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Depending on where and how frequently treatment will be offered may make it difficult for patients to access it.
Patient population	
13. Are there any groups of patients who might benefit	I have no view on this

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	I cannot think of any equality issues
Other issues	
15. Are there any other issues that you would like the committee to consider?	The emotional issues and impact on mental health and 'hidden' symptons (such as fatigue) need to be considered alongside the physical symptoms of MS. These can have an impact on family and social life as well as the productivity of employees.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • The unpredictability of MS and how it will develop is very daunting and frightening for patients and their families • It can affect the ability of sufferers to carry out tasks we take for granted, such as walking, driving, sleeping	

- Symptoms such as fatigue are not visible and therefore are difficult for others to understand and accommodate
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr David Hunt**
2. Name of organisation	**NHS Lothian and Anne Rowling Multiple Sclerosis Clinic, University of Edinburgh**

3. Job title or position	**Wellcome Trust Clinician Scientist and Honorary Consultant Neurologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. Reduction of relapse frequency in relapsing-remitting multiple sclerosis 2. Reduction of disability progression in relapsing-remitting multiple sclerosis
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. Reduction in annual relapse rate 2. Reduction in sustained disability progression
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Relapsing-remitting multiple sclerosis remains an incurable disease with an unpredictable course which causes an exceptionally high burden of neurological disease in young adults(1). The primary unmet needs are: (i) High efficacy immunotherapy with favourable safety profile (ii) Therapies which halt inflammatory disease activity within the brain.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The Association of British Neurologists (ABN) has produced guidelines for the treatment of relapsing-remitting multiple sclerosis(2). The ABN distinguishes between disease modifying drugs of high efficacy (natalizumab and alemtuzumab) and those of moderate efficacy (all other licenced immunotherapies).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is significant variation in clinical approach to the treatment of relapsing-remitting multiple sclerosis across the UK(2). A key source of variation is the threshold to initiate treatment and the level of risk taken with immunotherapies. (My clinical practice is based in Scotland but I am aware of prescribing practices across the nations of the UK.)
• What impact would the technology have on the current pathway of care?	It is likely that ocrelizumab will become a first-line treatment for active relapsing-remitting MS, in particular those with high inflammatory disease activity (patients currently treated with natalizumab/alemtuzumab). At the current time the efficacy of the drug appears to be similar to that of natalizumab/alemtuzumab, but the serious side effect profile may be favourable.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	Administration and monitoring is similar compared to other available infused drugs (alemtuzumab/natalizumab).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment is likely to be used in specialist neurological centres, by neurologists experienced in the treatment of multiple sclerosis.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most nurses experienced in delivering multiple sclerosis intravenous therapies should be able to deliver the therapy in an established infusion unit, with appropriate training. The infusion requirements of this therapy do not seem to be more onerous or complex than existing therapies.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	There is some evidence that people with multiple sclerosis have a slightly reduced life span and that the introduction of higher efficacy therapies has coincided with improvement in life expectancy, though this effect may be confounded(3).

• Do you expect the technology to increase health-related quality of life more than current care?	The multiple sclerosis functional composite score and SF-36 quality-of-life physical-component summary results in the OPERA I and OPERA II trials were not consistently significantly higher in the ocrelizumab group compared to beta interferon, though were significant in the OPERA II study(4). There are no trials comparing ocrelizumab to higher efficacy MS immunotherapies.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Multiple sclerosis patients who have evidence of infection with the JC virus (about half of MS patients) are at particular risk of developing a serious brain infection (progressive multifocal leukoencephalopathy, PML) if treated with natalizumab(5). Many of these affected individuals would not be prepared to take the c.1% risk of PML associated with natalizumab and therefore ocrelizumab may offer a high efficacy alternative (together with alemtuzumab), with lower PML risk.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The practical implementation of the technology will be equivalent to other high efficacy monoclonal antibodies that are already in use. This will require bi-annual intravenous infusion and monitoring of treatment response with yearly MRI scans in accordance with the ABN recommendations(2). The monitoring requirements may be less than other monoclonal antibodies in certain circumstances (e.g. natalizumab in high risk patients requires 3 monthly MRI scans, alemtuzumab requires long-term monthly monitoring of renal and thyroid function)

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The technology will be used in accordance with EMA licence. It is unlikely that any formal or informal rules, other than EMA, MHRA, ABN or NICE guidance or restrictions will govern use of the technology. At present there is insufficient data to guide at what point treatment might be paused or stopped. Other cell-depleting monoclonal antibodies (alemtuzumab) can induce long-term remission in patients without the need for re-treatment. It is not clear whether ocrelizumab can be used in the same manner. Equally the risks of long-term treatment are not clear.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in	Yes

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The efficacy data presented in the phase III trials, in terms of effect on relapse activity, MRI activity and relapse-related disability, is impressive(4). The finding that almost all inflammatory activity is supressed on MRI brain scans is not observed in any other clinical trial of which I am aware, other than haematopoetic stem cell transplantation(6).
• Does the use of the technology address any particular unmet need of the patient population?	At present the use of high efficacy monoclonal antibodies is limited by significant adverse event profiles. For example, the risk of PML, a severe opportunistic brain infection which is frequently fatal, reaches 1% in individuals with MS who have the JC virus(5). The use of alemtuzumab is similarly restricted by a 30% risk of developing a secondary autoimmune disease. Noting its limited postmarketing use, the side effect profile of ocrelizumab appears to compare favourably at this stage to other high efficacy monoclonals.
18. How do any side effects or adverse effects of the technology affect the	The short-term safety profile in phase III clinical trials appears to be similar to the comparator group treated with interferon-beta, which has been considered a low-risk treatment. However long-term safety data will be

management of the condition and the patient's quality of life?	needed to address key issues of (i) longterm cancer risk (ii) risk of hypogammaglobulinaemia and associated infection and (iii) PML.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials were performed on patients with relapsing-remitting MS with an EDSS score 0-5.5. It is reasonable to extrapolate these findings to current UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	(1) Reduction in annualised relapse rate and (2) Reduction in confirmed disability progression. These were both measured in OPERA I and OPERA II clinical trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	In the clinical trials, MRI outcome measures were used as a secondary outcome measure, rather than a surrogate. These results are consistent with the clinical outcomes described above.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	0.5% of ocrelizumab-treated patients in clinical trials developed cancer (compared to 0.2% in interferon comparator group) and it is not yet clear whether this represents an important delayed safety signal. This is particularly important given that patients might be exposed to the drug over a prolonged period of time.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA32, TA127, TA254, TA303, TA312, TA441, TA475]?	No
22. How do data on real-world experience compare with the trial data?	I am not aware of high quality real-world data on ocrelizumab. A recent paper reporting real-world use of rituximab suggests that the real-world efficacy of this class of drug is high, perhaps the highest efficacy treatment currently available(8). However it should be noted that this is a related but different drug. Both are anti-CD20 monoclonals, but rituximab is a chimeric human/mouse antibody while ocrelizumab is a

	humanised monoclonal antibody, although they share similar pharmacodynamics effects on B-cell depletion, with similar phase II trial results in multiple sclerosis(7, 9).
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is daclizumab considered to be established clinical practice in the NHS for treating relapsing-remitting multiple sclerosis? How is this expected to change given that its licence has recently been	24. Daclizumab is broadly considered to be a drug of last resort in most centres. Use in the UK is low, and expected to remain low following the EMA restrictions. It is unlikely that data will emerge in the short term that will reassure prescribers of the safety profile of this drug, most notably the risk of unpredictable fatal hepatotoxicity. In my experience of treating patients with highly active MS, the large majority respond adequately to either natalizumab or alemtuzumab, although the safety profiles of both are a major concern.

