Title: *Ofatumumab for treating relapsing multiple sclerosis [ID1677]*

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Contributions of authors

Yen-Fu Chen (Associate Professor), Wendy Knerr (Independent Researcher) and Fatai Ogunlayi (Public Health Specialty Registrar) critiqued the indirect treatment comparisons and critiqued the clinical effectiveness evidenced; Peter Auguste (Research Fellow) and Mandana Zanganeh (Research Fellow), supported by Ji-Eun Park (Research Fellow), reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Mubarak Patel (Research Assistant) reviewed and critiqued the statistics and undertook any additional analyses; Haseeb Moiz, (Academic FY2) provided the clinical summary, Amy Grove (Associate Professor) critiqued the decision problem; co-ordinated and conducted the critique of the clinical effectiveness evidence and co-ordinated the project and the report; Anna Brown (Information Specialist) and Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Carl Counsell (Clinical Reader), Olga Ciccarelli (Clinical Professor), and Dr Tarunya Arun (Consultant Neurologist), provided expert clinical advice Xavier Armoiry (Honorary Clinical Fellow) reviewed and critiqued the company submission, clinical and cost-effectiveness evidence and report.

Please note that: Sections that contain ‘academic in confidence’ and ‘commercial in confidence’ information have been redacted.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AE	Adverse events
ABN	Association of British Neurologists
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ARR	Annualised relapse rate
BNF	British National Formulary
BSC	Best Supportive Care
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CDW	Confirmed disability worsening
CEAC	Cost-effectiveness acceptability curve
CI	Confidence intervals
CrI	Credible intervals
CRD	Centre for Research and Dissemination
CS	Company submission
CSR	Clinical study report
DMT	Disease-modifying therapies
EDSS	Expanded disability status scale
EM	Effect modifiers
ERG	Evidence review group
ESS	Effective sample size
EU	European
FAS	Full analysis set
FDA	Food and drug administration
GA	Glatiramer acetate
HCHS	Hospital and Community Health Service
NHS	National Health Service
HA RRMS	Highly Active Relapsing Remitting Multiple Sclerosis
HR	Hazard ratio
HRQoL	Health related quality of life
HSU	Health state utility
ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G1
IPD	Individual patients data

IM	Intramuscular
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
LY	Life-years
LYG	Life-years gained
MA	Marketing authorisation
MS	Multiple sclerosis
MTC	Mixed treatment comparison
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net Monetary Benefit
ONS	UK Office for National Statistics
PAS	Patient Access Scheme
PH	Proportional hazards
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PSA	Probabilistic sensitivity analysis
PSS	Personal social service
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
RCT	Randomised controlled trials
RES RRMS	Rapidly evolving severe relapsing remitting multiple sclerosis
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
RoB	Risk of bias
SAE	Severe adverse events
SAF	Safety set
SC	Subcutaneous
SMD	Standardised mean difference
SLR	Systematic literature review
SPMS	Secondary progressive multiple sclerosis
S1P	Sphingosine-1 phosphate
VAS	Visual analogue scale
WTP	Willingness-to-pay

Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report (Section 2).

All issues identified represent the ERG's view, not the opinion of NICE.

1 Overview of the ERG's key issues

The issues presented in Table 1 provide an overview of the key issues identified following the ERG's critique of the company submission (CS) that are likely to affect decision making.

The ERG's preferred assumptions are based on the critique of the company's clinical and economic evidence used in the cost-effectiveness analysis. The key differences between the company assumptions and the ERG preferences are detailed in Section 6.3; the most influential in the cost-effectiveness analysis is the inclusion of waning of the treatment effect.

Table 1. Summary of key issues

ID1677	Summary of issue	Report sections
Issue number 1	**Generalisability of ASCLEPIOS trial populations:** The ERG questions the extent to which the patients in the ASCLEPIOS trials reflect people who would be eligible for ofatumumab in NHS practice. Only a small number (n=[redacted]) of participants are from the UK (ASCLEPIOS I and II: [redacted] patients [from 3 centres] and [redacted] patients [from 4 centres] respectively). The largest number of trial population were from	Section 1.4 of this summary and Section 3.2.9 of the main report.

	[redacted], the ERG query that patients in [redacted] are likely to be comparable to the UK in characteristics and the care and treatment they receive. The company state in the CS Doc B and appendices that randomisation of the trial was stratified by regions and by MS subtype (RRMS or SPMS). Stratifications were included in the model adjustment for ARR. However, there was a lack of information provided in the CS which detailed effectiveness results stratified by geographical region and MS subtype.	
Issue number 2	**Trials included in the company network meta-analysis (NMA):** Two eligible trials were excluded from the NMA for annualised relapse rate.[1, 2] The ERG suggests inclusion of available data from the omitted trials in the NMA. The expected effect on the cost-effectiveness estimates is small as the trials concerned had relatively small sample sizes.	Section 1.6 of this summary and Section 3.3.3 of the main report.
Issue number 3	**Lack of transparency in the process of selecting studies from systematic literature review (SLR) into the NMA.** The ERG identified inconsistencies and highlighted the lack of sufficient information provided in the CS with regard to the process of including/excluding studies from SLR to NMA. The ERG could not establish the reasons for two trials to be excluded from the company NMA feasibility assessment: GOLDEN,[3] and BECOME.[4] To resolve this issue, the company could explain the discrepancies between stated NMA inclusion criteria and the actual criteria used for selecting studies from SLR into NMA, with a clear justification of studies excluded in this process.	Section 1.4 of this summary and Section 3.3.1 of the main report.
Issue number 4	**Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS:** The NICE final scope[8] listed HA RRMS and RES RRMS patient subgroups in relation to previous NICE guidance, and the CS provided cost-effectiveness analyses for these subgroups. The ERG consider the clinical effectiveness evidence for both ofatumumab and relevant comparators to be very limited. Full ASCLEPIOS trial results and relevant NMAs were used to inform cost–effectiveness estimates for HA RRMS and RES RRMS subgroups. Therefore, estimates were based on the assumption that relative treatment effects do not vary between these patient	Section 1.6 of this summary and Section 3.2.8, and 3.5.4 of the main report.

	subgroups for ofatumumab and all the comparators. This approach may underestimate the uncertainties related to the cost-effectiveness estimates.	
Issue number 5	**Inclusion of disease management costs associated with treating people with SPMS**: Tyas et al. (2007)[77] have collected resource use and costs for treating people with SPMS, which is based on a large UK MS study. For consistency with other recent MS technology appraisals,[5] the ERG suggest that these disease management costs associated with treating people with SPMS should have been included in the economic analysis.	Section 1.6 of this summary and Section 4.3.8.3 of the main report.
Issue number 6	**Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis (SPMS):** For consistency with a recent MS technology appraisal (TA624)[5] and a previous health technology assessment (TA527),[6] the ERG suggests that transition probabilities from RRMS to SPMS obtained from these previous appraisals are more appropriate to be used in the economic analysis.	Section 1.6 of this summary and Section 4.3.6.3 of the main report.
Issue number 7	**Source of annualised relapse rates (ARR):** The values used by the company for RRMS show that there is a steady decrease in the ARR. Those used for SPMS show that at more severe EDSS levels, there is a greater frequency of relapses when compared to less severe EDSS levels. The ERG is aware of other relapse frequencies values reported in TA527 assessment,[6] which are based on the British Columbia cohort. These values show that annual relapse rates decrease as EDSS levels increase.	Section 1.6 of this summary and Section 4.3.6.11 of the main report.
Issue number 8	**Source of health state utility values:** Orme et al. (2007)[7] has shown that utility values are lower in people with more progressive (SPMS and PPMS) forms of MS, which concurs with the clinical experience of our clinical advisor. Additionally, given the number of participants with SPMS included in the ASCLEPIOS trials,[6] the ERG consider that health state utility values may not be representative of a SPMS cohort. Therefore, the ERG considers that health state utility values should be obtained from Orme et al. (2007)[7] for people living with SPMS.	Section 1.6 of this summary and Section 4.3.7 of the main report.
Issue number 9	**Inclusion of waning of the treatment effect (25% reduction after 5 years, then 50%**	Section 1.5 of this summary

	reduction after 8 years). For consistency with other recent MS technology appraisals and due to the lack of long-term follow-up evidence for ofatumumab, the ERG supports a precautionary approach to use a conservative assumption of waning of the treatment effect, where drug effectiveness wanes, with a 25% reduction after 5 years, then a 50% reduction after 8 years.	and Section 4.3.6.12 of the main report.

1.1 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, in the RRMS population, ofatumumab increases QALYs by:

- Modest survival gains against all comparators except ocrelizumab
- Reduction in caregivers' disutilities against all comparators except ocrelizumab
- Reduction in adverse event disutilities
- In comparison to ocrelizumab, ofatumumab yielded fewer QALYs.

Overall, in the RRMS population, ofatumumab is modelled to affect costs by:

- [redacted]Lower administration and monitoring costs
- Lower adverse event and relapse costs.

The modelling assumptions introduced by the ERG that have the greatest effect on the ICER are:

- Altered probability of progressing from RRMS to SPMS obtained from TA624[5]
- Use of annualised relapse rates for a natural history cohort obtained from TA527[6]

- Use of health state utility values from Orme et al., 2007[7] for people living with SPMS
- Inclusion of SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year
- Addition of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years).

1.2 The decision problem: summary of the ERG's key issues

The company decision problem partially aligns to the NICE Final Scope.[8] The intervention and outcomes were similar, but the population and comparators included in the CS differed to those outlined by NICE. Section 2.3 outlines the key differences in the population and comparators provided in the company decision problem. The anticipated marketing authorisation (MA) for ofatumumab is for all Relapsing MS (RMS) patients which is partially consistent with the evidence provided by the company. The company restricts the population, and therefore the comparators, to patients with RRMS only.

The ASCLEPIOS trials do not provide sufficient subgroup data to perform indirect comparisons or cost-effectiveness analyses in the active SPMS population. The company state that the pivotal trial evidence for patients with active SPMS represent only a small proportion of patients in the trial ([redacted]%) and therefore, supplementary evidence from alternative SPMS populations used in previous appraisals[9] is used in the cost-effectiveness analysis (see Section 4.3.6.1). The ERG agree that the evidence base for the active SPMS group provided in the CS is insufficient to perform meaningful analysis. In the absence of other identified literature, this issue is unlikely to be resolved unless further head-to-head trials are conducted in this MS patient group. The ERG consider that all clinically meaningful outcomes have been included in the submission.

1.3 The clinical effectiveness evidence: summary of the ERG's key issues

In this section we highlight our concerns with the clinical effectiveness evidence submitted by the company. These include:

- Issue 1: Generalisability of trial evidence to NHS practice
- Issue 3: Lack of transparency in the process of selecting studies from SLR into the NMA.

Issue 1: Generalisability of ASCLEPIOS trial populations to NHS practice

Report section	Section 3.2.9
Description of issue and why the ERG has identified it as important	The ERG questions the extent to which the patients in the ASCLEPIOS trials reflect people who would be eligible for ofatumumab in NHS practice. As stated in the company CSRs, only a small number (n=[redacted]) of participants are from the UK (ASCLEPIOS I & II: [redacted] patients [from 3 centres] and [redacted] patients [from 4 centres] respectively). The largest number of trial population were from [redacted], the ERG query that patients in [redacted] are likely to be comparable to the UK in characteristics and the care and treatment they receive. The company state in the CS Doc B and appendices that randomisation of [redacted]How ever, there was a lack of information provided in the CS which detailed effectiveness results stratified by [redacted].
What alternative approach has the ERG suggested?	The ERG has not presented an alternative approach as this is the totality of evidence that could be identified.
What is the expected effect on the cost-effectiveness estimates?	Not applicable.
What additional evidence or analyses might help to resolve this key issue?	The generalisability issue is an unresolvable uncertainty, as further head-to-head trials conducted in majority NHS settings would be required. The lack of information presented in the CS regarding the effectiveness of the technology by [redacted] means that this issue could not be interrogated. The ERG would need the effectiveness evidence stratified by geographical region to be made available.

Issue 3: Lack of transparency in the process of selecting studies from SLR into NMA

Report section	Section 3.3.1
Description of issue and why the ERG has identified it as important	The ERG identified inconsistencies and highlighted the lack of sufficient information provided in the CS with regard to the process of including/excluding studies from SLR to NMA. The ERG identified two studies that could have been included in the NMA (GOLDEN[3] and BECOME[4]).
What alternative approach has the ERG suggested?	The company could explain the discrepancies between stated NMA inclusion criteria and the actual criteria used for selecting studies from SLR into NMA, with a clear justification of studies excluded in this process.
What is the expected effect on the cost-effectiveness estimates?	Where major inconsistency and incoherence exist in the evidence network, the validity of clinical effectiveness estimates, and consequently cost-effective estimates may be compromised.
What additional evidence or analyses might help to resolve this key issue?	The company could describe this step of study selection in more detail, provide clear justifications for studies excluded during this process, and if necessary, re-run the NMA with additional studies as a scenario.

1.4 The cost-effectiveness evidence: summary of the ERG's key issues

In this section we highlight our concerns with the cost-effectiveness evidence submitted by the company, including:

- Issue 9: Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years).

Issue 9: Inclusion of waning of the treatment effect

Report section	Section 4.3.6.12
Description of issue and why the ERG has identified it as important	Treatment waning was not included in the company submission. Due to little information available about the long-term treatment effect of ofatumumab, and to be in line with recent MS technology appraisals.
What alternative approach has the ERG suggested?	For consistency with other recent MS technology appraisals and the lack of long-term follow-up information for ofatumumab, the ERG supports a precautionary approach to use a conservative assumption of waning of the treatment effect, where drug effectiveness wanes, with a 25% reduction after 5 years, then a 50% reduction after 8 years.

What is the expected effect on the cost-effectiveness estimates?	The treatment effect is one of the key inputs in the economic model. We would expect there to be a reduction to the effectiveness; thus, causing the ICER to increase. However, we expect this to hold if there is a greater number of people on treatment compared to if less people were on treatment. If most of the cohort had discontinued treatment, treatment benefit would be applied to the remaining cohort on treatment, so applying treatment waning to those on treatment would not have a much impact to the ICER.
What additional evidence or analyses might help to resolve this key issue?	In response to our clarification question, the company provided details, inclusive of analyses supporting no waning of the treatment effect. Additionally, the company submitted a revised model that allowed for waning of the treatment effect based on conservative assumptions.

1.5 Other key issues: summary of the ERG's view

The ERG found additional issues related to the clinical and cost-effectiveness evidence which may materially affect decision making. These are described in:

- Issue 2: Trials included in the company NMA
- Issue 4: Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS
- Issue 5: Inclusion of disease management costs associated with treating people with SPMS
- Issue 6: Probability of progressing from RRMS to SPMS
- Issue 7: Source of annualised relapse rates
- Issue 8: Source of health state utility values.

Issue 2: Trials included in the company NMA

Report section	Section 3.3.3
Description of issue and why the ERG has identified it as important	Two eligible trials were excluded from the NMA for annualised relapse rate.[1, 2]
What alternative approach has the ERG suggested?	The ERG suggests inclusion of available data from the omitted trials in the NMA.

What is the expected effect on the cost-effectiveness estimates?	The expected effect on the cost-effectiveness estimates is small as the trials concerned had relatively small sample sizes.
What additional evidence or analyses might help to resolve this key issue?	The ERG re-run the analyses and did not find a major impact. Therefore, no change to the economic analyses.

Issue 4: Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS

Report section	Section 3.5.4
Description of issue and why the ERG has identified it as important	The NICE final scope has mentioned HA RRMS and RES RRMS patient subgroups in relation to previous NICE guidance, and the CS provided cost-effectiveness analyses for these subgroups, the ERG consider the clinical effectiveness evidence for both ofatumumab and relevant comparators to be very limited.
What alternative approach has the ERG suggested?	In view of the paucity of evidence, the ERG agrees with the company's approach in the CS of using full results from the ASCLEPIOS trials to estimate treatment effects.
What is the expected effect on the cost-effectiveness estimates?	The use of full ASCLEPIOS trial results and relevant NMAs to inform cost-effectiveness estimates for HA RRMS and RES RRMS subgroups mean that the estimates were based on the assumption that relative treatment effects do not vary between these patient subgroups for ofatumumab and all the comparators. Evidence from ASCLEPIOS trials is consistent with the assumption for ofatumumab versus teriflunomide, however the assumption is not verified for comparisons with other treatments. The approach may also underestimate the uncertainties related to the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	This issue is unlikely to be resolved unless further head-to-head trials are conducted in these patient subgroups and/or more subgroup data and analyses related to the subgroups are made available from previously completed trials.

Issue 5: Inclusion of SPMS-specific disease management costs

Report section	Section 4.3.8.3
Description of issue and why the ERG has identified it as important	SPMS-specific disease management costs which differ from those associated with treating people with RRMS were not included in the company submission.

What alternative approach has the ERG suggested?	For consistency with other recent technology appraisals,[5] SPMS-specific disease management costs which differ from those associated with treating people with RRMS should have been included in the economic analysis.
What is the expected effect on the cost-effectiveness estimates?	The company did not identify this parameter as a key driver of the economic model. Hence, the ERG would expect that there will be little change to the company's base-case ICER. More specifically, we would expect these changes to change the total mean costs and no change to the effectiveness results.
What additional evidence or analyses might help to resolve this key issue?	No additional analyses are required. However, the use of these costs and inflating to current prices are increasingly becoming outdated, and there are several assumptions made when doing so. For example, it is being assumed that MS management practices have not changed over time. The ERG consider that the resource use and costs associated with treating people with MS are needed, as we assume that care has changed over time.

Issue 6: Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis (SPMS)

Report section	Section 4.3.6.3
Description of issue and why the ERG has identified it as important	The availability of alternative transition probabilities, which had been used in recent MS technology appraisals.
What alternative approach has the ERG suggested?	For consistency with a recent MS technology appraisal (TA624)[5] and a previous health technology assessment,[6] the ERG suggests that transition probabilities from RRMS to SPMS obtained from these previous appraisals should have been included in the economic analysis.
What is the expected effect on the cost-effectiveness estimates?	The company did not identify this parameter as a key driver of the economic model. Hence, the ERG would expect that there will be little change to the company's base-case ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests that transition probabilities from RRMS to SPMS be obtained from previous appraisals.

Issue 7: Source of annualised relapse rates

Report section	Section 4.3.6.11
Description of issue and why the ERG has identified it as important	The values used by the company for RRMS show that there is a steady decrease in the ARR. Those used for SPMS show that at more severe EDSS levels, there is a greater frequency of relapses when compared to less severe EDSS levels.
What alternative approach has the ERG suggested?	The ERG is aware of other relapse frequency values reported in TA527 assessment,[6] which is based on the British Columbia cohort. These values show that annual relapse rates decrease as EDSS levels increase.
What is the expected effect on the cost-effectiveness estimates?	The company did not identify this parameter as a key driver of the economic model. Hence, the ERG would expect that there will be little change to the company's base-case ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG is aware of other relapse frequencies values reported in TA527 assessment,[6] which can be used in the economic analyses.

Issue 8: Source of health state utility values

Report section	Section 4.3.7
Description of issue and why the ERG has identified it as important	In the CS, the company derived and used health state values from all participants in the ASCLEPIOS trials, including those with active SPMS. The company stated that there were [redacted]% of participants with SPMS. Hence, the ERG considered that these values may not be generalisable to people with SPMS.
What alternative approach has the ERG suggested?	The ERG is aware of alternative health state values from Orme et al. (2007)[7] for people living with SPMS.
What is the expected effect on the cost-effectiveness estimates?	By making this change, the ERG would expect total mean costs and incremental costs to remain unchanged, and there to be a decrease in total QALYs, with the incremental QALYs remaining unchanged. Company base-case, including ERG preferred assumptions, and incremental results are presented in Sections 6.3 and 6.3.1.
What additional evidence or analyses might help to resolve this key issue?	The ERG is unaware of any additional evidence outside of health state values from Orme et al. (2007)[7]

1.6 Summary of ERG's preferred assumptions and resulting ICER

The ERG outline their preferred assumptions below. In Table 2 we provide numerical estimates of the resulting ICER(s) in a fully incremental analysis and indicate the change from the company's base case ICER(s) to ERG base-case ICER(s).

- SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year
- Probability of progressing from RRMS to SPMS obtained from TA624[5]
- Annualised relapse rates for a natural history cohort obtained from TA527[6]
- Health state utility values from Orme et al.[7] for people living with SPMS
- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years).

Table 2. Summary of ERG's preferred assumptions and ICER: comparison between the company and ERG base-case deterministic results for people with RRMS

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base-case					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
ERG base-case results					
[redacted]					
[redacted]					
[redacted]					

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

The ERG did not identify any major errors in the company's model.

The results reported in the CS reflected those in the model submitted.

For further details of the exploratory and sensitivity analyses performed by the ERG, please see Section 6.1 in the main report.

1.7 Summary

The company provided a relatively complete clinical effectiveness submission with regards to the clinical evidence and data within those studies. The company decision problem partially aligns to the NICE Final Scope.[8] Of note, the company restricts the population, and therefore the comparators, to patients with RRMS only. The main clinical effectiveness evidence came from the ASCLEPIOS I & II trials, which are judged to be of good quality with low risk of bias. The ASCLEPIOS I & II trials demonstrated that ofatumumab is more effective compared with teriflunomide for all main clinical outcomes, and had no unexpected safety concerns.

Comparative effectiveness data relies on NMAs, which were undertaken for ARR, CDW-3, CDW-6 and all-cause discontinuation (see Section 3.4.1). The ERG found inconsistent and insufficient information concerning the criteria and process of selecting studies from SLR to be included in the NMAs. Results of the NMAs for key economic model inputs (ARR and CDW-6) suggest that for ARR ofatumumab [redacted]

[redacted] The ERG observed some clinical heterogeneity in patient population between included trials. The volume of evidence is limited for many of the linking comparisons in the evidence network resulting in wide confidence intervals for some of the estimates.

The ERG did not identify any major errors in the company's model. However, there were some concerns, which have been outlined in Section 4.2. Under the company's assumptions and the economic model used, the company's incremental results for RRMS showed that ofatumumab was [redacted] against dimethyl fumarate and teriflunomide. When compared to glatiramer acetate the [redacted]. Ocrelizumab was [redacted] treatment strategy, [redacted] when compared to ofatumumab. The difference between these ICERs is a result of the incremental costs between these drugs and the marginal incremental gain. The company's PSA results for RRMS showed that ofatumumab had a [redacted] probability of being cost-effective at a WTP threshold of £30,000 per QALY.

The ERG made some amendments to the company's economic model inputs, which formed the basis for the ERG's base-case model. These changes resulted in differences between the company's base-case results and those reported by the ERG. The company's results were presented based on using the PAS price for ofatumumab and fingolimod and list prices for all other comparators, and this was the basis/approach to the ERG's analysis. The ERG's amendments using alternative sources of information are provided:

- SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year
- Transition probabilities from RRMS to SPMS obtained from TA624[5]
- Annualised relapse rates for a natural history cohort from TA527[6]
- Health state utility values from Orme et al.[7] for people living with SPMS

- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years).

In general, the company's results were robust to individual changes made by the ERG, with the inclusion of waning of the treatment effect having the greatest impact to the ICER. Based on the changes made simultaneously, the ERG base-case incremental results for RRMS showed that [redacted], ofatumumab compared to glatiramer acetate was [redacted]. The ERG PSA results for RRMS demonstrated that at a WTP threshold of £30,000 per QALY ofatumumab had a [redacted] probability of being cost-effective. However, it should be noted that these results were based on the PAS price for ofatumumab and fingolimod and list prices for all other comparators; hence the analysis does not incorporate commercial agreements between the companies and the Department of Health and Social Care for the other comparators.

Evidence Review Group Report

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The objective of this report was to appraise the clinical and cost-effectiveness of ofatumumab for treating RMS. Ofatumumab has been studied in clinical trials compared with teriflunomide in people with RMS. In August 2020, the US Food and Drug Administration (FDA) approved ofatumumab for use in both RRMS and active SPMS MS types. The FDA report states that ofatumumab is "… *for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.*"[10]

Ofatumumab is not currently authorised for treating MS in the UK. The anticipated full EU MA wording for ofatumumab is "for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS)", which includes patients both with RRMS or active SPMS (CS Document B, pg.20). However, the CS states that the *"submission focuses on patients with relapsing-remitting multiple sclerosis (RRMS) only*" (CS Document B, pg. 10). The CS (Document B, pg. 10) states that a MA application was submitted to the European Medicines Agency (EMA) in [redacted] 2020. The company expect the Committee for Medicinal Products for Human Use (CHMP) opinion in [redacted] and MA to follow in [redacted] 2021.

Ofatumumab is anticipated to receive a marketing authorisation for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS), including patients both with RRMS or active SPMS.

Ofatumumab is a "*fully human monoclonal immunoglobulin G1 (IgG1) antibody against human CD20 for the treatment of MS. It selectively binds CD20 on B lymphocytes to trigger their destruction"*. It is administered by subcutaneous (SC) injection and will be provided in autoinjector pens pre-filled with the recommended dose (20 mg in 0.4 mL solution) (Document B, Table 2, pg. 16).

2.2 Background

The ERG considers the CS to have provided a clear and concise overview of MS, summarising the pathogenesis, common clinical manifestations and early symptoms that can be expected in patients with the disease (Document B, B.1.3). The CS alludes to the wide-ranging and debilitating effects of MS as a chronic, disabling neurological condition. The CS correctly states that MS can affect 2 to 3 times more women than men and states that the most common age group affected is between 20 and 40, (although the age group proposed is in contrast to the NHS MS overview cited (which refers to the most common patient age group affected being "20s to 30s").[11] The exact aetiology of MS is unknown, although the company correctly suggest there is a strong genetic association (CS Document B, pg.17). Risk factors such as obesity, smoking and the Epstein Barr virus are accurately identified as associations with MS, although other risk factors such as low Vitamin D are also well-established.[12] The CS provides a clear summary of the three distinct disease classifications of MS; relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) and the approximate number of patients affected by MS is considered appropriate (CS Document B, pg.17).

The CS correctly asserts that the impact of MS on patient lives is extensive, stating that 75% of MS patients may be unemployed, fifteen years after diagnosis.[13] The CS suggests that the burden of hospital visits and time required for intravenous (IV) infusions may affect adherence, citing a worldwide MS study that found that "practical issues from taking the treatment" was the third most common cause for treatment interruption or discontinuation.[14] However, the ERG note that this study used a sample of 331 patients from only seven countries and that the study did not ask patients to define what "practical issues" meant.[14] The ERG supports the company's assertion that quality of life (QOL) in MS patients is significantly lower than the general population in several aspects and worsens with increasing EDSS score.[15] The ERG concurs with the significant economic and healthcare burden posed by MS, as stated in the CS (CS Document B, pg.18).

The CS summarises the 12 DMTs recommended by NICE for use in patients with RRMS (CS Document B, pg.19). The NHS England treatment algorithm 2019 is cited to support definitions for both HA RRMS and RES RRMS.[16] However, definitions

provided by the CS are not complete. In defining RES RRMS, the CS (CS Document B, pg.19) states a patient must have "*2 or more relapses within one year with MRI evidence of disease activity*" but does not expand on this to clarify that "MRI evidence of disease activity" refers to "one or more gadolinium enhancing lesions or a significant increase in T2 lesion" when compared to a previous MRI.[18]

The CS emphasises that ofatumumab is positioned "*for use in UK clinical practice in adults patients with RRMS only*" due to the limited supporting evidence in phase 3 trials with active SPMS (CS Document B, pg.20). Figure 1 in the CS (CS Document B, pg.20) presents the intended positioning of ofatumumab in the UK treatment pathway, anticipating its use to be in RRMS, HA RRMS and RES RRMS patients, but not active SPMS patients. Seven DMTs are listed under RRMS, four under HA RRMS and four DMTs under RES RRMS. The ERG considers the DMTs listed in Figure 1 of the CS under the classifications of RRMS, HA RRMS and RES RRMS to be appropriate, however, it should be noted that certain drugs with specific indications (as recommended by individual NICE guidelines)[6, 19, 20] are not alluded to in CS Figure 1 or explained in the text. These include:

- Interferon beta-1b: recommended for RRMS only where a patient has had 2 or more relapses within the last 2 years (and the company provides it according to the commercial arrangement).[6]

- Ocrelizumab: recommended for RRMS in adults with active disease defined by clinical or imaging features, only if alemtuzumab is contraindicated or otherwise unsuitable (and the company provides it according to the commercial arrangement).[19]

- Alemtuzumab*: recommended in patients who have HA RRMS despite a full and adequate course of treatment with at least one DMT (in addition to its authorised use for RES RRMS).[20]

    - ** In October 2019, the EMA pharmacovigilance risk assessment committee recommended restricting alemtuzumab to use in adults with RRMS that is highly active despite adequate treatment with at least one DMT or if the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage.*

Starting and stopping criteria for DMTs with respect to the UK treatment pathway is not described in the CS. From the NHS England treatment algorithm for MS 2019,

starting criteria common to all DMT treatment requires the patient to have an EDSS less than seven, with no evidence of non-relapsing progressive MS.[16] Stopping criteria common to all DMTs includes: ineffectiveness, intolerable effects, confirmed development of secondary progressive disease or inability to walk.[16]

The CS states that an estimated one third of patients may have sub-optimal response rate to first line therapies (CS Document B, pg.19) due to intolerable side effects or lack of efficacy, citing a paper by Hutchinson (2009).[21] The ERG notes that this claim is uncited in the original paper by Hutchinson and therefore, its accuracy is unclear. Moreover, the paper discusses the intolerable adverse effects of beta interferon but does not refer to adverse effects of dimethyl fumarate, glatiramer acetate and teriflunomide.[21] The CS also does not clarify, when referring to lack of efficacy with first line therapies, that lack of efficacy refers to beta-interferon neutralising antibodies in this paper.[21]

The CS proposes that ofatumumab offers RRMS patients a treatment option which may "*shift the treatment paradigm towards early high efficacy treatment*" and that this will result in delayed disease progression and disability for patients (CS Document B, pg.19). In support of this, the CS cites two papers, one of which is an opinion paper (lacking objectivity)[22] and the second is a cohort study with limitations including having a study population limited to south-east Wales and producing limited data on adverse events (an aspect critical to assessing the risks versus benefits of early intensive therapy).[23] In both studies, the authors disclosed multiple conflicting interests including consulting fees from more than one pharmaceutical company.[22, 23]

The CS describes the benefits of ofatumumab as being a subcutaneous (SC), self-administered and high efficacy treatment in the treatment pathway (CS Document B, pg.19 and pg.20). It suggests that IV ocrelizumab administration is subject to infusion capacity constraints and limitations in patient travel, although data provided in the CS to support this statement was via IQVIA Inc. market research and Novartis advisory board sources. Using market research by IQVIA Inc., commissioned by Novartis in 2020 (supplied in the CS reference pack), the CS highlights the use of inpatient admission for IV DMTs. This IQVIA Inc. market research shows [redacted]% of patients using IV ocrelizumab required inpatient treatment, with the CS suggesting

an unmet need for a high efficacy therapy that can be timely and self-administered (CS Document B, pg.20).

However, the ERG note that the IQVIA Inc. market research comprised surveys of 31 nurses only (which may not be fully representative across the UK as a whole) and that [redacted]% of surveys were from an “unknown” location within the UK. Key data (including infusion time and inpatient stay) was provided only through survey feedback, rendering results susceptible to recall bias. The CS further states that ofatumumab will reduce inequalities for patients due to it being more accessible as a self-administered SC therapy and avoiding attendance at hospital. The ERG considers the CS’s assumptions regarding equality and improved accessibility to be reasonable in view of potential home administration and avoidance of transportation or disability barriers for MS patients.

2.3 Critique of company’s definition of decision problem

The ERG provide a comparison of the NICE final scope[8] and CS decision problem in Table 3*.*

The company state that a confidential simple PAS has been submitted which would provide ofatumumab at a net price of [redacted] (exc. VAT) per unit. This PAS would represent a discount of approximately [redacted]% from the list price. Annualised cost of ofatumumab at with-PAS price for Year 1: [redacted] and Year 2+: [redacted].

Table 3: Summary of decision problem

	Final scope issued by NICE	*Decision problem addressed in the company submission*	*Company rationale if different from the final NICE scope*	ERG comment
Population	People with relapsing MS	*Adults with RRMS*	*"This submission considers patients with RRMS only. The anticipated licence for ofatumumab is only for adult patients.* *The evidence base for ofatumumab in patients with active SPMS is based on only a small proportion of patients (■%) in the pivotal phase III trials (ASCLEPIOS I and II), and as such does not provide sufficient subgroup data to perform meaningful indirect comparisons or allow robust cost-effectiveness analyses in active SPMS."*	The evidence submitted in the CS partially matches the patient population described in the final scope. The ERG considers the wording 'adult' instead of 'people' to be appropriate and in line with the anticipated licence. The full anticipated MA for ofatumumab is for all RMS patients, which is broader than the evidence provided by the company in the CS for this appraisal. RMS is inclusive of the RRMS and active SPMS subtypes. However, the company limits the population in the CS to RRMS only. The company state that the pivotal trial evidence (ASCLEPIOS I & II) for patients with active SPMS represents only a small proportion of patients in the trial (■%). The CS does not provide sufficient subgroup data to perform indirect comparisons or cost-effectiveness analyses in the active SPMS population. The ERG note that supplementary evidence from alternative SPMS populations is used in the cost-effectiveness analysis (see Section 4.3.6.1).
Intervention	Ofatumumab	*Ofatumumab*	*NA – in line with the NICE final scope*	The ERG considers the intervention in the CS to match the intervention described in the NICE final scope.
Comparator(s)	For people with active relapsing–remitting multiple sclerosis: • beta interferon • dimethyl fumarate	*For people with RRMS:* • *beta interferon*	*Some of the comparators listed under "active RRMS" have not been restricted by NICE to "active" RRMS (e.g. glatiramer acetate). This*	The ERG considers that the comparators described in the CS partially match the comparators described in the final scope.

	• glatiramer acetate • teriflunomide • ocrelizumab • peginterferon beta-1a • ozanimod (subject to ongoing NICE appraisal) For people with highly active relapsing–remitting multiple sclerosis despite previous treatment: • alemtuzumab[1] • cladribine • fingolimod • ocrelizumab (only if alemtuzumab[1] is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) For people with rapidly-evolving severe relapsing–remitting multiple sclerosis: • alemtuzumab[1] • cladribine • fingolimod • ocrelizumab (only if alemtuzumab[1] is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) For people with active secondary progressive multiple sclerosis	• *dimethyl fumarate* • *glatiramer acetate* • *teriflunomide* • *ocrelizumab* • *peginterferon beta-1a* *For people with HA RRMS despite previous treatment:* • *alemtuzumab* • *cladribine tablets* • *fingolimod* • *ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)* *For people with RES RRMS:* *alemtuzumab* • *cladribine tablets* • *natalizumab* • *ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)*	*submission instead considers the RRMS comparators listed and ofatumumab to be suitable for patients with RRMS, both with and without active disease.* *This submission does not consider ozanimod as a comparator as agreed during the decision problem call on 27th May 2020 since its use is not established clinical practice at the time of submission.* *This submission considers cladribine tablets as a comparator, in line with NICE's response to the draft scope consultation that the scope would be amended to specify cladribine tablets.* *This submission does not consider comparators for active SPMS due to its focus on an RRMS population (see Population section above).*	As described in the 'population' section above, the following comparators for people with active SPMS (evidenced by continuing relapses) have excluded from the submission as the CS focuses on the RRMS population: • established clinical management (including interferon beta-1b or other DMTs used outside their MA) • Siponimod (subject to ongoing NICE appraisal). The exclusion of ozanimod from the CS is appropriate as the NICE appraisal for this comparator is ongoing at the time of submission. The amendment of cladribine to cladribine tablets is appropriate.