restricted to people whose disease has responded inadequately to at least 2 disease modifying therapies? Approximately how many people have disease that responds inadequately to at least 2 disease modifying therapies and would be eligible for treatment with daclizumab? 25. Are glatiramer acetate, IFNB-1a (Avonex), IFNB-1a (Rebif), pegIFNB-1a and IFNB-1b routinely used in clinical practice and could they all collectively be displaced from NHS practice by ocrelizumab? 26. In which cases would it not be suitable to recommend treatment with alemtuzumab	25. It is likely that there will still be a role for GA/IFN injectable treatments. For example GA is often prescribed during pregnancy. While it is debatable whether these modestly effective therapies offer value for money, or any form of long-term disease modification, many patients are established on this therapy and unkeen to switch. However I do not see the proportion of patients treated with these drugs increasing. 26. The main issue with alemtuzumab is immune reconstitution and secondary autoimmunity rather than immunosuppression. The only major opportunistic infection which appears to be an issue is listeria meningitis, but there is a defined window around treatment and it is likely that this risk can be mitigated. Therefore it is often the risk of secondary autoimmunity that dissuades people with MS from taking this drug, rather than immunosuppression. 27. The length of treatment of high efficacy monoclonals such as alemtuzumab or ocrelizumab remains unclear, in particular the need for retreatment. It is very clear that disease activity returns with some monoclonal antibodies such as natalizumab almost immediately after the drug is eliminated. This is less clear for cell depleting monoclonal antibodies and longer-term data will be needed. Ideally ocrelizumab would be used as an “induction” therapy to induce lasting remission from the disease (in the same way that rituximab is use to treat vasculitis), but I have not seen data suggesting that this is the case.

due to immunosuppressive effects? How would these patients differ to other patients? 27. What is your opinion on the likely duration of treatment effect of Ocrelizumab and the possibility of a treatment waning effect?	
Key messages	

28. In up to 5 bullet points, please summarise the key messages of your statement.

- Ocrelizumab is a high efficacy therapy for preventing relapses in relapsing-remitting MS(4, 9)
- The two pivotal phase III clinical trials provide some of the strongest data yet that strong suppression of inflammatory activity reduces relapse-associated disability(4)
- At this stage, the safety profile of the drug compares favourably with other immunotherapies licensed for RRMS, although further postmarketing studies are needed to clarify potential safety signals with serious infections and cancer.
- There is an increasing consensus that early treatment of MS with high efficacy drugs can prevent the development of disability(2), although to date this approach has been limited by significant adverse event profiles of such monoclonal antibodies (natalizumab, alemtuzumab). The efficacy and safety profile of ocrelizumab suggest that drug may become treatment of choice for patients with active disease early in disease course.
- Real-world observational data from anti-CD20 drugs of this class (note: rituximab rather than ocrelizumab) suggest B-cell depletion may be the most effective treatment strategy in MS to date.(8)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. N Engl J Med. 2018;378(2):169-80.
2. 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. Pract Neurol. 2015;15(4):273-9.
3. Lunde HMB, Assmus J, Myhr KM, Bo L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry. 2017;88(8):621-5.
4. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221-34.
5. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366(20):1870-80.
6. Atkins HL, Bowman M, Allan D, Anstee G, Arnold DL, Bar-Or A, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet. 2016;388(10044):576-85.

7. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676-88.
8. Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. JAMA Neurol. 2018.
9. Kappos L, Li D, Calabresi PA, 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(9805):1779-87.

NICE National Institute for Health and Care Excellence

Patient expert statement

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Evelyn King**
2. Are you (please tick all that apply):	☐ a patient with the condition?

3. Name of your nominating organisation	Multiple Sclerosis Society
4. Did your nominating organisation submit a submission?	☐ yes, they did
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with Multiple Sclerosis (MS) can be very challenging due to the unpredictability of the onset of temporary symptoms and the loss of function brought on after relapses. After my first relapse and subsequent diagnosis with MS, I had been left with numbness in my left hand resulting in a loss of fine motor skills. I was left unable to differentiate whether an item was wet or cold to the touch. I had previously enjoyed my hobbies of needlework and cake decoration which I could no longer manage due to a loss of dexterity. After my second relapse, I lost feeling in all of the toes of my left foot which affected my balance and I was left with repeated muscle spasticity in my left leg. My sleep became increasingly disturbed by the necessity to use the bathroom during the night, further adding to symptoms of fatigue. Prior to starting the Ocrelizumab therapy, I experienced constant “brain fog” and fatigue. Prior to diagnosis, I had been able to study and work in a physically demanding career for lengthy periods with no ill effect. After my first relapse, I was unable to continue with my studying for several months as my ability to concentrate was greatly impaired. If I had exerted myself physically or mentally one day, I would be suffering greater levels of fatigue,pain or brain fog on the next day. During exposure to cold and hot

	temperatures, I would experience temporary optic neuritis resulting in impaired visual sharpness. In addition I experienced a constant flu-like state once I started using the Disease Modifying Medication (DMM) Rebif. I would have to ensure I had twelve hours bed rest after injecting Rebif or else I would suffer wooziness and muscle weakness. This had a large impact on my day-to-day ability to function with any sort of normality.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	As there is no cure for MS, the current selection of DMMs for relapsing remitting MS (RRMS) available offer respite from prolonged relapses and the accompanying resultant damage. When patients are diagnosed with the condition and offered an option to prevent more frequent relapses but told of the potentially debilitating side effects, a significant proportion of patients refuse to start DMMs. They believe that the benefits do not outweigh the difficulties such as the thought of self-injection, stomach upsets, constant flu-like symptoms, injection site infections and scarring. Hence many people with RRMS do not take DMMs as they would rather adopt a “wait and see” approach. On many occasions I questioned whether the risk of relapse was the lessor of two evils compared to the significant side effects I experienced. Also some patients are not offered any DMMs as their MS is not considered sufficiently active but have to live with the symptoms of their disease with no respite.
10. Is there an unmet need for patients with this condition?	There are currently no medications offered for patients diagnosed with Primary Progressive MS (PPMS). There are currently no DMMs which offer respite from symptoms of MS such as “brain fog”, fatigue, vision problems, heat sensitivities, muscle weakness and spasticity. There are currently no DMMs which can reverse previous neurological damage.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Since starting the Ocrelizumab treatment, I have experienced huge improvements in my symptoms and in the previous neurological damage. From the day after my first infusion, the brain fog lifted. I had not realised how bad it was until it was no longer there as I had lived with it for six years and had normalised that level of function. My walking speed and stamina have all increased since taking Ocrelizumab. My fine motor skills have improved significantly. I can tolerate heat and freezing temperatures with no ill-effect. I have not experienced any temporary episodes of optic neuritis. If I physically or mentally exert myself, I do not need days afterwards to recover. In the past urinary tract infections have brought on full MS relapses requiring steroid treatment. I experienced such an infection recently and no full relapse occurred. A major time advantage is the six-monthly administering of the infusion. I can block out one day for treatment knowing that I will be covered for six months. Also the immediate side effects are minimal: a slight wooziness on the day of infusion but nothing worst than what I had experienced three times a week whilst taking Rebif.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Lack of local availability: I have a two hour journey to access the treatment (which I happily undertake for the huge health benefits I have obtained).
Patient population	
13. Are there any groups of patients who might benefit more or less from the	Any patients whose first DMM is starting to lessen in effectiveness. Anyone who is fearful of self-injection.

technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality of location as the treatment has to be administered under nursing supervision.
Other issues	
15. Are there any other issues that you would like the committee to consider?	While there is no cure for MS, this treatment has offered me a cure in all but name. Ocrelizumab has offered complete respite to my symptoms, both historic and current for the majority of the period between infusions. Between my first and second infusions, I had 20 weeks of living symptom free. Between my second and third infusions, I experienced 25 weeks. My quality of life and that of my family has been improved dramatically since starting Ocrelizumab. I no longer feel that I am living with MS, waiting for the next onslaught of symptoms and fearing the next relapse and subsequent neurological damage.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Ocrelizumab has offered me the opportunity to live symptom-free for the first time in six years. • It may not be a cure for Multiple Sclerosis but on a day-to-day basis, its feels like one.	

- I had no expectation of reversal of functional neurological damage, but this has happened for me.
- It is far more convenient, non-intrusive and with fewer side-effects than Rebif.
- I no longer fear the progression of degeneration from MS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Ocrelizumab for treating relapsing multiple sclerosis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors and clinical advisors

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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

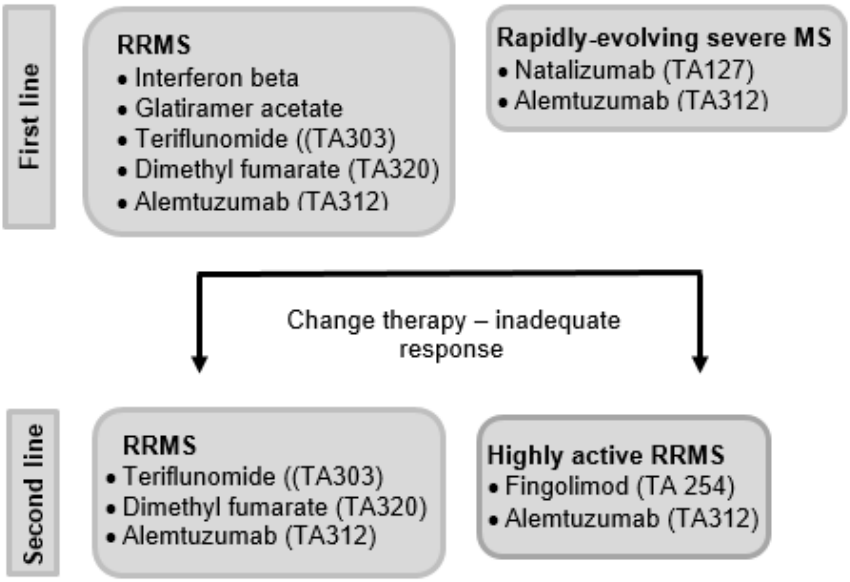
The CS suggests that the early use of DMTs is limited by safety concerns, as well as specific patient eligibility criteria as defined by EMA and NICE. ABN guidelines state that the safety profiles for DMTs such as of interferon β and glatiramer acetate have been established due to their long-term use, 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.

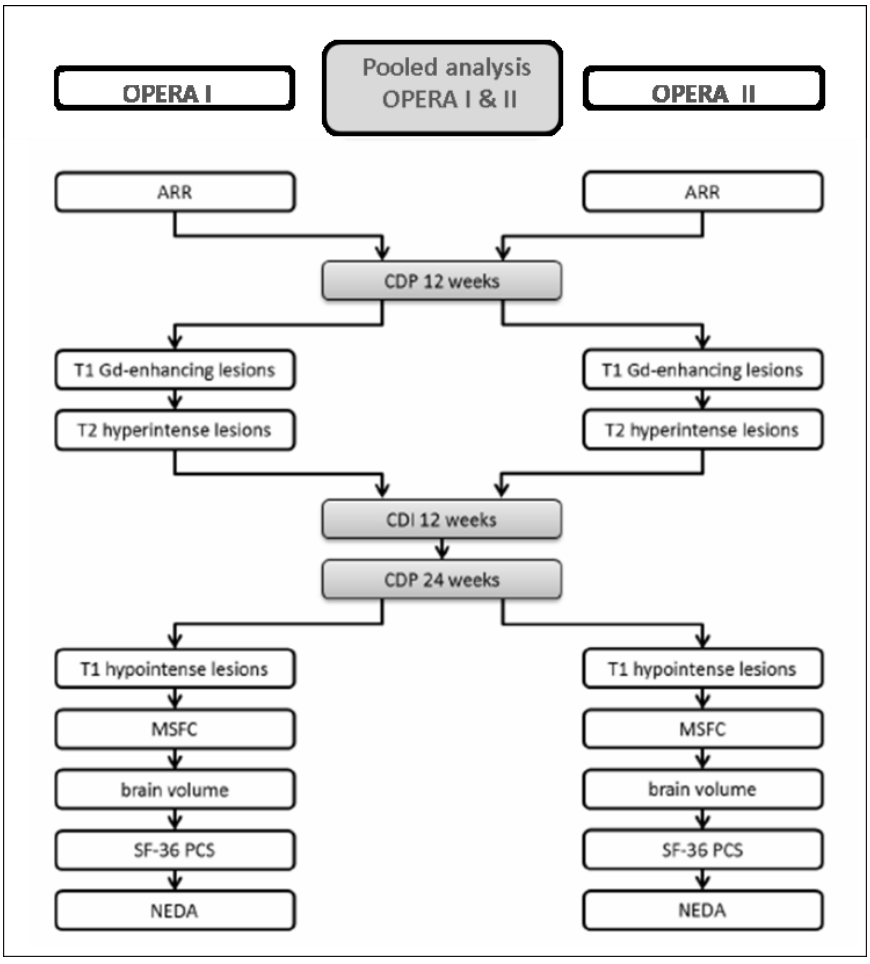


Figure 2 Hierarchical order of testing effectiveness outcomes in the OPERA trials (from CS Figure 3)

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.