	(evidenced by continuing relapses): • established clinical management, including interferon beta-1b or other disease modifying therapies used outside their marketing authorisations • siponimod (subject to ongoing NICE appraisal)			
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • disease progression • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom from disease activity (for example lesions on MRI scans) • mortality • adverse effects of treatment • health-related quality of life.	*The outcome measures used in this submission include:* • *Measures of relapse rate and severity: ARR, time to first relapse, relapse severity* • *Measures of disability and disease progression: 3- and 6-month CDW (as defined in the ASCLEPIOS trial protocol and re-analysed both in alignment with trials of other DMTs and in alignment with the OPERA trials) and 6-month CDI by EDSS* • *Measures of*	*NA – in line with the NICE final scope*	The ERG considers the outcomes in the CS to match the outcomes described in the NICE final scope.

		symptoms of MS: 6-month CDW by T25FW • *Measures of freedom from disease activity: number of T1 Gd-enhancing lesions, number of new and enlarging T2 lesions, serum neurofilament light chain levels, BVL, NEDA-4* • *Adverse effects of treatment including AEs, SAEs and deaths* • *Patient-reported outcomes: MSIS-29; WPAI:MS* • *Health-related quality of life: EQ-5D-5L*		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.			Please see Section 4.3 for detailed comments.

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	If the evidence allows, the following subgroup of people will be considered: • people who could not tolerate previous treatment	*This subgroup is not considered within this submission.*	Novartis is not aware of evidence that patients switching treatment due to intolerance differ systematically from patients who do tolerate treatment, or that the relative effectiveness of DMTs will vary between such patients. Switches due to intolerance are supported by the NHS England treatment algorithm for MS DMTs independent of patients meeting DMT eligibility criteria relating to recent relapses.[16] The population of 'people who could not tolerate previous treatment' is included in 'For people with RRMS' (see Comparators row above).	The subgroup 'people who could not tolerate previous treatment' was not specified in the pivotal trials and no available data was provided in the CS to allow subgroup analysis (e.g., as a *post hoc* subgroup). The evidence submitted in the CS from the pivotal trials for ofatumumab included 'previously treated patients' (ASCLEPIOS I 58.9/60.6, ASCLEPIOS II 59.5/61.8 [% intervention/comparator]), and therefore, 'people who could not tolerate previous treatment' is included in the trial population. A subgroup of newly diagnosed, treatment-naïve patients was pre-planned in the trials, HA RRMS and RES RRMS subgroup analyses were conducted *post hoc* in the CS but were not specified in the NICE final scope (see Section 3.2.8).
Special considerations	Guidance will only be issued in accordance with the marketing			The anticipated EU MA wording for ofatumumab considered in the CS is "*for the*

including issues related to equity or equality	authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			*treatment of adult patients with relapsing forms of multiple sclerosis (RMS)"* (CS Document B, pg. 10).

[1] In October 2019, the European Medicines Agency's pharmacovigilance risk assessment committee recommended restricting alemtuzumab to use in adults with relapsing remitting multiple sclerosis that is highly active despite adequate treatment with at least one disease-modifying therapy or if the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage. The recommendations in NICE TA312 will be updated to reflect this in due course.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The clinical effectiveness evidence for ofatumumab mainly came from two phase III trials, ASCLEPIOS I and ASCLEPIOS II, which compared the technology with teriflunomide. Data from these trials are presented in the CS and the CSRs have been provided to the ERG. The company conducted a SLR of various pharmacological treatments for RMS primarily to inform its NMAs, which were undertaken to estimate the relative effectiveness of ofatumumab against other DMTs. The SLR consisted of an original SLR and an updated SLR corresponding to two literature search dates in December 2019 and February 2020.

3.1.1 Searches

The CS searches are reasonably comprehensive, but the ERG have identified a few issues with them that may have had a small impact on retrieval of records. Searches in an appropriate set of bibliographic databases were undertaken on 25th December 2019, from database inception, with an update on 27th February 2020. Suitable terms for RMS, a wide range of treatments for RMS and various study types, including observational studies, were used. Searches were limited to English language. Searches in more than one database were conducted simultaneously via Ovid for the original SLR (Ovid and Wiley for the update), an approach that makes searches more complicated to construct, more prone to error and less transparent.

Whilst care has been taken to include terms from all relevant thesauruses in the main subject part of the search and some term mapping will have occurred, there remain several issues in the original search that may have had a small impact on retrieval: First, study type filters have inappropriately been used in specialist pre-filtered databases such as CENTRAL and CDSR; Secondly, there is occasional use of the .tw (text word) field code, which is not available in CDSR; Thirdly, the search uses the Ovid limit ‘humans’, which is not best practice because it limits to

only those articles indexed with humans as a thesaurus term and will miss the newest articles. The update search from 25th December 2019 to 27th February 2020 is better on these aspects, using two interfaces (Ovid and Wiley), not using filters in the specialist pre-filtered databases, and identifying animal-only studies first and then excluding only those from the search results.

However, the title of table 2 of CS Appendix D, indicates that the main Medline database may not have been searched for the update, which ERG testing suggests may have missed a few records. In addition to these database searches, the CS provides details of searches of six relevant conferences, several HTA and grey literature sources and two clinical trials registers (for ongoing, suspended or terminated clinical trials). References of relevant reviews were also checked. The ERG verified the comprehensiveness of the company's searches by checking the list of studies included in recently published systematic reviews against the list of studies identified in the company's SLR and did not identify any additional relevant RCTs missed by the company's searches (see Section 3.5.1).

3.1.2 Inclusion criteria and study selection

The inclusion criteria for the SLR (CS Appendix D, Table 8, pg.31-32) were consistent with the decision problem specified by the company (see Section 2.3), with the criteria for interventions and comparators being deliberately broad to cover all relevant comparators specified in the appraisal scope as well as several unlicensed interventions, placebo and best supportive care. Key inclusion criteria were adults with RMS (RRMS and active SPMS; CIS and PPMS were excluded), RCT designs (irrespective of blinding status), and publications with full-texts in the English language.

Study selection was carried out independently by two reviewers according to standard processes (CS Appendix D, Section 1.2, pg.30-31), with detailed lists of included and excluded articles provided. Overall, 731 publications reporting on 84 unique studies meeting the SLR inclusion criteria were identified across the original and updated SLRs (CS Appendix D, pg.103). The discrepancy in the

reported number of unique studies identified between CS Document B (Section B.2.9, pg.56) and CS Appendix D, pg.103 was resolved by the company at the clarification stage in response to ERG clarification question C1).

From these studies, the company selected 37 for NMA feasibility assessment. The process of selecting studies from SLR into NMA feasibility assessment was not clearly explained. Issues related to this process are examined by the ERG and described in detail later in Section 3.3.1 of the ERG report.

3.1.3 Data extraction

The CS stated that data from eligible studies were extracted by one reviewer and checked by a second reviewer (CS Appendix D, pg.31). The CS and its appendices only included data for studies and outcomes subsequently included in the NMAs. Data from other studies meeting the SLR inclusion criteria and for outcomes not used in the NMAs were not presented in the CS.

3.1.4 Quality assessment

Risk of bias (RoB) assessment appears to have been undertaken only for RCTs subsequently included in the NMAs. The company provided a quality assessment of the ASCLEPIOS trials in the CS, using the standard NICE RoB questions, which covered seven domains, without any explanatory supporting text (CS Document B Table 10 pg.37). It was not clear whether this was undertaken by more than one reviewer. Findings of the RoB assessment were presented in Table 40 in CS Appendix D (Section D.3, pg.143).

The ERG conducted a quality assessment of the ASCLEPIOS I and II trials, using the NICE criteria, which we compared to the company assessment in Table 4 (reporting a single judgement for each RoB category to cover both ASCLEPIOS I and II). We also conducted an assessment using the Cochrane RoB tool v1 (see Appendix A). The two trials were identical in design and reported jointly in the CS and the main trial publication,[24] and the ERG did not note any differences in the RoB between the trials.

The RoB in most domains was low, except for the treatment of missing data, and analysis based on intention to treat (ITT). While CS Document B (section B.2.5) indicates that all randomised patients were included in analyses of primary and secondary outcomes, the company's response to clarification question A2 explains that outcome analyses excluded patients who had missing values for covariates or completely missing values for post-baseline assessments. As a result, the ERG has rated the RoB in relation to ITT analysis as moderate. The ERG notes, however, that sensitivity analyses did include all randomised patients therefore, we have judged this domain to have a moderate, rather than high, RoB. Moreover, the trial was conducted by the manufacturer, which introduces an unclear RoB, but the ERG accepts that this is a risk in all trials of this type. Despite these issues, the ERG generally agrees with the company the overall RoB for the ASCLEPIOS trials to be low.

Table 4. Quality appraisal of ASCLEPIOS trials using NICE checklist (company vs ERG ratings)

NICE checklist item	*Company judgement*	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	*Yes*	Yes	A randomisation list was produced by the provider of Interactive Response Technology[24]
Was the concealment of treatment allocation adequate?	*Yes*	Yes	The randomisation list was provided by an organisation external to the company
Were the groups similar at the outset of the study in terms of prognostic factors?	*Yes*	Yes	Groups similar in relation to duration of MS since diagnosis and first symptom, recent relapses, EDSS and measures related to T1 and T2 lesions (CS Document B, Table 6 pg.32 and Appendix L, Table 134 pg.534)
Were the care providers, participants and outcome assessors blind to treatment allocation?	*Yes*	Yes	Double-dummy design ensured blinding of providers and participants, and assessors were blinded
Were there any unexpected imbalances in drop-outs between groups?	*No*	No	While there were more withdrawals from the comparator arm, the rates are considered acceptable

Is there any evidence to suggest that the authors measured more outcomes than they reported?	*No*	No	Outcomes not reported in the CS Document B are reported in Appendix L
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Yes*	No	Outcome analyses excluded patients who had missing values for covariates or completely missing values for post-baseline assessments (based on response to clarification priority question A2). Sensitivity analyses were based on ITT.
CS, company submission; EDSS, expanded disability status scale; ERG, Evidence review group; ITT, intention-to-treat			

A quality appraisal of the comparator trials for the NMA was performed by the ERG and is reported separately in Section 3.3.3.1 of this report.

3.1.5 Evidence synthesis

Findings from the two pivotal trials (ASCLEPIOS I & II) were presented in CS Document B, Section B.2.6 and ERG's critique is provided in Section 3.2. As described in Section 3.1.2, the SLR was primarily used to inform the NMAs and no synthesis of evidence appears to have been undertaken for studies that met SLR inclusion criteria but did not meet the NMA inclusion criteria or pass the feasibility assessment.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Evidence for the clinical effectiveness of ofatumumab is presented from ASCLEPIOS I and ASCLEPIOS II, which are described in CS Document B (Document B, B.2.1—B.2.7, and Appendix L), and for which CSRs were provided by the company. Neither the company nor the ERG identified any other relevant RCTs with available data that meet the NICE decision problem (see Section 3.5.1). The CS provides summary information about the trial design, intervention, population, patient numbers (e.g. how many were eligible, randomised, allocated and dropped out), outcomes and statistical analyses.

3.2.1 Conduct of the trial

The ASCLEPIOS I and II trials were concurrent phase 3, multicentre, randomised, parallel, double-blinded, active-comparator controlled trials, sponsored by the company (Novartis Pharma AG). The trials were conducted at 385 sites in 37 countries and lasted for approximately [redacted], with patients treated for a maximum of 30 months or until the end-of-study was declared, which was [redacted] (according to the CSR (ASCLEPIOS I, pg.5), this was the date when sufficient data were available to power analyses of the primary and key secondary outcomes, [redacted]).

The trials are also reported in a peer-reviewed publication[24] and CSRs and appendices for both trials, which were provided to the ERG for this appraisal.

3.2.2 Randomisation

ASCLEPIOS I and II were designed to investigate the safety and efficacy of ofatumumab versus teriflunomide in adults with RMS (RRMS or active SPMS). Participants were assigned randomly in a 1:1 ratio using interactive response technology to receive a 20 mg injection of ofatumumab every 4 weeks or 14 mg once daily of oral teriflunomide, for up to 30 months. Patients in the ofatumumab group also received oral placebo and patients in the teriflunomide group received an injection placebo (CS Document B, B.2.3.1, Table 4, pg.26). Randomisation was stratified by [redacted] (RRMS or SPMS). Enrolment took place between October 2016 and March 2018.[24]

The key inclusion and exclusion criteria are reported in the CS (Document B, Table 4, pg.26) and full exclusion criteria are reported in the CSRs (ASCLEPIOS I, Appendix 16, pg.7314-7319 and II pg.7940-7945). In summary, patients were included if they were aged 18-55 (inclusive) years and diagnosed with MS according to the 2010 Revised McDonald criteria; had RRMS or SPMS with disease activity, an EDSS of 0-5.5 (inclusive), and at least one relapse during previous year and/or two relapses during previous two years prior to screening

and/or a positive Gd-enhancing MRI scan within the year prior to randomisation; and were neurologically stable within one month prior to randomisation. Patients were excluded if they had PPMS or SPMS without disease activity, neuromyelitis optica, a disease duration of more than 10 years with an EDSS score of ≤2, any other disease or condition that could interfere with participation in the study or the ability to cooperate and comply with the study procedures, had been treated with specified medications or within specified timeframes.

The ERG notes that there are no differences in inclusion criteria between the ASCLEPIOS trial protocols[25, 26] and patient baseline characteristics (CS Document B, Table 6, pg.32). The ERG clinical expert considers the inclusion and exclusion criteria to be reasonable.

Flow-charts of participants through the ASCLEPIOS trials were presented in CS Appendix D (D.2, Figures 21 and 22, pg.141-142) and are reproduced in ERG Appendix B. In ASCLEPIOS I, 927 patients were randomised, and 465 received 20 mg ofatumumab while 462 received 14 mg teriflunomide; 100% of those randomised took at least one dose of treatment (CS Document B, Table 7, pg.33). There were 129 patients who discontinued the study, 48 from the ofatumumab group and 81 from the teriflunomide group (see Section 3.2.3). In ASCLEPIOS II, 955 patients were randomised: 481 the 20mg ofatumumab group and 474 to the 14mg teriflunomide group; 100% of those randomised took at least one dose (CS Document B, Table 7, pg.33). There were 167 patients who discontinued the study, 83 from the ofatumumab group and 84 from the teriflunomide group.

3.2.3 Patient withdrawals

In ASCLEPIOS I, attrition was 10.3% (48/465) in the ofatumumab arm and 17.5% (81/462) from the teriflunomide arm, for an overall rate of 13.9%. In ASCLEPIOS II the rates were 17.3% (83/481) and 17.7% (84/474) for an overall rate of 17.5%. The ERG calculated the combined attrition from both trials: 13.8% (131/946) from the ofatumumab arms and 17.6% (165/936) from the control arms (using data

from CS Document B, Table 8, pg.33-34). The ERG note that the main reasons for withdrawing from the studies were similar in ASCLEPIOS I and II, these included;

- Patient/guardian decision (ofatumumab 5% [48/946] vs control 9% [83/936])
- Adverse events (AE) (ofatumumab 3% [30/946] vs. control 3% [27/936]) (calculated by ERG using data from CS Document B, Table 8, pg.33-34).

The ERG notes the numerically higher level of drop-out in the teriflunomide (control) arm of ASCLEPIOS I, but a similar rate across both arms in ASCLEPIOS II. The drop-out rate due to AE is the same in all arms in both trials. The ERG clinical expert considers drop-out rates to be acceptable for this type of study.

The CSRs for ASCLEPIOS I (pg.125) and II (pg.114) also report rates of discontinuation of the study drug of [redacted] respectively, for an overall rate of [redacted] across both studies. The ERG calculated study drug discontinuation for the ofatumumab groups across both studies as [redacted] and for the control groups as [redacted] However, the CSRs and study protocol indicate that patients who discontinued the study drug (ofatumumab or teriflunomide) were encouraged [redacted] ERG calculations using data from the CSRs (ASCLEPIOS I pg.125 and II pg.114) found that the percentage of patients who discontinued the drug but remained in the study was similar for both the treatment and control arms across both studies (ofatumumab arms [redacted] and teriflunomide arms [redacted]

The ERG was unable to accurately determine the time and distribution of study withdrawal from the CS. However, the company provided additional information during clarification (question A9). In ASCLEPIOS I, the time to trial discontinuation was higher in the teriflunomide arm at the end of year 1 (Kaplan-Meier [KM] estimate [redacted]%, 95% CI: [redacted]) and at the end of year 2 (KM

estimate [redacted], 95% CI: [redacted]) than in the ofatumumab arm (year 1: KM estimate [redacted]%, 95% CI: [redacted]; year 2: [redacted] 95% CI [redacted]). In ASCLEPIOS II, the rate of discontinuation was similar in both arms throughout the trial (year 2 KM estimate for ofatumumab [redacted], 95% CI: [redacted]; for teriflunomide [redacted], 95% CI: [redacted]).

3.2.4 Missing data

The CS Document B (section B.2.5) states that all randomised patients were included in the Full Analysis Set (FAS) for primary and secondary efficacy outcomes, which were analysed following the ITT principle. The ERG queried this discrepancy during clarification (question A2). The company responded that in the main outcome analyses they excluded patients who had missing values for covariates or completely missing values for post-baseline assessments.