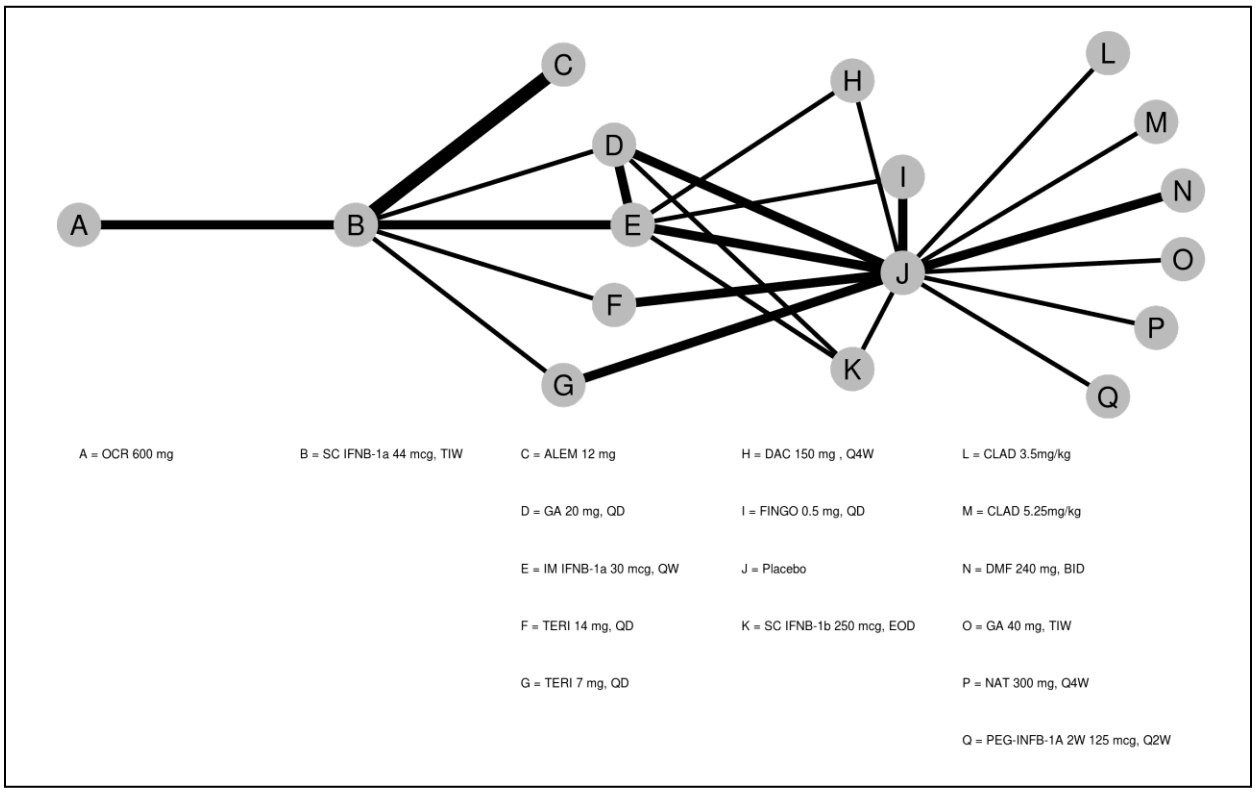
Note that the above considerations refer to clinical effectiveness outcomes, not safety outcomes (adverse events were not analysed in MTCs but are reported separately in the CS, including for the ocrelizumab phase II trial; for details see section 3.3.9 below).

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]

[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)

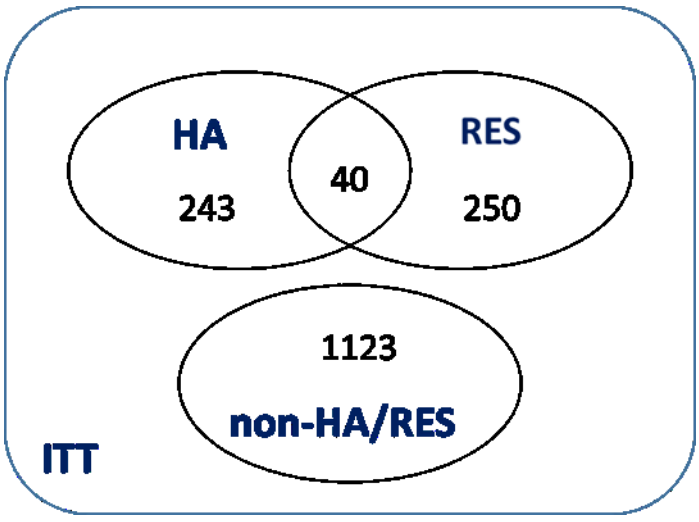
Comparators differ between groups 1 to 4 (see Table 34), so it is necessary that they are modelled separately. This suggests that, although labelled as 'relapsing-remitting multiple sclerosis', the first group should exclude people with RES or HA disease (because they are not

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.

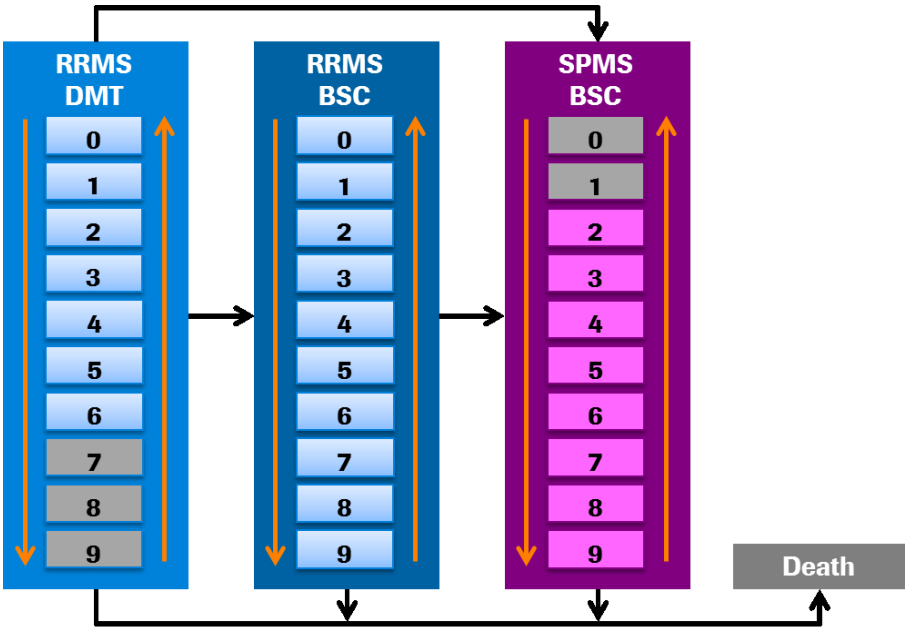


Figure 5 Illustration of model structure (copied from CS Figure 24)

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).

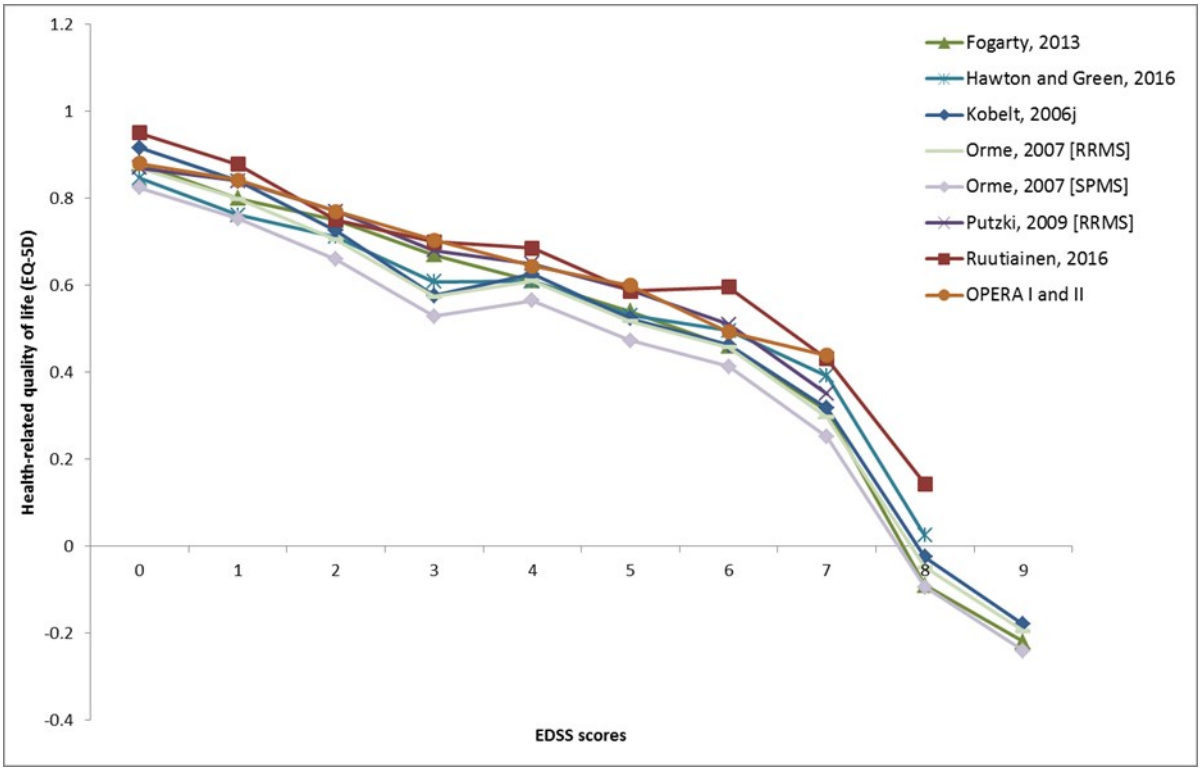


Figure 6 Consistency of EDSS-dependent utility values: CS Figure 25

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.

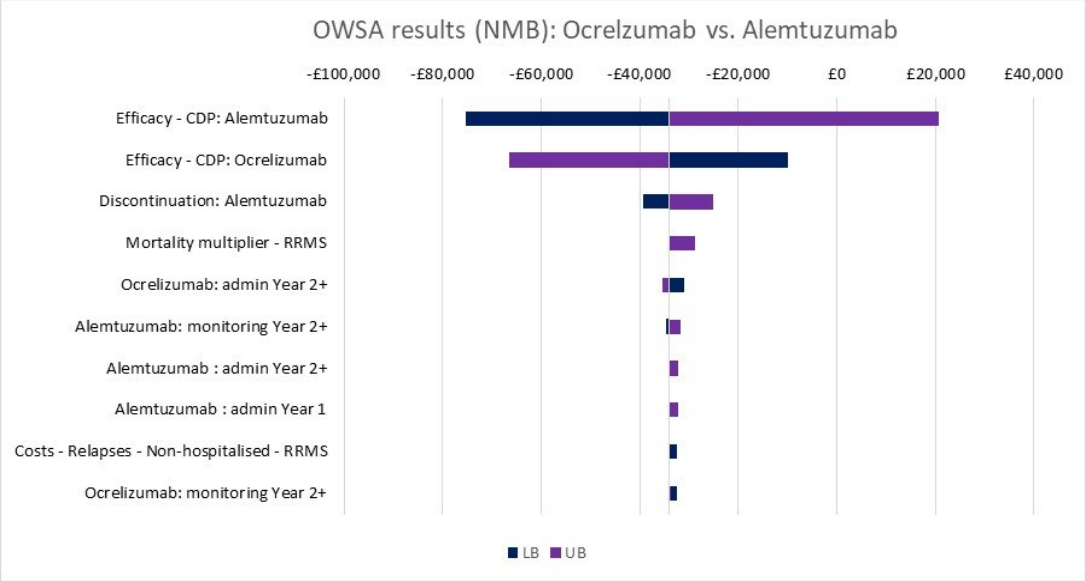


Figure 7 Tornado diagram: company ITT base case ocrelziumab vs alemtuzumab (PAS price for ocrelizumab)

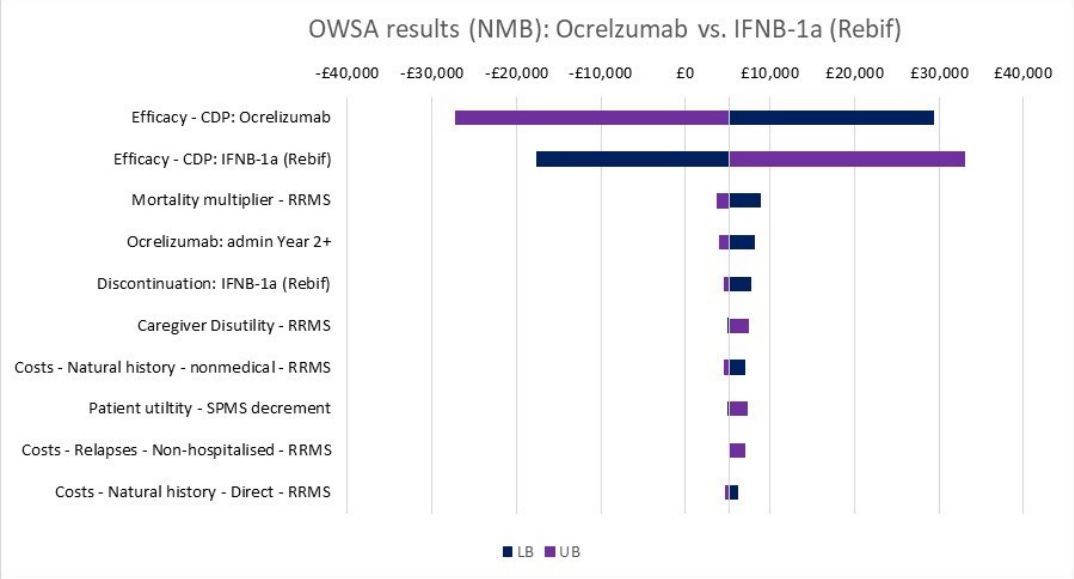


Figure 8 Tornado diagram: company ITT base case ocrelizumab vs IFNβ-1a (Rebif) (PAS price for ocrelizumab)

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

Appendix 2 continued

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).

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

You are asked to check the ERG report from Southampton Health Technology Assessment Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 16 February 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Updated page numbers in brackets refer to track changes view

Issue 1 Page 150 ***page in updated report: 147 (151)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incomplete representation of facts The ERG report states that "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 form the ocrelizumable OLE study. However, in the absence of a review, we cannot draw conclusions about the relative persistence of effects for different DMTs." It is important to mention that previous NICE appraisals also acknowledged the importance of neutralising antibodies in treatment waning, which is reflective of the viewpoints of other clinical experts.	"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, as well as the fact that previous NICE appraisals in RRMS have acknowledged the role of neutralising antibodies in treatment waning [...]"	The statement about neutralising antibodies is not representative of other viewpoints by clinical experts, including those referred to in official NICE and EMA documentation. The daclizumab NICE guidance refers to the role of neutralising antibodies in treatment waning (section 4.14: "It heard from clinical experts that most treatments for multiple sclerosis become less effective over time, either because of neutralising antibodies or because the disease becomes more severe and resistant to treatment.") The EPAR Scientific Discussion of natalizumab also refers to the role of persistent anti-drug antibodies in treatment waning ("Persistent antibodies were associated with a substantial decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions".) A more balanced consideration of the evidence provided by the	Not a factual inaccuracy. The statement accurately reflects the opinion of the ERG's clinical advisors. The NICE daclizumab guidance states in concluding its section 4.14 "However, the committee did not see evidence on the waning effect of individual therapies." We have updated the text in Table 51 to clarify that there is a need for a review of long-term follow-up studies for all DMTs.