The ERG note that sensitivity analyses using imputation and 'last observation carried forward' to address the issue of missing data were presented in the supplementary appendices of the published trial paper (Tables S3 and S4, p.40-44).[24] Overall, the sensitivity analyses assumed patients who dropped out had higher relapse rates and produced results similar to the main analyses (or suggesting a slightly larger treatment effect for ofatumumab).

While the ERG would like to emphasise that not using the ITT principle in the main analyses is a concern, the fact that the results of sensitivity analyses suggest similar or more favourable results for ofatumumab offers some assurance that the main results might be conservative.

3.2.5 Dosage

Patients received SC ofatumumab (20mg every 4 weeks after 20-mg loading doses at days 1, 7, and 14) or oral teriflunomide (14 mg daily) for up to 30 months. Patients in the ofatumumab group also received oral placebo and patients in the teriflunomide group received an injection placebo to correspond with the treatment received by the other group (CS Document B, Table 4, pg.26).

Ofatumumab was provided in autoinjector pens pre-filled with the recommended dose (20 mg in 0.4 mL solution). The first injection was performed under the guidance of a healthcare professional (CS Document B, Table 2, pg.16) and costs associated with this guidance was incorporated into the economic model (see Section 4.3.8.2).

Treatment compliance was calculated by counting the days when the drug was administered according to the protocol based on a Dosage Administration Record (DAR) Summary electronic case report form (eCRF). [redacted] Additional measures to ensure treatment compliance were reported in the CSRs, including training of patients on the correct procedure for self-administration of injections and demonstration of proper procedure before home-administration was allowed. Compliance was calculated as the duration of exposure to the study drug in (days)/duration of on-treatment period in (days) × 100%.[24]

The ERG clinical experts confirm that the method used to measure and report compliance in trials of this type was appropriate.

In ASCLEPIOS I, the CSR reports that [redacted] However, across both trials, the ERG calculated that compliance was slightly [redacted] in the ofatumumab group at [redacted] (based on data from CSR ASCLEPIOS I/II, Table 14.3-1.3, pg.705/686). The ERG clinical experts suggest that reporting these [redacted] compliance and retention rates provides [redacted] data on potential suitability for clinical use and informs clinicians on how patients using ofatumumab are likely to fare longer term.

3.2.6 Outcomes

The outcomes reported in the CS included those in the NICE final scope[8] and company decision problem (see Section 2.3) for both ASCLEPIOS I and II. A list of the primary and some secondary efficacy outcomes (CS Document B, Table 3,

pg.24), and non-key secondary outcomes (Appendix L, L.2.9, pg.544) are provided in the CS.

The company reports that the primary outcome was the ARR, defined as the number of confirmed relapses in a year, in the full ITT population. Key secondary outcomes were 3-month and 6-month confirmed disability worsening (CDW 3 and CDW6), defined as an increase from baseline in EDSS sustained for at least 3 or 6 months; 6-month confirmed disability improvement (CDI6); number of T1 Gd-enhancing lesions per scan; annualized rate of new or enlarging T2 lesions; and neurofilament light chain (NfL) serum concentration and rate of brain volume loss. Other secondary objectives included time to first confirmed relapse; evidence of disease activity (NEDA-4); and health quality of life measures based on the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), Multiple Sclerosis Impact Scale (MSIS-29), and Impact of MS Disease on Work Productivity and Activity (WPAI:MS).

The ERG judges the company's interpretation of outcome data and effectiveness as appropriate.

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

The company's approach to trial statistics is presented in the CS, Document B section B.2.4 (pg. 32). The primary outcome was frequency of confirmed relapses as evaluated by ARR. The analysis on ARR used a negative binomial regression model with a log-link, treatment and region as factors, and number of relapses in the previous year, EDSS, number of Gd-enhancing lesions and patient age at baseline as covariates. The outcome variable of this model is number of confirmed relapses observed, and the log of the patient's time in study in years as an offset variable.

Pre-specified pooled data analyses of the key secondary outcomes were tested in the following hierarchical order: CDW-3, CDW-6, CDI-6. Testing began with the primary null hypothesis in each study and continued to the next hypotheses only if each preceding null hypothesis was rejected in favour of ofatumumab with a two-sided p-value ≤0.04875. This analysis used Cox proportional hazards models. The stratification factor used was study, treatment and region were included as factor variables, and baseline EDSS was included as a continuous variable

Within-study analyses of key secondary outcomes were tested in the following order: ARR, Gd-enhancing lesion number, new or enlarging T2 lesions, NfL, BVL. Testing began with the primary null hypothesis and continued to the next hypotheses only if each preceding null hypothesis was rejected in favour of ofatumumab with a two-sided p-value ≤0.05 in a negative binomial regression model with log-link. The natural log of the number of MRI-scans was the offset variable, treatment and region were included as categorical variables, and age and number of Gd-enhancing lesions at baseline as continuous variables.

Section 2.5.3 of the ASCLEPIOS I and II statistical analysis plan (SAP) notes in detail the procedure to control for multiple testing and is presented visually in Figure 2.1 of the SAP. Firstly, the primary and all MRI-related key secondary

hypotheses were tested within study, starting with the primary, ARR, in order of hierarchy if the proceeding null hypothesis was rejected at the 5% level. If both studies rejected the null hypothesis, ARR is favour of ofatumumab, then the disability-related endpoints were to be combined across studies, and tested in hierarchical order at the 4.875% level, where $0.04875 = 2(0.025 - 0.025^2)$. The global null hypotheses, no difference between ofatumumab and teriflunomide, was tested at p≤0.000625 (0.025^2).

Table 9 of the CS and section 2.5.4 of the ASCLEPIOS trials' SAP detailed how missing data was to be handled. The use of the offset variable for time in study was done to adjust for missing data, and the primary analysis used all available data up to the end of treatment date.

3.2.7.1 Sample size calculations

Sample size requirements were primarily driven by the disability-related key events, which pooled the studies. To demonstrate the superiority of ofatumumab over teriflunomide, it was calculated that approximately 900 patients per study would be required to achieve 90% power, at a significance level of 2.5% and assuming an uninformative dropout rate of 20%, as stated in both ASCLEPIOS studies' CSRs (section 9.7.10). The ERG reproduced a similar sample size calculation to that presented by the company using the 'power two proportions' command in Stats SE 16 (64-bit).

For the pooled key secondary outcomes, a total of 1800 patients across the two studies was sufficient to demonstrate superiority of ofatumumab over teriflunomide at ≥90% power for CDW-3, and at ≥80% power for CDW-6 and CDI-6. Within-study analyses of key secondary outcomes required a 900 patients per study to achieve ≥80% power for all MRI endpoints, and ≥90% power for the NfL serum concentration endpoint.

3.2.7.1.1 Summary

In summary, the ERG are satisfied that the analyses based on ASCLEPIOS I and II performed by the company and presented in the CS are statistically robust and that each analysis was performed on the most relevant population. The trial was well designed and suitably powered to answer its primary hypothesis: testing the difference between subcutaneous 20 mg ofatumumab once monthly and oral 14 mg teriflunomide once daily in reducing the frequency of confirmed MS relapses as measured by ARR. It is important to highlight that the population relevant to this submission is narrower than that defined in the NICE scope (see 2.3). In the pivotal ASCLEPIOS trial data provided to the ERG, there were only 108 (5.7%) patients with SPMS across both treatment groups thus providing insufficient data to allow robust analyses in the active-SPMS population. Therefore, the population considered in the CS and cost-effectiveness analyses was adult patients with RRMS.

3.2.8 Subgroups

The CS Document B (B.2.7, Table 20, pg.49) reports the characteristics of two *post hoc* patient subgroups relevant to the economic analyses (see Appendix E). The HA RRMS and RES RRMS subgroups were not specified subgroups in the NICE Final Scope,[8] but were included as MS subtypes within the comparators (see the ERG critique of the company decision problem in Section 2.3).

The CS defined the *post hoc* subgroups as follows: HA RRMS are patients in the ITT population who were previously treated with any DMT and who discontinued their last DMT due to lack of efficacy; RES RRMS were those with ≥2 relapses in the previous year and ≥1 T1 Gd-enhancing lesions on baseline brain MRI. The ERG provides an extended definition in Section 2.2. The characteristics of these patient subgroups are summarised in Table 6 (Data from CS Document B, Table 20, pg.49).

Baseline characteristics were broadly similar across the two arms in the HA RRMS subgroup and when comparing the HA RRMS subgroup (Table 5) to the ITT population (see Table 6). There was, however, a smaller proportion of

women in the ofatumumab compared to the teriflunomide arms ([redacted]% vs. [redacted]%, respectively), which was the case across the two arms in the subgroup, and when comparing the subgroup to the ITT population. In addition, compared to the ITT population, the HA RRMS subgroup had a slightly longer duration of MS before the onset of symptoms across both arms ([redacted] years in the subgroup vs. 8.3 ITT).

Table 5: Baseline characteristics of HA and RES RRMS patients (pooled for ASCLEPIOS I and II) (Data from CS Document B, Table 20, pg.49)

Characteristic		HA RRMS patients		RES RRMS patients	
		Ofatumumab (N=197)	Teriflunomide (N=210)	Ofatumumab (N=99)	Teriflunomide (N=111)
Age (years), mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]
Duration of MS since first symptom in years, mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]
Previously treated patients, n (%)		[redacted](100.0)	[redacted](100.0)	[redacted]	[redacted]
Relapses in the 12 months prior to screening, mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]
EDSS	N	[redacted]	[redacted]	[redacted]	[redacted]
	mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total volume of T2 lesions	N	[redacted]	[redacted]	[redacted]	[redacted]
	cm^3, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients free of Gd-enhancing T1 lesions	N	[redacted]	[redacted]	[redacted]	[redacted]
	mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Gd-enhancing T1 lesions	N	[redacted]	[redacted]	[redacted]	[redacted]
	mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

In the RES RRMS subgroup of patients, the ofatumumab arm had a slightly smaller proportion of women compared to the teriflunomide arm ([redacted]% vs. [redacted]%), but otherwise characteristics were broadly similar across the two arms. Compared to the ITT population, patients in the RES RRMS subgroup were

younger ([redacted] years compared with 38.2 years in the ITT population) and had a shorter duration of MS since first symptom ([redacted] years vs. 8.3 in the ITT population). (The ERG notes that the CS Document B, pg.53, reports the mean duration since first symptom in the RES RRMS subgroup, including both the ofatumumab and control arms, as [redacted] years, while the supplementary subgroup analyses provided by the company in the CS reference pack reports [redacted] years.) There were differences between the RES RRMS subgroup patients and the ITT population in terms of the number of patients free of Gd-enhancing T1 lesions (0 in the subgroup) and thus a higher number of patients with Gd-enhancing T1 lesions per patient ([redacted] in the RES RRMS subgroup vs. [redacted] in the ITT population). The RES RRMS subgroup had a higher volume of T2 lesions ([redacted] as compared with around [redacted] in the ITT population) and a smaller percentage of patients who had previously been treated ([redacted]% vs. 60.2%).

Primary and key secondary outcome results for the HA and RES RRMS subgroups are summarised in Table 9.

The NICE Final Scope[8] also specifies that people who could not tolerate previous treatment, should be considered if evidence allows. As outlined in the critique of the decision problem in Section 2.3, the company state that this subgroup was not considered and is included in the population of people with RRMS, which the ERG feels is appropriate. The company state that a subgroup of "*newly diagnosed, treatment-naïve patients was pre-planned; these patients were stratified and analysed by their NfL serum concentration*" (Document B, Table 4, pg.28). However, this did not reflect the primary outcome or any key secondary outcomes, nor did it inform the economic model, so these results are not reported in the CS or discussed in this ERG report.

3.2.9 Baseline characteristics

The ERG generated Table 6 to summarise the key baseline characteristics of the trial ITT populations for the ASCLEPIOS I and II trials. The ERG considers that there were no numerically meaningful differences at baseline in demographic or disease characteristics between participants receiving ofatumumab or

teriflunomide. The ERG clinical advisor agrees that the baseline characteristics of patients in the pivotal trials are generally representative of those patients treated in the NHS. Additional baseline disease characteristics and treatment history of patients in the ASCLEPIOS I and II trials are provided in CS Appendix L, Tables 135 and 136 (pg.540-541), respectively.

Table 6: Baseline characteristics of ITT population[a]

Characteristic		ASCLEPIOS I		ASCLEPIOS II	
		Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Age (years), mean (SD)		38.9 (8.8)	37.8 (9.0)	38.0 (9.3)	38.2 (9.5)
Female, n (%)		318 (68.4)	317 (68.6)	319 (66.3)	319 (67.3)
Weight (kg), mean (SD)		74.8 (19.9)	75.5 (20.0)	73.6 (19.0)	74.0 (17.9)
Duration of MS since diagnosis (years), mean (SD)[b]		5.8 (6.0)	5.6 (6.2)	5.6 (6.4)	5.5 (6.0)
Years since first MS symptom	N	[redacted]	[redacted]	[redacted]	[redacted]
	mean (SD)	8.4 (6.8)	8.2 (7.2)	8.2 (7.4)	8.2 (7.4)
Type of MS at study entry, n (%)[b]					
RRMS		438 (94.2)	434 (93.9)	452 (94.0)	450 (94.9)
SPMS		27 (5.8)	28 (6.1)	29 (6.0)	24 (5.1)
Previously treated patients, n (%)		274 (58.9)	280 (60.6)	286 (59.5)	293 (61.8)
Relapses in the 12 months prior to screening, mean (SD)		1.2 (0.6)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
Relapses in the 12–24 months prior to screening[b]	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	0.9 (1.0)	0.9 (1.2)	0.7 (1.0)	0.8 (1.0)
Time since onset of most recent relapse[b]	N	[redacted]	[redacted]	[redacted]	[redacted]
	Months, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
EDSS	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	3.0 (1.4)	2.9 (1.4)	2.9 (1.3)	2.9 (1.4)
Total volume of T2 lesions	N	[redacted]	[redacted]	[redacted]	[redacted]
	cm^3, mean (SD)	13.2 (13.3)	13.1 (14.6)	14.3 (14.2)	12.0 (13.0)
Number of patients free of Gd-enhancing T1 lesions, n (%)		291 (62.6)	293 (63.4)	270 (56.1)	291 (61.4)
Gd-enhancing T1 lesions	N	[redacted]	[redacted]	[redacted]	[redacted]
	mean (SD)	1.7 (4.9)	1.2 (2.6)	1.6 (4.1)	1.5 (4.1)

EDSS: Expanded Disability Status Scale; Gd: gadolinium; MS: multiple sclerosis; N: number of patients in full analysis set; n: number of patients with non-missing values; SD: standard deviation [a]All data from CS Document B Table 6 pg. 32 except where noted. [b]Data from CS Appendix L Table 134 pg.534.

The CS (Document B, Table 4, pg.27) reports that a total of [redacted] patients from the United Kingdom were included in ASCLEPIOS I & II: [redacted] patients (from 3 centres) and [redacted] patients from 4 centres, respectively. The ERG cannot be certain of the extent to which the [redacted] patients in the ASCLEPIOS trials reflect people who would be eligible for ofatumumab in NHS practice. The largest number of trial population were from [redacted], therefore the ERG queries the extent to which patients in [redacted] are likely to be comparable to the UK in characteristics and the care and treatment they receive.

3.2.10 Primary and secondary clinical outcome results for ASCLEPIOS I and II

The primary and key secondary clinical outcome results for the pivotal trials were reported in CS Document B (pg.38-47) and CS Appendix L, Tables 141-143 (pg.539-541). The results have been reproduced by the ERG in Table 7 for completeness. The results for key outcomes by subgroups (HA and RES RRMS) were also reported, in CS Document B (B.2.7, pg.49) and are summarised by the ERG in Table 8.

The CS Document B reports that ofatumumab compared to teriflunomide reduced relapse rate (ARR ratio [95% CI]: ASCLEPIOS I, 0.50 [0.37, 0.65], p < 0.001; ASCLEPIOS II, 0.42 [0.31, 0.56], p < 0.001); disability worsening (hazard ratio [95% CI] pooled for ASCLEPIOS I and II: CDW-3, 0.66 [0.50, 0.86], p = 0.002; and CDW-6, 0.68 [0.50, 0.92], p = 0.012); and MRI activity (rate ratio [95% CI] for T1 lesions: ASCLEPIOS I, 0.03 [0.01, 0.05], p < 0.001; ASCLEPIOS II, 0.06 [0.04, 0.10], p < 0.001; for T2 lesions: ASCLEPIOS I, 0.18 [0.15, 0.22], p < 0.001; ASCLEPIOS II, 0.15 [0.13, 0.19], p < 0.001; and NfL concentration adjusted geometric mean ratio at 3 / 12 / 24 months: ASCLEPIOS I, 0.93 [0.89, 0.98], p = 0.011 / [redacted] [redacted], p < 0.001 / [redacted] [redacted], p < 0.001; ASCLEPIOS II: 0.89 [0.85, 0.93], p < 0.001 / [redacted] [redacted], p < 0.001 / [redacted] [redacted], p < 0.001).

The CS reports that ofatumumab compared to teriflunomide increased time to first confirmed relapse (rate ratio [95% CI]: ASCLEPIOS I, [redacted] [redacted], p < 0.001; ASCLEPIOS II, [redacted] [redacted], p < 0.001). While the rate of disability improvement (CDI-6) was higher for the ofatumumab group, the CS reports that the analysis

[redacted] and did not reach statistical significance (HR pooled for both trials 1.35, 95%CI: 0.95, 1.92, p=0.094). The annual rate of brain volume loss also did not reach statistical significance in ASCLEPIOS I (adjusted mean difference 0.07, 95%CI: −0.02, 0.15, p = 0.116) or ASCLEPIOS II (adjusted mean difference 0.07, 95%CI: −0.02, 0.15, p = 0.129).

CS Appendix L (pg.538) reports a patient-reported reduction in disease activity (NEDA-4) for participants in the ASCLEPIOS I trial at 12 and 24 months (OR [95% CI]: [redacted], p [redacted] and [redacted], p [redacted]) and in ASCLEPIOS II at 12 months but not 24 months (OR [95% CI]: [redacted], p [redacted] and [redacted], p [redacted]).

CS Appendix L (L.2.6 – L.2.8) also reports outcome results for health-related quality of life measures. Specifically, compared to teriflunomide, ofatumumab was shown to [redacted] the physical impact of MS on patient quality of life (using MSIS-29) at 5 time points (from 6 to 30 months) in ASCLEPIOS I and at most time points (from 12 to 30 months) in ASCLEPIOS II; while it [redacted] psychological impact in ASCLEPIOS I at only 2 times points (12 and 30 months) and in ASCLEPIOS II at the 18-month time point only, but not at the other 4 time points (6, 12, 24 and 30 months). Ofatumumab also showed a [redacted] impact on work productivity and activity (using the WPAI:MS) at 1 of the 4 time points (18 months) in ASCLEPIOS I and at 3 time points in ASCLEPIOS II (6, 18 and 24 months).

There was no statistically significant difference in health status among patients in the study arms based on the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) utility index in ASCLEPIOS I (adjusted mean difference at 24 months [redacted], 95%CI: [redacted], p [redacted]), but there was a slight difference in ASCLEPIOS II ([redacted], 95% CI: [redacted], p [redacted]), which the company noted was not clinically meaningful (CS Document B, Appendix L, pg.547). There were statistically significant differences based on the EQ-5D-5L Visual Analogue Scale (VAS) at 24 months in ASCLEPIOS I ([redacted], 95% CI: [redacted], p [redacted]) and II ([redacted], 95% CI: [redacted], p = [redacted]). Once again, in Appendix L (pg. 542), the company noted that these were not considered clinically meaningful. The ERG note that statistically, the differences are numerically significant at P<0.05. However, we could not corroborate the company statement which suggests that these differences do not represent clinically meaningful differences.

Table 7: Primary and key secondary outcome results for ASCLEPIOS I and II[a]

	ASCLEPIOS I	**ASCLEPIOS II**
Treatment arm	**Ofatumumab (N=454) vs Teriflunomide (N=452)**	**Ofatumumab (N=469) vs Teriflunomide (N=469)**
	ratio (95% CI), p-value	***ratio (95% CI), p-value***
ARR ratio	0.50 (0.37, 0.65), p<0.001	0.42 (0.31, 0.56), p<0.001
CDW-3 hazard ratio (pooled for both trials)	0.66 (0.50, 0.86), p = 0.002	NA
CDW-6 hazard ratio (pooled for both trials)	0.68 (0.50, 0.92), p = 0.012	NA
CDI-6 hazard ratio (pooled for both trials)	1.35 (0.95, 1.92), p = 0.094	NA
Number of T1 Gd-enhancing lesions – rate ratio	0.03 (0.01, 0.05), p < 0.001	0.06 (0.04, 0.10), p < 0.001
Number of new or enlarging T2 lesions – rate ratio	0.18 (0.15, 0.22), p < 0.001	0.15 (0.13, 0.19), p < 0.001
NfL serum concentration – adjusted geometric mean ratio 3 months	0.93 (0.89, 0.98), p = 0.011	0.89 (0.85, 0.93), p < 0.001
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Time to first confirmed relapse at month 24 – rate ratio[b]	[redacted]	[redacted]
No evidence of disease activity (NEDA-4)[c] - odds ratio 12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
	Adjusted mean difference (95% CI), p-value	***Adjusted mean difference (95% CI), p-value***
Rate of brain volume loss (indicates a difference in slope of brain volume loss)	0.07 (−0.02, 0.15), p = 0.116	0.07 (−0.02, 0.15), p = 0.129
EQ-5D-5L utility index[c] 12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
EQ-5D-5L VAS[c] 12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
MSIS-29[c] 6 months Physical impact score Psychological impact score	[redacted]	[redacted]
12 months Physical impact score Psychological impact score	[redacted]	[redacted]
18 months Physical impact score Psychological impact score	[redacted]	[redacted]

24 months Physical impact score Psychological impact score	[redacted]	[redacted]
30 months Physical impact score Psychological impact score	[redacted]	[redacted]
Impact of MS disease on work productivity and activity (WPAI:MS)[c] 6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]

ARR: annualised relapse rate; CDW-3: 3-month confirmed disability worsening; CDW-6: 6-month confirmed disability worsening; CDI-6: 6-month confirmed disability improvement; CI: confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; Gd: gadolinium; MSIS-29: Multiple Sclerosis Impact Scale; NA: not applicable; NEDA-4: no evidence of disease activity; Nfl: Neurofilament light chain; VAS: visual analogue scale.
[a]Outcome data from CS Document B Section B.2.6 pg.38-47.
[b]Based on a Cox regression model adjusted for treatment, region, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and patient age at baseline as covariates.
[c]Outcome data from CS Appendix L Tables 141-143 pg.539-541.

In Section 3.2.8 we report the characteristics of the two patient subgroups relevant to the economic analyses, and specified in NICE Final Scope[8] (see Section 2.3). The primary and key secondary outcomes for these groups are summarised in Table 9. The relapse rate (ARR ratio) for the HA and RES RRMS *post hoc* subgroups was pooled for both ASCLEPIOS I and II, whereas the ratio for the ITT population was reported separately for each trial (Table 8). The pooled ARR ratio for the subgroups (HA RRMS [redacted], 95% CI: [redacted], p [redacted], and RES RRMS [redacted], 95% CI: [redacted], p = [redacted]) was broadly similar to the ARR ratio of the ITT population in ASCLEPIOS I (0.50, 95% CI: 0.37, 0.65, p < 0.001), but differed slightly from the ratio of the ITT population in ASCLEPIOS II (0.42, 95% CI: 0.31, 0.56, p < 0.001), suggesting [redacted] relapses in the ITT population in ASCLEPIOS II than in the subgroups.

For the subgroups and for the ITT population, the disability worsening ratios at 3 and 6 months (CDW-3 and CDW-6) were pooled for ASCLEPIOS I and II. The pooled CDW-3 hazard ratio for the HA RRMS subgroup ([redacted], 95% CI: [redacted], p = [redacted]) was slightly [redacted] than that of the ITT population ([redacted], 95% CI: [redacted], p = [redacted]), suggesting a [redacted] in disability worsening for the HA subgroup compared to the ITT population. This effect was even greater for the RES RRMS *post hoc* subgroup ([redacted] 95% CI: [redacted], p [redacted]). A similar pattern was seen in the CDW-6 hazard ratio for the HA RRMS subgroup ([redacted], 95% CI[redacted] p = [redacted]) and the RES

subgroup ([redacted], 95% CI: [redacted], p = [redacted]) compared to the ITT population ([redacted], 95% CI: [redacted], p = [redacted]). This suggests a [redacted] effect for the subgroups than for the ITT population. However, these were *post hoc* subgroups and therefore, should be interpreted as exploratory only. Randomisation is not taken into account in these subgroup analyses, which leads to biased results.

Table 8: Primary and key secondary outcomes for RRMS subgroups, pooled for ASCLEPIOS I and II

Subgroup	ofatumumab vs teriflunomide	HA RRMS subgroup	RES RRMS subgroup
ARR ratio	N	[redacted]	[redacted]
	ratio (95% CI), p-value	[redacted]	[redacted]
CDW-3 hazard ratio	N	[redacted]	[redacted]
	ratio (95% CI), p-value	[redacted]	[redacted]
CDW-6 hazard ratio	n	[redacted]	[redacted]
	ratio (95% CI), p-value	[redacted]	[redacted]

ARR: annualised relapse rate; CDW-3: 3-month confirmed disability worsening; CDW-6: 6-month confirmed disability worsening; CI: confidence interval.
[a]Outcome data from CS Document B Section B.2.7 pg.49-56.

3.2.11 Safety (adverse events)

The CS provides an overview of safety related to ofatumumab (CS Document B, B.2.10) based on the ASCLEPIOS I and II trials. Adverse events in both trials are reported in the CS (Document B, Table 43 and Table 45, pg.101-103) and summarised in Table 9. The safety set (SAF) was used for all safety analyses of the ASCLEPIOS trials and was defined as all patients who received at least one dose of study treatment. Patients were analysed according to treatment received. Unless otherwise stated, only data up to and including the safety cut-off of 100 days after permanent study drug discontinuation will be included in the analysis and data beyond this point will be excluded from the SAF. There was a total of 927 patients in the SAF from ASCLEPIOS I and 955 patients in ASCLEPIOS II.

Treatment exposure rates of the SAF for both treatment groups in ASCLEPIOS I and II trials were presented in CS Table 44 (pg. 101) in Section B.2.10.2. In ASCLEPIOS

I, the mean exposure days in the ofatumumab group was [redacted] days and [redacted] days in the teriflunomide group. In ASCLEPIOS II, it was [redacted] and [redacted] days, respectively. There was no treatment switching in the studies.

The proportion of patients experiencing AE was similar in both ASCLEPIOS trials and across both the ofatumumab and teriflunomide arms. AEs were experienced by [redacted] of patients in the ofatumumab group and [redacted] in the teriflunomide arm of ASCLEPIOS I, and [redacted]% in the ofatumumab group and [redacted]% in the teriflunomide group of ASCLEPIOS II.

Table 9: Summary of adverse events in ASCLEPIOS I and II trials[a.]

Outcome, n (%)	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Patients with AE	382 (82.2)	380 (82.3)	409 (85.0)	408 (86.1)
Patients with study drug-related AE	[redacted]	[redacted]	[redacted]	[redacted]
Patients with SAE	48 (10.3)	38 (8.2)	38 (7.9)	36 (7.6)
Patients with AE causing study drug interruption	[redacted]	[redacted]	[redacted]	[redacted]
Patients with AE causing study drug discontinuation	27 (5.8)	24 (5.2)	27 (5.6)	25 (5.3)
AEs used in the economic model				
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Injection-related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reactionsc	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
PML	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]
Other AEs[d]				
Neoplasms[e]	[redacted]	[redacted]	[redacted]	[redacted]
Immunogenicity[f]	[redacted]	[redacted]	[redacted]	[redacted]

PML: progressive multifocal leukoencephalopathy; URTI: upper respiratory tract infection; UTI: urinary tract infection
a Data from CS Document B Section B.2.10.3, Table 45, pg.102.
b Injection-related reactions includes systemic injection reactions and local injection site reactions.
c Injection site reactions include local injection site reactions only.
d Although not included in the economic analysis, these adverse events were deemed important by ERG clinical experts.
e Includes all neoplasms (benign, malignant, cysts, polyps and unspecified).
f Overall number of patients with anti-drug antibodies; from CS Document B, Table 49, pg.107; analyses included only those with available data, specifically: ASCLEPIOS I n=454 and ASCLEPIOS II n=469.

3.2.11.1 Serious Adverse Events (SAE) and AE associated with drug interruption and drug discontinuation

Rates of SAE were similar across both arms in ASCLEPIOS II. While slightly [redacted] serious adverse events (SAE) were reported in ASCLEPIOS I, and particularly in the [redacted] the difference between the ofatumumab and teriflunomide arms in ASCLEPIOS I was not statistically significant (OR: 1.28. 95% CI: 0.80, 2.07, CSR ASCLEPIOS I, pg.172). Adverse events associated with drug interruption and drug discontinuation (see Section 3.2.3) were similar across both trials and all arms (CS Document B, Table 48, pg. 106-7). The CS reports that no deaths occurred during the study.

3.2.11.2 Immunogenicity

According to section B.2.10.7 (pg. 107) of the CS document B: *"As a fully human antibody, ofatumumab is expected to have reduced risks of eliciting hypersensitivity reactions and immunogenicity compared with an antibody of chimeric or humanised origin containing non-human sequences"*. A summary of the incidence of anti-drug antibodies throughout key ASCLEPIOS trials in the ofatumumab group is presented in Table 49 of the CS (pg. 107). Overall, incidence of anti-drug antibodies in the ofatumumab group was [redacted]. In each trial, [redacted] patient developed treatment-emergent anti-drug antibodies after baseline. In ASCLEPIOS I, [redacted] patients were found to have anti-drug antibodies at any timepoint in the trial ([redacted] at baseline; [redacted] at Week 4; [redacted] at Week 24; [redacted] at Week 48; [redacted] at Week 96). In ASCLEPIOS II, [redacted] patients were found to have anti-drug antibodies at any timepoint in the trial ([redacted] at baseline; [redacted] at Week 4; [redacted] at Week 24; [redacted] at Week 48; [redacted] at Week 96). From the above results, the company concludes that *"long-term treatment effect waning due to formation of neutralising antibodies is considered unlikely with ofatumumab"* (CS Document B, pg. 107). The ERG appreciate that the company's claim is plausible based on the observed level of patients with anti-drug antibodies. However, no longer-term data were presented in the CS. Therefore, the ERG cannot conclude that treatment waning does not occur as waning could be related to loss of effectiveness for any reason and not just the development of antibodies. Therefore, treatment waning is included in the ERG base case in the cost-effectiveness analysis (see Section 4.3.6.12).

3.2.11.3 AE summary

Overall, the safety data submitted by the company suggests that the most frequent AE experienced by patients receiving ofatumumab in both ASCLEPIOS trials were injection-related reactions, nasopharyngitis and headache. In the teriflunomide arms, the most commonly reported AE were nasopharyngitis, injection-related reactions (from the placebo dummy injections), and alopecia. The AE included in the cost-effectiveness analysis are detailed in Section 4.3.8.5. In ASCLEPIOS II, injection-related reactions (which includes systemic injection reactions and local injection-site reactions) occurred in [redacted]% of patients in the ofatumumab arm compared to [redacted]% in the teriflunomide arm (which received the placebo dummy injection). By contrast, injection-related reactions were [redacted]% in both groups in ASCLEPIOS I. Rates of local injection-site reactions only were more common in the ofatumumab arms in both ASCLEPIOS I and II ([redacted]% and [redacted]%, respectively) compared to the teriflunomide arms ([redacted]% and [redacted]%).

The CS references data, but does not present data from two other dose-finding RCTs of ofatumumab: Sorensen 2014[28] (N=38) and the MIRROR study[29] (N=232). The ERG agrees that these smaller, shorter-term trials provide less robust information about safety, when compared to the main RCTs. However, it is worth noting that the ofatumumab arms in the dose-finding trials, compared to the ASCLEPIOS trials, reported higher levels of any AE, but lower rates of SAE. The most commonly reported AE (injection-related reactions) was the same across both trials.

The ERG agrees with the company's assertion that ofatumumab has a generally similar safety profile compared to teriflunomide. However, ofatumumab has been used for treating other diseases, such as leukaemia, albeit at different doses, but for which there are some indications of potential adverse effects.[10] These potential adverse effects should be considered in assessing the safety profile of ofatumumab for RRMS.

3.2.12 Ongoing observational study

The CS (Document B, pg.108) refers to an open-label extension study of the ASCLEPIOS trials (ALITHIOS)[30], for which initial data are expected in [redacted], and a trial

of ofatumumab in Japan (APOLITOS trial of ofatumumab vs. placebo, N=64)[31], consisting of a 24-week randomised, double-blinded, placebo controlled treatment period followed by an open label Extension study of ofatumumab, which is expected to be completed in 2020. It refers to two other ongoing trials that assess effectiveness when MS patients switch from other treatments to ofatumumab, and whose results are not expected in the next 12 months: the ARTIOS trial (estimated N=550)[32] and OLIKOS trial (estimated N=100)[33]. The ERG's searches for ongoing trials did not identify any others relevant to the NICE scope (see Section 3.1.1).

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As evidence of head-to-head comparison was available only between ofatumumab and teriflunomide from the ASCLEPIOS trials, the company undertook NMAs to allow comparison between ofatumumab and other comparators relevant to this appraisal.

3.3.1 Selection of studies for the NMAs

From potentially relevant studies identified in the company's clinical effectiveness SLR (as described in Section 3.1), the company selected 37 RCTs (including the two ASCLEPIOS trials) in a feasibility assessment for inclusion in the NMAs (see Table 11). Key inclusion criteria for the NMAs (CS Document B, Table 28, p.57) were similar to those for the SLR described earlier in Section 3.1.2, but additionally required the duration of RCTs to be ≥48 weeks. The company justified the exclusion of trials with shorter duration based on the approach adopted in a published NMA,[34] which stated that "*these trials were not designed to study clinical outcomes and were therefore considered too different from the other trials for inclusion in NMAs*". The ERG notes that trials excluded by this criterion may have relevant included outcome measures such as ARR. In addition, trials of shorter duration may have included a placebo arm which would have improved the connection of evidence within the NMA networks. However, the ERG is aware that the same approach was adopted in the NMAs considered in previous TA (TA533 for ocrelizumab for treating RRMS).[19] Deliberation by the ERG for that assessment highlighted reasons for accepting this restriction, including the short trial duration (and placebo-controlled period within the

trial) in relation to the chronic features of MS and the tendency to focus on MRI outcomes for those studies (see Committee Papers of TA533).[19] The ERG agrees with this.

In accordance with the inclusion criteria for the SLR in the CS, the inclusion criteria for the NMA covered key effectiveness outcomes including CDP-3, CDP-6, ARR, proportion of patients with relapse/relapse-free, MRI outcomes and quality of life; and key safety outcomes including AE, SAE and withdrawals. Similarly, the NMA inclusion criteria covered a wide range of interventions and comparators including best supportive care, placebo as well as some unlicensed therapies.