		Company and previous clinical experts at NICE appraisals for RRMS may have led to a different conclusion about the clinical plausibility of applying treatment waning assumptions to ocrelizumab. In order to assist decision making, we would like to request clarification from the ERG what kind of review they would expect to see in order to assess relative persistence of effects for different DMTs. To our knowledge a review of OLE data from different DMTs has not been performed/published before. The presence of Gd lesions could be considered a leading indicator of long-term treatment waning as these lesions are a precursor to clinical disease activity (i.e. breakthrough disease).	

Issue 2 Page 22, 134, 149, 162, 170 ***pages in updated report: 21 (22), 131 (135), 146 (150), 160 (164), 168 (172)***

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Incomplete representation of facts The ERG report describes CDP-24 as a more robust measure of progression, because it is less likely to be confused with longer relapses without highlighting	In addition to the stated preference for CDP-24 as a clinical measure unaffected by long relapses, we propose that the ERG report also acknowledges the limitations of	CDP-12 was pre-specified as a primary or secondary endpoint in 71% of the trials included in the CDP-12 ITT MTC while CDP-24 was pre-specified in only 48% of the trials included in the CDP-	Pages 21,160 & 168: Not factual inaccuracies. These are statements of the ERG's view. No changes made.

the limitations of CDP-24.	this measure: "There are other factors such as quality and quantity of data that diminish the robustness of CDP-24, particularly in the context of evaluating comparative efficacy using MTCs."	24 ITT MTC. When outcomes are not pre-specified, there is no regulatory requirement to report results, leading to potential publication bias. The CDP-12 network also contains more data than the CDP-24 MTC: the ITT analysis is informed by 27 hazard ratio data inputs from 24 studies, for a total of 38 000 person-years, and includes 25 pairwise comparisons and 6 loops of evidence. Conversely, the CDP-24 ITT network is informed by 23 data inputs from 21 trials for a total of 31 000 person-years, 18 pairwise comparisons and 3 loops, fewer than CDP-12 MTC on every measure.	Page 131: Not a factual inaccuracy. (1) It is a statement of ERG's view; (2) ERG report states correctly that CDP24 is the preferred measure by NICE and EMA; (3) ERG report clearly states the company's concern that "CDP24 is less robust due to the lower quality and quantity of data". No changes made. Page 146: Not a factual inaccuracy. The statements in Table 51 accurately reflect both the company's and the ERG's viewpoints on CDP12 and CDP24 outcomes. No changes made.

Issue 3 Page 118, 119 ***pages in updated report: 115 (118), 116 (119)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Statement not in line with the scope and with previous appraisal The ERG report states "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	Please remove this section and subsequent mentions of non-HA/RES cost-effectiveness results.	We agree that the scope could have been defined more clearly. However, it states 'relapsing-remitting multiple sclerosis' without specifying this excludes people with RES or HA disease. Previous NICE appraisals had similar scopes which were interpreted by other Companies and Committees	Pages 115 and 116: Not a factual inaccuracy. The term non-HA/RES avoids unnecessary ambiguity surrounding the kind of patients in each group- the three subsets of ITT are eligible for different comparators and should not be

above is therefore better thought of as 'non-HA/RES' RRMS." This cannot be concluded as such from the NICE scope, and is contrary to previous NICE appraisals and can be seen as being misleading.		as including patients with active RRMS, RES RRMS, and HA RRMS. Therefore, we argue that the CS is aligned to the scope. The definitions for RES or HA disease were first coined during the regulatory approval process for natalizumab and fingolimod. Older studies in RRMS, i.e. most of the studies evaluating interferons-beta and glatiramer acetate, do not consider these sub-populations. The studies that do report results for RES or HA rarely report the converse results for non-RES or non-HA, and a MTC for non-RES/non-HA would likely not have been feasible or would have had significant limitations due to sparsity of data and risk of publication bias. This is acknowledged on page 169 of the ERG report ("However, conducting a revised MTC for people without HA or RES MS […] might not be possible at all unless sufficient other trials report results excluding HA and RES subgroups.").	combined in a single incremental analysis. No changes made.

Issue 4 Page 10 (and page 42, 53, 182) ***pages in updated report: 10 (11), 41 (43), 52 (54), 180 (184)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Statement not in line with the scope and	Disability is specified in the NICE scope, not EDSS scores. We	The decision problem requests disability (for example, expanded	Pages 10, 41, 52: Not factual inaccuracies. EDSS scores are

with previous appraisal The ERG report states that EDSS scores are specified in the NICE scope and not reported in the CS.	suggest to remove EDSS scores from the discussion about outcomes specified in NICE scope but not reported in the CS.	disability status scale [EDSS]) to be measured. In RRMS, disability is measured by confirmed disability progression on the EDSS scale sustained for 12 or 24 weeks (CDP-12 or CDP-24, respectively). This is what the CS reported, and as such is in line with the NICE decision problem and previous appraisals in RRMS. EDSS scores on their own, without a definition for clinically meaningful progression or improvement, do not describe disability as an outcome. The impact of this error is minimal, but amending it avoids the impression that the Company did not adhere to the NICE scope for reporting of disability outcome.	explicitly stated as an outcome in the NICE scope (CS Table 1). We do not agree with the assertion that EDSS scores do not measure disability. The company's decision problem in CS Table 1 does not mention any of the issues raised here in the factual inaccuracy check response and states the outcomes were "as per NICE scope", which is not correct. No changes made. Page 180: Not a factual inaccuracy. We correctly point out that EDSS scores were exploratory outcomes that were measured but not reported. No changes made.

Issue 5 Page 162 ***page in updated report: 160 (164)***

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Missing references and incomplete representation The ERG report states that caregiver disutility in the CS base case is "Sourced from TA127 (maximum disutility 0.14 at EDSS 9)".	"Sourced from TA127, TA254, TA303, TA312, and TA320 (maximum disutility 0.14 at EDSS 9)."	We followed NICE's recommendation at the decision problem meeting to use data inputs for the model that are consistent with previous appraisals in RRMS. As such, many of the data inputs were in line with the majority of previous RRMS appraisals (see Table 25 in the CS). Five of the seven previous RRMS appraisals applied the	Page 160, Table 60: Not a factual inaccuracy. TA127 was the original source of the 0.14 disutility figure; therefore, it is not necessary to list subsequent sources. A justification for our choice of caregiver disutilities is already provided in Table 60 and no further justification has been

		same source for caregiver disutility. The ERG choice of source was only used in one of the seven previous RRMS appraisals as summarised in Table 25 of the CS. In the wider context of consistency across appraisals in the same disease area and precedents set of previously accepted data inputs, we suggest the ERG report includes a justification for their choice of source for caregiver disutility.	added. We based our analysis on the most recent relevant committee judgement.

Issue 6 Page 120 ***page in updated report: 117 (120)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Statement not based on evidence The ERG report states "Thus the cost-effectiveness of ocrelizumab is likely to be worse for patients without HA or RES than is suggested in the company's base case results."	"Thus the cost-effectiveness of ocrelizumab may be different (better or worse) for patients without HA or RES than is suggested in the company's base case results."	No conclusion can be drawn about likely improvement or worsening of cost effectiveness of ocrelizumab in patients without HA or RES without knowing the results for the comparators in patients without HA or RES.	The description conveys our estimation correctly. For clarity, we have added "compared with IFNβ-1a" to the sentence; and we have added a further sentence stating that "The effect of excluding patients with HA or RES from the comparisons with other DMTs is uncertain."

Issue 7 Page 162 ***page in updated report: 160 (164)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Costs were not inflated to current year in	Please update the costs to	No justification is given for not uprating	This was an error in our

the ERG base case The ERG base case applies UK MS Survey 2007 uprated to 2011/12, […]	current year or add a commentary regarding the likely impact of not inflating costs to current year.	the cost estimates to a more recent year, and no discussion is included of the impact of using costs from 2011/12.	reporting. In fact, the health state costs that we used in the ERG base case (UK MS Survey estimates extracted from the Warwick addendum to their report for TA320) had already been inflated to 2014/15 prices. This has been corrected in Table 60 (page 162) and also in the last paragraph on page 140. Note that we have also uprated these cost estimates to 2015/16 prices in an addendum to the ERG report (Addendum 2, which updates Addendum 1).

Issue 8 Page 15 and 99 ***pages in updated report: 15 (16), 99 (103)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Misleading statement The ERG report states: "Ocrelizumab was not effective at reducing relapses or progression events when compared against alemtuzumab, cladribine (not in the scope) or natalizumab."	"There is no evidence of a difference between ocrelizumab, natalizumab, or alemtuzumab in reducing relapses or progression as the credible intervals cross 1."	The statement in the ERG report may be misinterpreted to mean that ocrelizumab is less effective than natalizumab or alemtuzumab. The MTCs demonstrated that there is no statistical difference between these high-efficacy DMTs and they can be considered to have similar efficacy.	Pages 15 & 99: We agree that the company's suggested wording is more appropriate and we have updated the text on both pages accordingly

Issue 9 Page 13, 21, 58, 59, 92, 98, 169, 182 ***pages in updated report: 13 (14), 21 (22), 58 (60), 59 (61), 92 (95), 98 (101), 167 (171), 180 (184)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect statement The ERG report states at various points that "The secondary MRI outcomes, NEDA, MSFC score and SF-36 PCS score outcomes have unexplained missing data compared to the ITT population, with more data missing from the interferon β-1a arm than from the ocrelizumab arm in both OPERA trials."	The missing data is explained in the CS and we therefore propose to amend this statement to "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 footnote to Table 11 in the CS explains the reasons for missing data: • MRI outcomes: based on number of patients with MRI scans at week 96 • Brain volume: based on number of patients with MRI scans at week 24 and week 96 • NEDA: based on number of pts with EDSS >= 2 (in order to minimise measurement error) • SF36 and MSFC: based on number of patients with measurements at baseline and week 96 No patients were excluded but rather only those with actual data within the design constraints of the endpoint, were included in the analysis. The unbalance between treatment arms is a result of the higher proportion of patients in the IFNB-1a arm who withdrew from treatment, see Figure 3 in the CS Appendix.	Not a factual inaccuracy. The footnotes for CS Table 11 specify the number and type of missing data but do not explain reasons for the data being missing (i.e. <u>why</u> scans or questionnaire scores were missing). This cannot be inferred from Figure 3 in the CS Appendix since the Figure does not specify missing data by outcome. The rationale for restricting NEDA to a subgroup was not explained; the current explanation provided here by the company ("to minimise measurement error") is unclear as no rationale is given for the specific EDSS cut-off used. As the company has now explained in this document that the missing outcomes data were due to the more frequent dropout in the IFN β1-a arm we have adjusted text to reflect this on pages 14, 22, 59, 167 and 180 (no changes have been made to

			pages 58, 92, 98).

Issue 10 Page 22, 113, 169 ***pages in updated report: 21 (22), 110 (113), 167 (171)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect statement The ERG report states that "The company provided summary data on adverse event rates in the OPERA trials open-label extension study but did not detail specific adverse events that occurred."	"The company provided summary data on adverse event rates in the OPERA trials open-label extension study and detailed data for the specific adverse events included in the economic analysis."	In response to clarification question A28b the list of adverse events included in the economic analysis was updated with safety data from the open-label extension study.	We agree that adverse event rates that occurred in ≥5% of patients in any arm have been provided for the OLE study in clarification A28b and do not appear to raise any safety concerns. The text has been updated accordingly: Pages 21 and 167: bullet removed. Page 110: final sentence removed.

Issue 11 Page 22, 162, 170 ***pages in updated report: 21 (22), 160 (164), 168 (172)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Misleading statement The ERG report states that "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." And related to the long-term	"Rates of retreatment for alemtuzumab in the company base case model assume that 13% of patients are retreated after year 5. Long-term estimates of alemtuzumab re-treatment in routine practice are	The evidence that forms the basis of this estimate is from an analysis of the individual patient level data as reported by Tuohy et al 2015, which describes long-term use of alemtuzumab in UK routine practice. The statement that this is unrealistic in current UK practice is therefore not supported by data from this	Pages 21, 160 and 168: Not a factual inaccuracy. Our experts advised that the NHS would not fund such ongoing levels of retreatment. And the Tuohy et al. paper does not provide evidence for this – 1 of 87 people had five cycles over

alemtuzumab re-treatment rate “CS assumption not backed by evidence.”	uncertain.”	observational study. However, what can be said is that the estimate is uncertain.	maximum follow up of 12 years (median 7 years).

Issue 12 Page 116 ***page in updated report: 113 (116)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Misleading statement The ERG report states that “Alemtuzumab is also excluded from results for the HA and RES subgroups.”	“Alemtuzumab is not included in results for the HA and RES subgroups due to lack of reported CDP-12 data.”	The ERG statement may be misinterpreted to mean that the Company decided to exclude alemtuzumab. However, the only reasons this comparator was not included in results was because there was no data available for CDP-12.	Page 113: Not a factual inaccuracy. The CS does not include Alemtuzumab in any HA or RES analyses and scenario with CDP24 in subgroups is not reported.

Issue 13 Page 122 ***page in updated report: 119 (122)***

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Completeness of statement Related to blended ABCRs, the ERG report states that “The company justify this by stating that these drugs are ‘generally considered by clinicians to be broadly equivalent’ (CS page 125).”	“The company justify this by stating that these drugs are ‘generally considered by clinicians to be broadly equivalent’ (CS page 125), but are not identical due to different modes of administration, dosing regimens, auto-immunogenicity, efficacy and safety profiles, and costs (response to clarification question B2).”	We elaborated on the reason for blending these comparators in our response to clarification questions.	Page 119: Not a factual inaccuracy. The suggested wording does not further explain the reason for using a blended ABCR comparator. On the contrary, it suggests reasons why it might not be appropriate.