Overall the ERG considered the NMA inclusion criteria which covered a broader 'evidence space' than the 'decision space' to be appropriate, as it may be necessary to use RCTs in the wider evidence space to enable evidence for different therapies within the decision space to be connected (e.g. through placebo or other treatments). Nevertheless, the ERG is concerned that the process of selecting the 37 RCTs for NMA feasibility assessment from the 84 studies (based on CS Appendix D, Section D.1.3) lacked transparency as reasons for exclusion were not provided for individual studies. It appears that the selection of the 37 RCTs has been guided by a different set of criteria rather than the stated NMA criteria.

The ERG collated references in Table 9 (n=82) and Table 10 (n=21) of CS Appendix D, which correspond to studies retained in the company's original and updated SLR, respectively. These yielded 103 references related to 88 unique studies which were examined by the ERG. Of the 51 studies not selected for NMA feasibility assessment, 24 appear to have been excluded because they lasted less than 48 weeks; 17 tested unlicensed doses or DMTs that are outside the appraisal scope and that would not help connecting evidence between DMTs within the scope, five included irrelevant comparisons or outcomes, and one due to being unavailable in English language. Two trials (SPECTRIMS[35] and EUSPMS[36]) might have been excluded as they focused on SPMS population (which, although not listed as SLR/NMA exclusion criterion, was excluded from the company's decision problem. The ERG could not establish the reasons for the remaining two trials from feasibility assessment: GOLDEN,[3] and BECOME.[4] Key characteristics of these studies are presented in Table 10.

Table 10: Trials excluded from the company's NMA assessment for unclear reasons

Trial name	Blinding	Treatment groups	Key eligibility criteria	Relevant outcomes reported
GOLDEN[3] NCT01333501	Open-label	Fingolimod (n=104) IFN β -1b (n=47)	Age 18-60 RRMS with cognitive impairment EDSS ≤ 5	ARR Fingolimod 0.12 (20 events/167 person-years0 IFN β -1b 0.39 (22 events/56 patient-years0
BECOME[4]	Unclear	Total n=75 Glatiramer acetate (n=39) IFN β-1b (n=36)	Age 18-55 RRMS or clinically isolated syndromes (CIS) suggestive of MS EDSS 0-5.5	Combined active lesions (CAL) (median / 75th percentile, per patient per scan for months 1–12): IFN β-1b 0.63 (2.76) Glatiramer acetate 0.58 (2.45) MRI activity (new brain lesions) (median / 75th percentile, per patient per scan for months 1—12: IFN β-1b 0.50 (1.56) Glatiramer acetate 0.33 (1.10)

Table 11: Characteristics of the RCTs included in the company's NMA feasibility assessment

	Blinding	Allocation	Phase	Treatment groups	Key Eligibility Criteria	Included in NMA
ADVANCE	Double	Parallel	3	- Peginterferon β-1a SC 125 µg Q2W -Placebo	Aged 18-65 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive)	Scenario
AFFIRM	Double	Parallel	3	-Natalizumab IV 300 mg Q4W -Placebo	Aged 18-50 (inclusive) Diagnosis of RMS EDSS 0-5 (inclusive) Documented history of relapse in past 12 months	Yes
ASCLEPIOS I **ASCLEPIOS II**	Double	Parallel	3	-Ofatumumab SC 20 mg Q4W -Teriflunomide PO 14 mg QD	Aged 18-55 (inclusive) at screening Diagnosis of MS Diagnosis of RMS EDSS 0-5.5 (inclusive) at screening Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
ASSESS	Single	Parallel	3b	-Fingolimod PO 0.5 mg QD -Glatiramer acetate SC 20 mg QD	Aged 18-65 (inclusive) Diagnosis of RRMS EDSS 0-6 (inclusive) Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
BEYOND	Mixed	Parallel	3	-IFN β-1b SC 250 µg Q2D -Glatiramer acetate SC 20 mg QD	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive) Documented history of relapses of at least 1 in the past year	Yes
Boiko et al., 2018a	Double	Parallel	3	-Glatiramer acetate SC 20 mg QD -Glatiramer acetate SC 20 mg QD (Timexon) -Placebo	Aged 18-55 (inclusive) Diagnosis of RMS EDSS 0-5.5 (inclusive) Documented history of relapses of at least 1 in the past 12 months No relapse in previous 4 weeks Disease duration of one year or more	No
Boiko et al., 2018b	Double	Parallel	3	-IFN β-1a SC 44 µg TIW -IFN β-1a SC 44 µg TIW (Teberif) -Placebo	Aged 18-55 (inclusive) Diagnosis of RMS EDSS 0-5.5 (inclusive) No relapse in previous 28 days Disease durations of one year or more	No
Bornstein et al., 1987	Double	Parallel	-	-Glatiramer acetate SC 20 mg QD -Placebo	Aged 20-35 (inclusive) Diagnosis of RRMS EDSS 0-6 (inclusive) Documented history of relapses of at least 2 in past 2 years	Yes
BRAVO	Open label	Parallel	3	-IFN β-1a IM 30 µg QW Placebo	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0-5.5 (inclusive) No relapse in previous 30 days Documented history of relapses of at least 1 in the past year or 2 in past 2	Yes

					years, or at least 1 in previous 1-2 years and 1 Gd+ lesion in previous 1 year	
Calabrese et al., 2012	-	Parallel	4	-IFN β-1a SC 44 µg TIW -IFN β-1a IM 30 µg QW -Glatiramer acetate SC 20 mg QD	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive)	Yes
CAMMS223	Open label	Parallel	2	-Alemtuzumab IV 12 mg -IFN β-1a SC 44 µg TIW	Diagnosis of RRMS within 36 months of screening At least 2 clinical episodes in the past 2 years EDSS 0-3 (inclusive)	Yes
CARE-MS I	Open label	Parallel	3	-Alemtuzumab IV 12 mg -IFN β-1a SC 44 µg TIW	Aged 18-50 (inclusive) Diagnosis of RRMS	Yes
CARE-MS II	Open label	Parallel	3	-Alemtuzumab IV 12 mg -IFN β-1a SC 44 µg TIW	Aged 18-55 (inclusive) Diagnosis of RRMS At least one relapse on interferon beta or glatiramer	Yes
CLARITY	Double	Parallel	3	-Cladribine PO 3.5 mg/kg -Cladribine PO 5.25 mg/kg -Placebo	Aged 18-65 (inclusive) Diagnosis of RRMS Lesions consistent with MS At least one relapse in the 12 months prior to study EDSS 0-5.5 (inclusive)	Yes
CombiRx	Double	Factorial	3	-IFN β-1a IM 30 µg QW -Glatiramer acetate SC 20 mg QD	Aged 18-60 (inclusive) Diagnosis of RRMS EDSS 0-5.5 (inclusive) No acute exacerbation in previous 30 days At least two exacerbations in previous 3 years	Yes
CONFIRM	Mixed	Parallel	3	-Dimethyl fumarate PO 240 mg BID -Glatiramer acetate SC 20 mg QD -Placebo	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive) No relapse in previous 50 days At least 1 relapse in previous year, or at least 1 Gd+ lesion in prior 6 weeks	Yes
Copolymer I MS trial	Double	Parallel	3	-Glatiramer acetate SC 20 mg QD -Placebo	Aged 18-45 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive) No relapse in previous 30 days At least 2 relapses in previous 2 years	Yes
DEFINE	Double	Parallel	3	-Dimethyl fumarate PO 240 mg BID -Placebo	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive) Documented history of relapse in past 12 months or MRI which showed at least one GD-enhancing lesions 6 weeks prior to study	Yes
Etemadifar et al., 2006	Single	Parallel	-	-IFN β-1a IM 30 µg QW -IFN β-1b SC 250 µg Q2D	Aged 18-50 (inclusive) Diagnosis of RRMS EDSS 0-5 (inclusive)	No

				-IFN β-1a SC 44 µg TIW	At least 2 relapses in previous 2 years	
EVIDENCE	Single	Parallel	-	-IFN β-1a SC 44 µg TIW -IFN β-1a IM 30 µg QW	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0-5.5 (inclusive) At least 2 relapses in previous 2 years	Yes
FREEDOMS	Double	Parallel	3	-Fingolimod PO 0.5 mg QD -Placebo	Aged 18-55 (inclusive) at screening Diagnosis of MS Diagnosis of RRMS EDSS 0-5.5 (inclusive) at screening Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
FREEDOMS II	Double	Parallel	3	-Fingolimod PO 0.5 mg QD -Placebo	Aged 18-55 (inclusive) at screening Diagnosis of RRMS EDSS 0-5.5 (inclusive) at screening Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
GALA	Double	Parallel	3	-Glatiramer acetate SC 40 mg TIW -Placebo	Aged 18-55 (inclusive) at screening Diagnosis of RRMS EDSS 0-5.5 (inclusive) at screening No relapses in previous 30 days Disease durations at least one year Documented history of relapses of at least 1 in the past year or 2 in past 2 years, or at least 1 in previous 1-2 years and 1 Gd+ lesion in previous 1 year	Yes
IFNB MS	Double	Parallel	-	-IFN β-1b SC 250 µg Q2D -Placebo	Aged 18-50 (inclusive) Diagnosis of RRMS EDSS 0-5.5 (inclusive) At least two exacerbations in the previous 2 years	Yes
INCOMIN	Open label	Parallel	-	-IFN β-1a IM 30 µg QW -IFN β-1b SC 250 µg Q2D	Aged 18-50 (inclusive) at screening Diagnosis of RRMS EDSS 1-3.5 (inclusive) at screening No relapses in previous 30 days At least 2 relapses in previous 2 years	No
MSCRG	Double	Parallel	3	-IFN β-1a IM 30 µg QW -Placebo	Aged 18-55 (inclusive) at screening Diagnosis of RMS EDSS 1.0-3.5 (inclusive) at screening No relapses in previous 2 months At least 2 relapses in previous 3 years	Yes
OPERA I **OPERA II**	Double	Parallel	3	-Ocrelizumab IV 600 mg -IFN β-1a SC 44 µg TIW	Aged 18-55 Diagnosis of MS EDSS 0-5.5 (inclusive) Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
Pakdaman et al., 2018	Double	Parallel	-	-IFN β-1a IM 30 µg QW -IFN β-1a IM 30 µg QW (CinnoVex)	Aged 18-65 Diagnosis of RRMS EDSS 0-4.5 (inclusive)	No

PRISMS	Double	Parallel	-	-IFN β-1a SC 22 µg TIW -IFN β-1a SC 44 µg TIW -Placebo	Adult Diagnosis of RRMS EDSS 0-5.0 (inclusive) Disease duration of one year or more History of relapses of at least 2 in the past 2 years	Yes
REGARD	Open label	Parallel	4	-IFN β-1a SC 44 µg TIW -Glatiramer acetate SC 20 mg QD	Aged 18-60 (inclusive) Diagnosis of RRMS At least one relapse in the previous 12 months	Yes
Stepien et al., 2013	-	Parallel	-	-IFN β-1a IM 30 µg QW -IFN β-1b SC 250 µg Q2D	Adult Diagnosis of RRMS EDSS 0-6.5 (inclusive)	Yes
TEMSO	Double	Parallel	3	-Teriflunomide PO 7 mg QD -Teriflunomide PO 14 mg QD -Placebo	Aged 18-55 (inclusive) Diagnosis of RMS EDSS 0-5.5 (inclusive) Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
TENERE	Single	Parallel	3	-Teriflunomide PO 7 mg QD -Teriflunomide PO 14 mg QD -IFN β-1a SC 44 µg TIW	Aged 18+ Diagnosis of RMS EDSS 0-5.5 No relapses in previous 30 days	Yes
TOWER	Double	Parallel	3	-Teriflunomide PO 7 mg QD -Teriflunomide PO 14 mg QD -Placebo	Aged 18-55 (inclusive) Diagnosis of RMS EDSS 0-5.5 (inclusive) Documented history of relapses of at least 1 in the past year or 2 in past 2 years	Yes
TRANSFORMS	Double	Parallel	3	-Fingolimod PO 0.5 mg QD -IFNB-1a IM 30 µg QW	Aged 18-55 (inclusive) Diagnosis of RRMS EDSS 0–5.5 (inclusive) Recent history of at least one relapse	Yes

3.3.2 Feasibility assessment

The company's feasibility assessment highlighted variations in study design (in particular outcome definitions) and baseline patient characteristics between the 37 selected RCTs (CS Document B, Section B.2.9.2), but considered that overall the trials were sufficiently similar for the purpose of NMAs. The following sub-sections provide the ERG's critique of the company's approaches to addressing these sources of heterogeneity.

3.3.2.1 Definitions of relapse and ARR

The CS outlined variation in the definitions of relapse and in the methods for calculating and reporting of ARR among the 37 RCTs (CS Document B, pg.63-64). The company excluded three trials (Boiko et al 2018b,[37] Etemadifar et al. 2006[2] and Pakdaman et al. 2018[38]) due to different definitions and/or non-reporting of relapse and ARR. The ERG agrees with the exclusion of two of the trials but considered that it would have been possible to include data from Etemadifar et al. 2006 (see Table 12).[2] The trial has a relatively small sample size (n=90 overall; 30 patients each for IFN β-1a IM 30 µg QW, IFN β-1b SC 250 µg Q2D and IFN β-1a SC 44 µg TIW) and therefore, the potential impact on NMA findings and cost-effectiveness analysis is likely to be very small. The ERG explored the inclusion of this additional ARR data and data from another trial excluded from the company's base case (Boiko et al. 2018a[1]) in Section 3.5.2.

Table 12: Company's approaches to addressing differences in the definitions of relapse/ARR and the ERG's comments

Differences in outcome definition and reporting	Company's approaches	ERG's comments
Relapse		
ASCLEPIOS I & II and 23 other trials: New/recurrent/worsening neurological symptoms or abnormalities that lasted for at least 24 hours Nine other trials: same events as above but lasted for at least 48 hours	Definitions were considered sufficiently similar for overall comparison	ERG agreed – unlikely to substantially affect relative measures (ratios) of ARR.
Boiko et al. 2018b: reported only MRI-confirmed relapse	Excluded the trial	ERG agreed with the exclusion – the trial would have only allowed comparison between different brands of IFN β-1a anyway.

ARR		
ARR not reported in four trials: Bornstein et al. 1987, PRISMS, Etemadifar et al. 2006 and Pakdaman et al. 2018	Calculated ARR for Bornstein et al. 1987 and PRISMS by dividing the number of relapses per patient over two years by two Excluded Etemadifar et al. 2006 and Pakdaman et al. 2018.	ARR could have been calculated for Etemadifar et al. 2006: IFN β-1b SC 250 µg Q2D: 1.08 (Betaferon) 65 events/60 person-years) IFN β-1a (Rebif) SC 44 µg TIW: 1.10 (66 events/60 person-years) IFN β-1a (Avonex) IM 30 µg QW: 0.95 (57 events/60 person-years) Agreed that Pakdaman et al. 2018 should be excluded.

3.3.2.2 3-month and 6-month confirmed disability progression

The company mapped out and highlighted differences in the criteria for CDW-3 and CDW-6 between trials. All trials (including ASCLEPIOS I & II) required an increase in EDSS score of ≥1.0 to be considered as disability progression/worsening if the patient's baseline EDSS was between 1 and 5. However, different criteria were adopted in ASCLEPIOS I & II for patients with a baseline EDSS score of 0 or 5.5 (see CS Document B, Tables 33 and 34, pages 66-70). In these two trials, an increase in EDSS score of ≥1.5 was required for disability progression if the patient's baseline EDSS was 0, whereas an increase in EDSS of ≥0.5 was required for patients with a baseline score of 5.5.

As these criteria differed from many other trials, the company undertook an additional analyses of CDW-3 and CDW-6 data from ASCLEPIOS I & II using "*aligned criteria*" that were commonly used in previous trials, which required an increase of ≥1.0 in EDSS score from any baseline between 0 and 5.5 to be considered a disability progression event. The company's economic analysis also uses efficacy data based on the "*aligned criteria*" (see Section 4.3.6.10). The aligned criteria also better matched the company's economic model, which only considered whole number EDSS scores. To allow easier distinction between the criteria, the company referred to the original ASCLEPIOS criteria as "*pre-defined criteria*".

In addition to the re-analysis based on the aligned criteria and the pre-defined criteria, the company undertook a further set of analysis of the ASCLEPIOS trial data according to the methods specified in the protocol of OPERA trials,[39] which were pivotal trials for ocrelizumab in the RMS population. The company mentioned

discrepancies in the time intervals of increased EDSS required, assessment of baseline EDSS and whether CDW could be confirmed during a relapse between ASCLEPIOS and OPERA trials, with the differences between the pre-defined criteria and the OPERA-aligned criteria detailed in CS Appendices D Table 18, pg.81. The three sets of criteria are shown in Table 13 alongside the estimated HR for CDW-3 and CDW-6 when the respective criteria were applied to data from the ASCLEPIOS trials.

Table 13: Alternative criteria for CDW-3 and CDW-6 used in the CS and corresponding estimates for the ASCLEPIOS trials

	Pre-defined criteria (ASCLEPIOS trials)	Aligned criteria	OPERA-aligned criteria
Used in CS economic model	Scenario analyses	Base case	Scenario analyses
Baseline EDSS	Increase in EDSS required to be considered disability progression/worsening		
0	1.5	1.0	1.0
1 – 5	1.0	1.0	1.0
5.5	0.5	1.0	1.0
>5.5[a]	0.5	0.5	0.5 [b]
Minimum interval of increase in EDSS required	CDW-3: 3 months (90 days) [c] CDW-6: 6 months (166 days) [c]	CDW-3: 3 months (90 days) [c] CDW-6: 6 months (166 days) [c]	CDW-3: 12 weeks CDW-6: 24 weeks

[a] Patients with an EDSS score of >5.5 at screening were not eligible for inclusion in the ASCLEPIOS trials and almost all other trials, but the EDSS score of patients could deteriorate to >5.5 between screening and baseline measurement.
[b] According to the OPERA trial protocol, p.101 (document page 254).[39]
[c] According to the ASCLEPIOS trial protocol, page 79.[24]

The ERG agrees that differences in the criteria used to define CDW-3 and CDW-6 could introduce additional heterogeneity and potential bias into the NMAs, and it is helpful to provide analyses using both the "*aligned criteria*" and the "*pre-defined criteria*" for the ASCLEPIOS trial data (see Section 4.3.6.10). As the company did not have access and could not re-analyse data from other trials using these criteria (where different criteria were originally used), the analyses did not completely remove the heterogeneity in the definition of disability progression between trials and potential bias associated with the heterogeneity.

The ERG also agrees that the attempt to align the methods used for CDW-3 and CDW-6 between ASCLEPIOS and OPERA trials using "*OPERA-aligned*" criteria is informative. However, we suggest great caution in the interpretation of findings based on these analyses given their *post hoc* nature and other differences in the

design and conduct of the trials and in patient populations that could not be addressed by the use of the criteria.

3.3.2.3 Baseline patient characteristics and event rates in placebo arms

The CS highlighted heterogeneity in most baseline patient characteristics among the trials included in the feasibility assessment, in particular with regard to; time since first MS symptoms, the volume of T2 lesions and the proportion of patients who had prior DMT experience. The company suggested that heterogeneity was not likely to have a significant effect on the results of the NMA (CS Document B, p.73). While some heterogeneity is expected with evidence networks involving several treatments, the ERG considered that the heterogeneity in the company's feasibility assessment warrants further investigation. We carried out further evaluation of comparability between ASCLEPIOS trials and other key trials in the evidence network. The findings are presented in Section 3.5.3.

3.3.3 Studies included in the efficacy NMAs

For ease of identifying the contribution of individual trials towards the NMAs, the ERG mapped the 37 RCTs included in the feasibility assessment to the evidence network reported in the CS. The resulting evidence network is shown in Figure 1

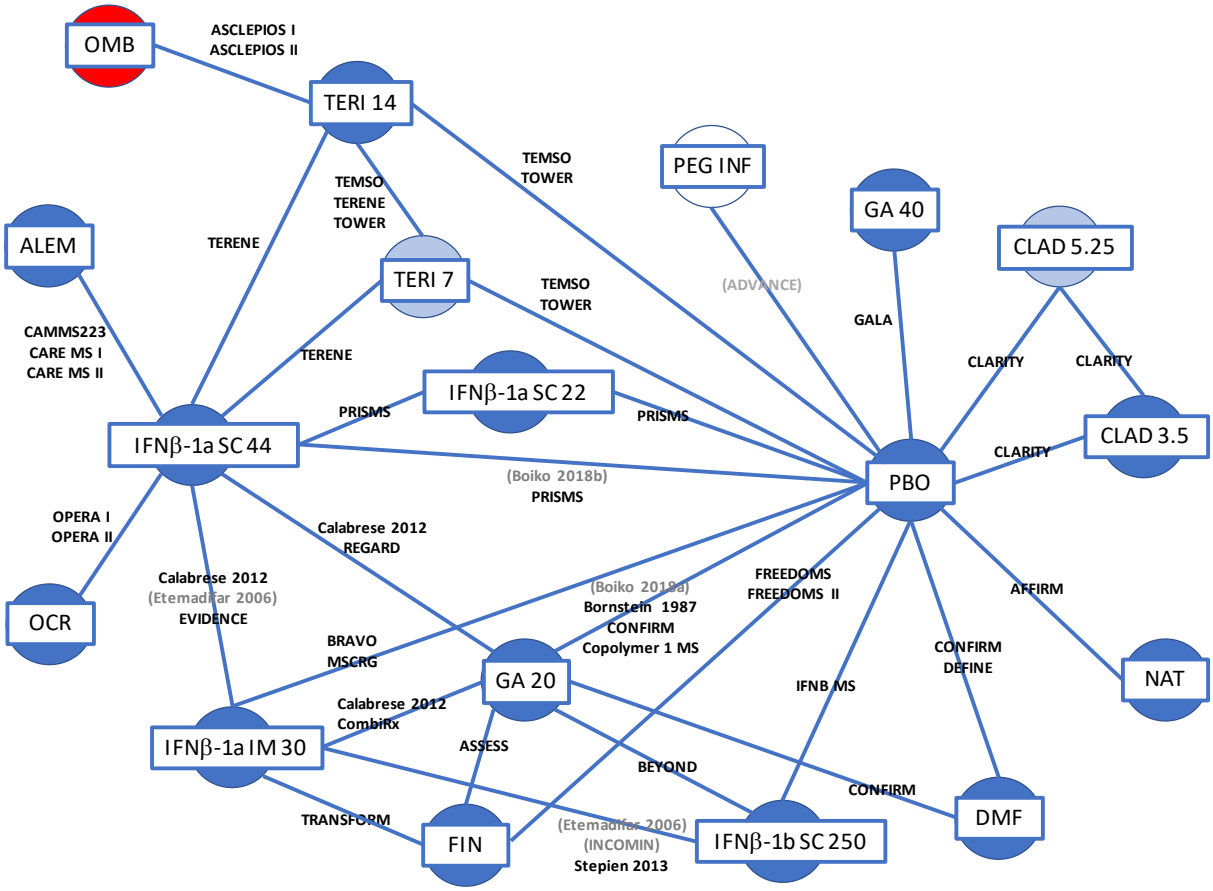

Figure 1. ERG mapped evidence network showing all trials included in the company's feasibility assessment for the NMAs

Trial names listed in grey colour in brackets indicate that the trial was excluded from the company's base case analyses. The unlicensed doses of cladribine (5.25 mg/kg) and teriflunomide (7 mg) were run in the company's NMA, but results were not presented as these doses were not relevant to UK clinical practice and this appraisal.

Abbreviations: ALEM: alemtuzumab IV 12 mg; BID: twice a day; CLAD 3.5: cladribine PO 3.5 mg/kg; CLAD 5.25: cladribine PO 5.25 mg/kg; DMF: dimethyl fumarate PO 240 mg BID; FIN: fingolimod PO 0.5 mg QD; GA 20: glatiramer acetate SC 20 mg QD; GA 40: glatiramer acetate SC 40 mg TIW; IFNB-1a IM 30: IFN β-1a IM 30 µg QW; IFNB-1a SC 22: IFN β-1a SC 22 µg TIW; IFNB-1a SC 44: IFN β-1a SC 44 µg TIW; IFNB-1b SC 250: IFN β-1b SC 250 µg Q2D; IM: intramuscular; IV: intravenous; NAT: natalizumab IV 300 mg Q4W; OCR: ocrelizumab IV 600 mg; OMB: ofatumumab SC 20 mg Q4W; PBO: placebo; PO: orally; Q2D: once every 2 days; QD: once a day; Q4W: once every four weeks; QW: once every week; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

The company undertook NMAs for three key effectiveness outcomes: ARR, CDW-3 and CDW-6 (see Section 1.3.1 for NMA results). Some of the 37 RCTs included in the feasibility assessment did not report one or more of these outcomes, and therefore the number of trials included in each of the NMAs varied by outcome: 31 RCTs for ARR, 21 RCTs for CDW-3 and 20 RCTs for CDW-6 for the company's base case analyses (see Section 4.3). Six trials were excluded from base case analyses for all three outcomes. The reasons for exclusion stated in the CS and ERG's comments are summarised in Table 14.

Table 14: Reasons stated in the CS for exclusion of trials from efficacy NMAs and ERG's comments

Trials excluded	Reasons for exclusion (CS Document B, p.77-78)	ERG comments
Boiko et al. 2018a	A non-inferiority trial comparing different formulations of the same DMT (two formulations of glatiramer acetate).	The trial (n=150) also included a placebo arm and therefore could have been included in the NMA: Glatiramer acetate (Timexon) SC 20 mg QD: 0.20 (11 events; 61 persons x [48/52] year = 56 person-years) Glatiramer acetate (Copaxone-Teva) SC 20 mg QD: 0.20 (11 events; 61 persons x [48/52] year = 56 person-years) Placebo: 0.27 (7 events; 28 persons x [48/52 year] = 26 person-years)
Boiko et al. 2018b	Did not report relevant outcomes for ARR, CDW-3 or CDW-6.	ERG agrees with the exclusion. ARR was reported for two formulations of IFN β-1a, but patients in the placebo arm switched to one of the IFN β-1a preparations from week 17 onwards, and therefore no usable data were available for the NMA.
Pakdaman et al. 2018	Did not report relevant outcomes for ARR, CDW-3 or CDW-6.	ERG agrees with stated reasons for exclusion.
Etemadifar et al. 2006	Did not report relevant outcomes for ARR, CDW-3 or CDW-6.	ARR could have been calculated for this trial as described earlier in Table 12.
INCOMIN	Results were considered to be an outlier not reflective of clinical practice, as has been recognised in the literature since the early 2000s; exclusion was consistent with TA533 and recently published NMAs	ERG agrees with the exclusion (see the main text below)
ADVANCE	Was excluded from a previous NICE appraisal (ocrelizumab in RRMS [TA533]), as inclusion of ADVANCE found pegylated IFN to be more effective than other β-interferons as well as known high-efficacy treatments (such as natalizumab and alemtuzumab), which was contrary to clinical experience. Pegylated IFN had also been excluded from TA527 for being an outlier.	ERG agrees with the exclusion (see the main text below)

The stated reason for the exclusion of four of the six RCTs was data being not available/reported. The ERG agreed with two of the exclusions but identified evaluable data for Boiko et al. 2018a[1] and Etemadifar et al. 2006[2] (see Table 15). In addition, the company excluded the INCOMIN and ADVANCE trials (with the latter retained in a scenario analysis presented in the CS), stating that they were considered as outliers and had been excluded from previous NICE appraisals for ocrelizumab[19] and IFN-β and glatiramer acetate.[6] We provide details of these trials in

Table 15 and a brief summary of the reasons put forth by the company below, along with the ERG's opinion on these decisions.

Table 15. Summary details of INCOMIN and ADVANCE trials

	INCOMIN[a]	**ADVANCE[b]**
Population	People age 18-50 years with RRMS, EDSS score 1.0-3.55, >=2 relapses in the last 2 years	People age 18-65 years with RRMS, EDSS score 0.0-5.0, >=2 relapses in last 3 years and >=1 in last 12 months
Intervention(s)	Interferon beta-1b, 250 µg [8 MIU] subcutaneous every other day (n=96)	Peginterferon beta-1a: 125 µg subcutaneous every 2 weeks (n=512) or every 4 weeks (n=500)c
Comparator	Interferon beta-1a, 30 µg [6 MIU] intramuscularly, once a week (n=92)	Placebo (n=500)
Outcome(s)	Primary: proportion of patients who were relapse free and the proportion of patients without new T2 lesions. Secondary: ARR; number of patients with treated relapses; EDSS; number of patients with Gd+ lesions; and percentage of patients with MRI activity	Primary: ARR Secondary: proportion of patients relapsed at 1 year; number of relapses requiring IV steroid use; number of MS-related hospitalisations; disability progression (EDSS an MSFC); VFT; SDMT
Design/description	INCOMIN was a multicenter, randomized, open-label study	1-year, phase 3, double-blind, parallel-group, multi-centre, RCT
Study length	2 years	1 year (in year 2 patients were blinded only to treatment frequency)

ARR: annualised relapse rate; EDSS: expanded disability status scale; INCOMIN: Independent Comparison of Interferon; MSFC: Multiple Sclerosis Functional Composite; RRMS: relapsing remitting multiple sclerosis; VFT: Visual Function Test; SDMT: Symbol Digit Modalities Test.
a[19 40].
b [41]
c The licensed dosage is 125 µg every 2 weeks.

3.3.3.1 INCOMIN trial

INCOMIN was a 2-year, prospective, randomised, multicentre trial, comparing interferon beta-1b every other day to interferon beta-1a weekly.[42] It did not have a double-blind design. The CS states that INCOMIN was excluded from the network because its results were considered to be an outlier. This is confirmed in previous, NICE guidance[19] and in other studies, which indicate that the results of INCOMIN are not consistent with the results from phase III trials of interferon β-1b and interferon β-1a. For example, the INCOMIN trial found that patients receiving interferon beta-1b every other day had better results than those receiving a weekly dose of interferon beta-1a, while five other studies indicated no clinically significant differences

between the two treatments.[40] Another study noted that the INCOMIN trial did not blind assessors, which is associated with a high risk of bias, and excluded the trial after sensitivity analyses indicated that it produced inconsistent results.[43]

The ERG agrees with the exclusion of the INCOMIN trial in line with the approach taken in the previous NICE appraisal.

3.3.3.2 ADVANCE trial

The ADVANCE trial[41] was a phase 3, double-blind, multi-centre, placebo-controlled RCT, which lasted 1 year (48 weeks). After year 1 of the trial, patients in the placebo group were re-randomised to receive treatment. Participants were assigned randomly in a 1:1:1 ratio to receive an injection of either peginterferon beta-1a 125 mcg every 2 weeks (Q2W) or every 4 weeks (Q4W), or placebo, for a double-blind controlled period of 48 weeks (only the 2-week dosage frequency is licensed). The CS states that the ADVANCE trial was excluded from the NICE guidance on ocrelizumab[19] and beta interferons and glatiramer acetate,[6] because it was shown to be more effective than other beta-interferons and high-efficacy treatments, which was contrary to clinical experience. This is noted in section 3.11 of the guidance (pg.11). The CS presents scenario analyses that include ADVANCE, and also reports outcome values for ADVANCE in Appendix D (pg.106).

The ERG recognises that peginterferon is included in the final scope of this appraisal and ADVANCE is the only RCT that would allow anchored indirect comparison to be made between ofatumumab through the NMA. In addition, ADVANCE was included in a previous health technology assessment and NMA of beta-interferons and glatiramer acetate[27] and in the NMA of CS for the previous appraisal for ocrelizumab.[19] The ERG further notes that evidence from the ADVANCE trial only links the NMA evidence network through placebo without forming a loop with any other comparators (see Figure 1 on page **Error! Bookmark not defined.**), and therefore its impact on estimates of relative effectiveness between other comparators should be fairly limited, as shown in CS Appendix.

The ERG therefore, considers that the exclusion of ADVANCE trial by the company from its base case does not have material impact on the effect estimates for other interventions. Findings from sensitivity analyses with the inclusion of this trial were

informative and could have been used to inform cost-effectiveness estimates for peginterferon beta-1a, with due caution paid to the interpretation of the relative effectiveness between peginterferon beta-1a and other comparators given the source of single trial and potential issues raised in the previous NICE guidance.[19]

3.3.3.3 RoB assessment for studies included in the NMAs

The company assessed the RoB for 34 RCTs that met the NMA inclusion criteria and passed the feasibility assessment. Fifteen of the RCTs were judged to be of low risk for all domains and 6 RCTs had one or more domains judged to be of unclear risk (but had no domain judged to be of high risk). Thirteen RCTs had at least one domain judged to be of high risk related to: allocation concealment (3 RCTs), baseline comparability (4 RCTs), blinding (8 RCTs) and statistical methodology (1 RCT). The CS stated that "*No trials were found to be of sufficiently poor quality to necessitate their exclusion*" (CS Appendix D, p.142), but no further details were provided. No sensitivity analyses were undertaken to explore the potential impact of the risk of bias identified in these trials.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company performed NMAs for three effectiveness outcomes: ARR, CDW-3 and CDW-6, and separately an NMA for all-cause discontinuation.

The company also considered the feasibility of carrying out NMAs for two subgroups of interest, HA and RES RRMS, but concluded that NMAs were not feasible for these patient subgroups as no RCT data were available to allow connection of data from ASCLEPIOS trials to the wider evidence network. The CS also indicated that alternative methods were explored such as population-adjusted methods. However, as baseline characteristics of the subgroups in comparator trials were not presented, these methods also seemed infeasible.

The ERG acknowledged the lack of trial data and hence the unfeasibility of conducting NMAs for estimating relative effectiveness of ofatumumab compared with other treatments for HA and RES RRMS subgroups. The ERG also noted that while attempts at subgroup NMAs were made in the previous appraisal of ocrelizumab for

RRMS,[19] the committee considered the results highly uncertain due to paucity of data. However, the ERG wish to highlight that as a consequence of limited data, findings from analyses of relative cost-effectiveness in these subgroups between different treatments would also be highly uncertain (see Appendix E and F for the cost-effectiveness analysis of these subgroups).

3.4.1 NMAs for effectiveness outcomes

The company used a continuous survival model on the log hazard scale for time to CDW-3 and CDW-6, and a Poisson model for ARR, with a 60,000 burn-in samples and then 60,000 iterations. All of the models were random effects models with vague prior distributions. To assess model fit, the posterior mean of the residual deviance was compared to the corresponding number of unconstrained data points, and the deviance information criterion (DIC) was used, which the ERG consider to be acceptable. NMA analyses were conducted using R version 3.6.1, Just Another Gibbs Sampler version 4.3.0, and WinBUGS version 1.4.3.

Key issues impacting on the validity of NMAs include consistency and transitivity assumptions and coherence of evidence. Consistency (or homogeneity) refers to reasonable agreement between the findings of different studies within a given pair-wise comparison. Transitivity refers to the assumption that patients in the studies within an NMA could be regarded as drawing from a similar population such that the relative effectiveness estimated in one study would be observed in another study if it had the same comparators. Both could be affected by differences in the distribution of effect modifiers between studies or sets of studies. The ERG provides more comments on this in Section 3.5.3.

Coherence refers to the equivalence of direct and indirect evidence. This can be assessed quantitatively in various ways, for example, by calculating the indirect comparison around a closed loop of the network and comparing that result to the direct comparison. The CS did not include any formal assessment of coherence. The ERG explored the loop consisting of teriflunomide 14 mg, IFN beta-1a SC 44 and placebo and found the indirect comparison to be consistent with the direct comparison.