Spelling mistakes and other corrections

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47 All three studies were sponsored by F. Hoffman-La Roche.	All three studies were sponsored by F. Hoffmann-La Roche.	Correct spelling of the Company name	Thank you, this has been corrected [page 46 in updated report]
Page 75 The mean time since first symptoms (presumably measured in years, although this is not stated) was reported in 22 trials (CS Appendix Table 12).	The mean time since first symptoms (measured in years) was reported in 22 trials (CS Appendix Table 12).	Table 8 of Dossier B reports *"Mean time since symptom onset, years (SD)"* from the OPERA trials; as those exact values are repeated in Table 12 of the Appendix it can be concluded that the values reported have been measured in years.	We agree that the company's suggested wording is more appropriate and have updated the text accordingly [page 74 in updated report]
Page 80 […] and a discussion, in varying in detail across comparisons […]	[…] and a discussion, varying in detail across comparisons […]	Correction	Thank you, this has been corrected [page 80 in updated report]
Table 21 (Page 90) Within the table, the grey shadowed rows state CPD12 and CPD24	Change to CDP12 and CDP24	Correction of spelling mistake	Thank you, this has been corrected [page 90 in updated report]
Page 107 […] Based on an overall anlaysis […]	[…] Based on an overall analysis […]	Correction of spelling mistake	Thank you, this has been corrected [page 104 in updated report]
Page 107 The CS reports the baseline prevalence and post-baseline incidence of anti-drug antibodies (ADA) to ocrelizamab […]	The CS reports the baseline prevalence and post-baseline incidence of anti-drug antibodies (ADA) to ocrelizumab […]	Correction of spelling mistake	Thank you, this has been corrected [page 105 in updated report]

Page 130 The company uses the same matrix to reflect transition in the higher risk subgroup.	The company uses the same matrix to reflect transition in the HA subgroup.	Correction	Thank you, this has been corrected [page 126 in updated report]
Page 132 As with disability progression in RRMS, the ITT transition probability matrix was applied to the RES and HA subgroups for patients with SPMS.	As with disability progression in RRMS, the ITT transition probability matrix was applied to patients with SPMS.	Correction	We have clarified our meaning: "The company applied the British Columbia transition matrix for the RES and HA subgroups after conversion to SPMS." [page 128 in updated report]
Page 150 We acknowledge the evidence of sustained benefit form the ocrelizumable OLE study.	We acknowledge the evidence of sustained benefit from the ocrelizumab OLE study.	Correction	Thank you, this has been corrected [page 147 in updated report]
Page 162 Assume maximum, disutility of 0.05 with		Unfinished sentence	We have completed this sentence: "Assume maximum disutility of 0.05 at EDSS 9". [page 160 in updated report]
Page 168 Overall, given the limitations of the subgroup analyses, including that they post-hoc and potentially at risk of selection bias, […]	Overall, given the limitations of the subgroup analyses, including that they were post-hoc and potentially at risk of selection bias, […]	A word is missing and needs adding	Thank you, this has been corrected [page 166 in updated report]
Page 172 Compared with natalizumab, ocrelizumab has favourable ICERs (note that ocrelizumab is estimated to be less effective but also less costly than ocrelizumab, so the high ICERs are favourable) […]	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) […]	Correction	Thank you, this has been corrected and repetitive text has been deleted [page 170 in updated report]

Additional errors and inconsistencies corrected by the ERG

Location (page numbers in brackets refer to track changes view)	Issue and correction made
Page 2	Some missing table and figure numbers have been added to the copyright assignment statement
Page 2	Clinical expert professor Ciccarelli updated her conflict of interest declaration and text has been added to reflect this
Page 8 and throughout	Inconsistent abbreviations for CDP12, CDP24, CDI12, CDI 24 have been standardised to CDP-12, CDP-24, CDI-12, CDI-24 in the abbreviations list and throughout. Missing CDP and CDI abbreviations have been added to the list.
Page 9 and throughout	The abbreviation for ocrelizumab was inconsistent (OCB / OCR / OCM) and has been standardised to OCR in the abbreviations list and throughout
Page 9	Unused abbreviations LOCF and WTP have been removed from the abbreviations list
Page 10 (11)	Missing word 'problem' has been added in the second bullet
Page 18 (19)	Second paragraph, references to Tables 1, 2 and 3 have been corrected
Page 19 (20)	Spelling of 'definitions' has been corrected in the second bullet
Page 21 (22)	Incorrect word 'allows' in 7th bullet has been removed
Pages 22-23 (23-24)	References to Tables 4, 5 and 6 in the text have been corrected
Pages 18 (19), 22 (23), 23 (24), 137(141), 149 (153), 155 (159), 157 (161), 161 (165), 163 (167), 164 (168), 169 (173), 170 (174)	The addendum containing the PAS analysis results was referred to inconsistently and the reference has been standardised to "Addendum 1 to this ERG report"
Page 46 (48)	Table number has been corrected for the continuation of Table 10
Page 49 (51)	As Table 11 splits across non-facing pages, a repeat header row and table continuation caption have been inserted to assist readers of the printed copy
Page 49 (51)	Footnote c for the mean EDSS score in Table 11 has been removed as there is no corresponding footnote definition

Pages 83-84 (85-86)	Text has been moved from above Table 16 to below Table 16 so that the Table does not split across pages
Page 85 (88)	Missing word ‘to’ has been inserted in confidence interval ranges in Table 17
Pages 88 (91)	Pooled OPERA trial data in Table 19 and Table 20 are from the trial publication and differ slightly from those in CS Table 11 (as used in NICE PMB slides). Footnote c has been added to clarify this.
Page 98 (101)	The rate ratios for the three MRI lesion types given in the first paragraph were for OPERA I only. Missing rate ratios for OPERA II have been inserted.
Page 99-100 (102)	Text has been moved from above Table 28 to below Table 28 so that the Table does not split across pages
Page 113 (116)	EMA reference citation corrected
Page 118 (121)	References to footnotes a and b in Table 34 have been added
Page 125 (129)	Paragraph under heading for 4.3.4.2, text has been corrected to “with only best supportive care”
Page 126 (130)	Second paragraph, British Columbia database, text has been corrected to “age ≥ 28”
Page 128 (132)	Under heading ‘Relapse rates’, text has been corrected to “based on pre-treatment natural history data”
Page 131 (135)	Inconsistent reference citation format at end of page has been corrected
Page 133 (137)	Table 43 caption has been updated to clarify the source data
Page 138 (142)	First paragraph, text has been updated to clarify that we added the 5% uplift in half the cost of ocrelizumab to adjust for the HCC in the ERG base case analysis (not as a scenario analysis)
Page 140 (144)	AIC markup in Table 47 has been adjusted to match NICE standard (block highlighting replaced with highlighting per AIC data value)
Page 145 (149)	First bullet point, “Re” has been corrected to “We”
Pages 146-148 (150-152)	As Table 51 splits across non-facing pages, a repeat header row and table continuation caption have been inserted to assist readers of the printed copy
Page 155 (159)	Spelling of “estimated” has been corrected
Page 161 (165)	First paragraph, corrected spelling of ‘comparators’, ‘treatments’ and ‘preferred’

Page 161 (165)	Corrected reference to PAS ERG base case scenario analysis: Table 9 in the confidential addendum
Page 163 (167)	Corrected reference to PAS ERG HA analyses: Tables 10 and 11 in the confidential addendum
Page 164 (168)	Repetitive text repeating that ICERs are favourable has been deleted
Tables 33-44, 46-66 Figures 4-8	Inconsistent table and figure captions have been standardised to 11 point bold