We focus our critique on ARR and CDW-6 as they were the outcomes included in the company's economic model (see Section 4.3). Results of the base case NMA for ARR, CDW-3 and CDW-6 for ofatumumab versus comparators are presented in Table 16, where the comparators are used as the reference treatment in relation to ofatumumab, and the overall rank of the treatments in the network.

Table 16: Results of the base case NMA

	ARR		CDW-3 (aligned)		CDW-6 (aligned)	
	HR (95% CrI)	**Rank**	**HR (95% CrI)**	**Rank**	**HR (95% CrI)**	**Rank**
Ofatumumab vs:		2	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	1.06 (0.75, 1.61)*	1	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5	0.70 (0.46, 1.08)	5	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	0.59 (0.42, 0.85)	7	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	0.67 (0.49, 0.96)	6	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20	0.47 (0.35, 0.66)	9	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40	0.45 (0.30, 0.69)	10	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a IM	0.37 (0.28, 0.52)	14	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 22	0.43 (0.30, 0.64)	13	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 44	0.47 (0.35, 0.66)	8	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1b SC 250	0.43 (0.31, 0.62)	12	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	0.94 (0.64, 1.42)	3	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	0.88 (0.62, 1.33)	4	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	0.30 (0.22, 0.40)	15	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14	0.45 (0.36, 0.56)	11	[redacted]	[redacted]	[redacted]	[redacted]

* Calculated by inversing the HR and 95% CrI in Figure 20/23/26
Abbreviations: ARR: annualised relapse rate; CDW: confirmed disability worsening; IM: intramuscular; SC: subcutaneous; HR: hazard ratio; CrI: credible interval; IFN: interferon

3.4.1.1 ARR

The network for ARR is shown in Figure 19 of the CS (page 84) and the results are presented in Table 16. Ofatumumab was the second most effective treatment versus placebo compared to the other DMTs included in the network, with alemtuzumab being more effective. Mean SUCRA scores also reflects the above results, with ofatumumab having the second highest mean SUCRA after alemtuzumab. The ERG explored the NMA for ARR inclusive of additional trials identified in Section 3.3.3, the result of this is described in Section 3.5.2.

3.4.1.2 CDW-6

The network for CDW-6 is shown in Figure 25 of the CS (page 90) and the results are presented in Table 16. Ofatumumab was the fourth most effective treatment versus placebo compared to the other DMTs included in the network, with alemtuzumab, natalizumab and ocrelizumab being more effective. Mean SUCRA scores also reflects the above results, with ofatumumab having the fourth highest mean SUCRA. As with the ARR NMA, the ERG tested the consistency of the CDW-6 NMA by testing a closed loop, and found no inconsistencies between indirect and direct estimates.

3.4.1.3 CDW-3

The network for CDW-3 is shown in Figure 22 of the CS (page 87) and the results are presented in Table 16. Ofatumumab was the second most effective treatment versus placebo compared to the other DMTs included in the network, with ocrelizumab being more effective. Mean SUCRA scores also reflects the above results, with ofatumumab having the second highest mean SUCRA.

3.4.1.4 Scenario analyses

Since the company used the aligned-criteria for CDW in the base case NMA, two scenario analyses were performed to test the efficacy of ofatumumab using the pre-defined criteria and using the OPERA-aligned criteria (see 1.1.6.1.2). The CS suggests that ocrelizumab "*has the most similar mechanism of action to ofatumumab*" and therefore the most relevant appraisal to consider as a comparison (CS Document B, pg. 136).

3.4.1.4.1 Pre-defined criteria for CDW

The pre-defined criteria for CDW uses the definition for confirmed disability worsening that was used in the ASCLEPIOS trials (see Section 3.3.2.2). Since this definition was different to the other trials included in the NMA, and not in concordance with the economic model, this was included as a scenario analysis to test the sensitivity of the results compared to the base case NMA. Table 17 presents the scenario NMA results for ofatumumab versus each of the comparators, and the relative rankings of all of the DMTs.

For the CDW-3 outcome, [redacted] efficacy compared to ofatumumab. The HR was [redacted] to the base case NMA for alemtuzumab. In this scenario NMA, [redacted].

For the CDW-6 outcome, [redacted] efficacy compared to ofatumumab. The HRs was [redacted] to the base case NMA across all of the treatments.

Table 17: Scenario NMA results using the pre-defined criteria for CDW

Pre-defined	CDW-3		CDW-6	
	HR (95% CrI)	Rank	HR (95% CrI)	Rank
Ofatumumab vs:		[redacted]		[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a IM	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 22	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 44	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1b SC 250	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14	[redacted]	[redacted]	[redacted]	[redacted]

* Calculated by inversing the HR and 95% CrI in Figure 28/30
Abbreviations: ARR: annualised relapse rate; CDW: confirmed disability worsening; IM: intramuscular; SC: subcutaneous; HR: hazard ratio; CrI: credible interval

For a summary of the OPERA-aligned criteria for CDW please see ERG Appendix C.

3.4.2 NMA for adverse events

The company outlines common limitations associated with assessment of comparative risk of AE using trial data (CS Document B, Table 42, p.100), such as lack of information to adjust for varied lengths of exposure to different treatments in

published trials, potential influence and confounding of different administration method and dosing schedule, statistical power to analyse safety events, varied definitions of AE and outcome severity. As a result, no NMA was undertaken for safety outcomes/adverse events. Instead, the company reviewed United States Prescribing Information and SmPC for each DMT, and provided a brief list of major safety concerns or black box warnings across different DMTs.

In the absence of an NMA, the company used data from the ASCLEPIOS trials for estimating AE probability for ofatumumab and teriflunomide; data from the CLARITY trial for cladribine,[44] and sourced other AE data from TA533[19] for its cost-effectiveness model (see Section 4.3.8.5). The ERG considers that the caveats regarding assessment of AE using trial data do not necessarily preclude NMAs to be undertaken, and notes that the lack direct comparison data beyond ASCLEPIOS trials and the absence of NMAs mean that the risk of AE was essentially compared between different treatments using naïve indirect comparison (with the exception of ofatumumab vs. teriflunomide). While this is not ideal, data from ASCLEPIOS trials did not raise specific safety concerns (see Section 3.2.11) (although there is insufficient data for assessing rare, serious and/or long-term AE), and the risk of AE do not appear to be an important driver for cost-effectiveness estimates (see Section 4.3.8.5).

3.4.3 NMA for all-cause discontinuation

The company conducted an NMA for all-cause discontinuation, and presented its results briefly in CS Document B (pg.100) and in further detail in CS Appendix D.1.6. (pg.117-124). Figure 16 of CS Appendix D presents the network of this all-cause discontinuation NMA, which included 30 RCTs and covered 17 different treatments (including placebo). Table 18 below summarises the results of the NMA.

[redacted]. ERG considers the validity of the NMA questionable as no apparent adjustment was made to account for different durations of included trials.

Table 18: NMA results for the outcome all-cause discontinuation

	All-cause discontinuation	
	HR (95% CrI)	**Rank**
Ofatumumab vs:		
Alemtuzumab		
Cladribine 3.5		
Dimethyl fumarate		
Fingolimod		
Glatiramer acetate 20		
IFN beta-1a IM		
IFN beta-1a SC 22		
IFN beta-1a SC 44		
IFN beta-1b SC 250		
Natalizumab		
Ocrelizumab		
Placebo		
Teriflunomide 14		
Teriflunomide 7		

* Calculated by inversing the HR and 95% in Figure 17 of CS Appendix D
Abbreviations: ARR: annualised relapse rate; CDW: confirmed disability worsening; IM: intramuscular; SC: subcutaneous; HR: hazard ratio; CrI: credible interval

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG has undertaken the work described in the following sections to assess the robustness of clinical effectiveness evidence presented in the CS.

3.5.1 Verification of the comprehensiveness of the company's literature searches

Given some issues in the search strategy that the ERG identified in Section 3.1.1, the ERG attempted to test the comprehensiveness of company's searches by comparing trials identified in other recent reviews with those identified in the CS. The lists of included studies from a recent scoping review of outcome measures of MS trials[45] and the most recent Cochrane review (NMA) of immunomodulators and immunosuppressants for RRMS[46] were checked against the list of included and excluded RCTs in the CS. Seven RCTs were identified that did not appear to have been captured in the company's searches, although none of them would have been suitable for inclusion in the SLR and NMAs (e.g. due to interventions outside the scope of this appraisal).

3.5.2 Revising the NMA for ARR

As described in Section 3.3.3, the ERG identified that data for ARR could be calculated (in the same way as the company has done) for two of the RCTs that the company excluded from its NMA due to non-reporting of data. The ERG undertook an updated NMA with these additional data included. The results suggest that the additional data have very minor impact on the estimated relative ratios of ARR between treatments and hence are not explored in the ERG's exploratory economic analysis.

3.5.3 Assessing the transitivity between ASCLEPIOS trials and other key trials in the NMA evidence networks

As mentioned in Section 3.3.2.3, the company's feasibility assessment for the NMAs highlighted heterogeneity in patient characteristics between the included trials. The ERG notes that baseline characteristics such as time since first MS symptoms and proportion of patients with prior DMTs could be potential treatment effect modifiers, and substantial differences in these characteristics between trial populations could be a threat to the validity of the NMAs. The ERG therefore, undertook further detailed assessment of the comparability of key trials included in the NMAs. Findings of the detailed assessment are presented in ERG Appendix D. The Cochrane RoB tool was used for quality assessment and comparability was assessed based on the following; patient selection criteria, study population and outcomes reported. The outcome measures of interest for comparability are relapse rate, CDW-3 and CDW-6.

Evidence from the ASCLEPIOS I & II trials were linked with rest of the evidence network via three trials; TEMSO,[47] TOWER[48] and TENERE[49] (see Figure 1, Section 3.3.3). Therefore, these three trials were assessed further for quality and comparability by the ERG:

- TEMSO (comparing teriflunomide 7 mg and teriflunomide 14 mg with placebo)[47]
- TOWER (comparing teriflunomide 7mg and teriflunomide14mg with Placebo)[48]

- TENERE: (comparing teriflunomide 7mg and teriflunomide 14mg with interferon beta-1a)[49]

Ocrelizumab has a similar mechanism of action with ofatumumab and similar target patient population, and was considered a key comparator in the CS. Therefore, the ERG also assessed the quality and comparability of the following:

- OPERA I and II[50]: (comparing ocrelizumab with interferon beta-1a):

The key findings from our detailed assessment of the comparability suggest that:

- In terms of methodological and clinical heterogeneity, there are slight differences in methodology but a major difference is in study population where TEMSO and TOWER had higher proportion of patients with no previous DMTs.
- ARR: Based on the common comparator teriflunomide 14 mg, the ARRs observed in TEMSO and TOWER seem significantly higher than the ARRs observed in ASCLEPIOS studies. These might reflect the clinical heterogeneity mentioned above.
- CDW-3 and CDW-6: most comparisons linking ofatumumab and teriflunomide to the wider evidence network were supported by no more than two trials. Amongst the wider NMA, there were too few to allow an assessment of whether clinical heterogeneity as demonstrated in variation in absolute event rates cause transitivity issues for relative effectiveness.

3.5.4 Comparison between full analysis set, HA RRMS and RES RRMS subgroups of results from ASCLEPIOS trials

As described in Section 3.4, the company could not undertake NMAs for subgroup population of HA RRMS and RES RRMS due to lack of available trial data. The company therefore, used data from the whole trial population (full analysis set) in their cost-effectiveness analysis for HA RRMS and RES RRMS patient subgroups (see Appendix E). Data from the full analysis set and the HA RRMS and RES RRMS subgroups are shown in Figure 2 and Figure 3 created by the ERG.

[redacted]

[redacted]

[redacted]

[redacted]

The ERG considers that overall, the trial results for the subgroups of HA RRMS and RES RRMS were relatively consistent with the full results including all patients. For the ratio of ARR (vs. teriflunomide), the estimate from full analysis set (ratio of ARR 0.46, 0.38 to 0.56) might be [redacted] compared with the HA RRMS subgroup ([redacted]) and is [redacted] to the RES RRMS subgroup ([redacted]). For CDP-6, the point estimates for each of the subgroups are [redacted] for ofatumumab compared with the full analysis set, and so using the latter is a [redacted] approach. Therefore, the ERG conclude that the company's approach is unlikely to introduce substantial bias in favour of ofatumumab (and might bias against it).

3.6 Conclusions of the clinical effectiveness section

In conclusion, the company provided a relatively complete clinical effectiveness submission with regards to the clinical evidence and data within those studies. The company decision problem partially aligns to the NICE Final Scope.[8] The intervention and outcomes were similar, but the population and comparators included in the CS differed to those outlined by NICE. Section 2.3 outlined the key differences in the population and comparators provided in the company decision problem. Of note, the company restricted the population, and therefore the comparators, to patients with RRMS only. Points for considerations are as follows:

- The main clinical effectiveness evidence came from the ASCLEPIOS I & II trials, which are judged to be of good quality with low RoB. The trials included

a large proportion of participants from [redacted] and included only a small number of patients from the UK (n=[redacted]). No analyses stratified by geographical regions/MS subtype were reported in the CS and therefore, the ERG has some concerns with regard to the generalisability of findings to patients receiving treatment in the NHS.

- The ASCLEPIOS I & II trials demonstrated that ofatumumab is more effective compared with teriflunomide for all main clinical outcomes, and no unexpected safety concerns. Serious AE such as PML cannot be ruled out due to small volume of data.
- Comparative effectiveness data relies on NMAs, which were undertaken for ARR, CDW-3, CDW-6 and all-cause discontinuation (see Section 3.4.1) Results of the NMAs for key economic model inputs (ARR and CDW-6) suggest that
- [redacted]There was inconsistent and insufficient information concerning the criteria and process of selecting studies from SLR into NMAs. As described in 3.3.2, the ERG identified two studies that we suggest could have been included in the NMA.
- No details were presented for assessment of consistency of evidence for individual pair-wise comparison and coherence between direct and indirect evidence, although ERG's coherence check did not identify particular issues.
- Some clinical heterogeneity in patient population was observed between included trials. Across the network there is no clear evidence of violation of the transitivity assumption, although evidence allowing its assessment was very limited.
    - Our assessment of three trials (TEMSO,[47] TOWER[48], TENERE[49]) which linked the ASCLEPIOS I & II trials to the rest of the evidence network suggested that TEMSO and TOWER had higher proportion of patients with no previous DMTs.

- The volume of evidence is limited for many of the linking comparisons in the evidence network (see ERG Figure 1), resulting in wide credible intervals for some of the estimates.

Other issues worth noting are:

- Omission of a small number of trials from the NMA for ARR (see Section 3.5.2). However, the results of the ERG additional analysis suggest that the additional data have very minor impact on the estimated relative ratios of ARR between treatments.
- No NMA for AE was provided in the submission (see Section 3.4.2). This mean comparative risk of AE between different treatments was not properly assessed (although data from ASCLEPIOS trials do not suggest specific concerns.

4 COST EFFECTIVENESS

This section focuses on the economic evidence and analyses submitted by Novartis, and additional information received from the company in response to the ERG's clarification questions. The ERG critically appraised the evidence and examined the company's electronic model that was submitted in Microsoft Excel.

The section starts with a summary of the company's economic analysis, then describes that the systematic review, methods, and results (base-case, sensitivity and scenario analyses) as reported in the company's submission documents. We compare the economic analysis to the NICE reference case,[51] and provide a critique using frameworks on best practice for reporting economic evaluation and economic modelling in order to assess the overall reporting quality and validity of these analyses. In the subsequent chapter, where possible, we have addressed our concerns in the form of additional analyses.

The submission received by the ERG included:

- A systematic review of the economic evidence for the management of people living with RRMS.
- Clinical and cost-effectiveness evidence, and methods used to undertake the economic analysis. The company's economic analysis results (base-case, scenario analysis and sensitivity analysis results).
- Electronic version of the Markov model built in Microsoft Excel.

4.1 Summary of the company's economic analysis

Novartis undertook an economic analysis to assess the cost-effectiveness of ofatumumab compared to other DMTs for treating people with RRMS, HA RRMS and RES RRMS. A Markov model was used to depict the natural history of people with RRMS. Information required about the natural history of people with RRMS was based on a transition matrix using the British Columbia dataset.[52] RRMS disease progression was simulated by means of 10 EDSS levels ranging from EDSS 0 to 9. The hypothetical population that entered the model was distributed across EDSS

levels 0 to 6, which reflected the distribution of the participants in the ASCLEPIOS trials. The mean age of the population was [redacted] years, with [redacted] females.

Based on the transition matrix, in each yearly cycle people could remain in the same RRMS EDSS health state, progress to a more severe EDSS state, regress to a less severe state, progress to SPMS or die. On progression to SPMS, people discontinued DMTs; SPMS followed a natural history progression, which was based on the transition matrix derived from the EXPAND trial[53] and supplemented with information from the London, Ontario dataset,[9] when data were missing. Additionally, in each cycle, people may have experienced relapses (mild, moderate, or severe), treatment-related AE or discontinued treatment.

Treatment effects were assumed to reduce/delay the progression of RRMS and reduce the frequency of relapses. Information about treatment effects was based on the company's NMA (CS Document B, B.2.9). Information about health state utilities for RRMS and SPMS by EDSS were based on information collected from the ASCLEPIOS trials and supplemented with information from Orme et al. (2007).[7] Caregivers utility decrements were based on information obtained from TA127.[18] Utility values for AE associated with each DMT were included in the economic analysis and these were obtained from TA533.[19] It was assumed that there is an increased risk of mortality for people with MS compared to the general population. Age- and gender-specific all-cause mortality rates for a UK general population were derived from the UK ONS data, and adjusted using the mortality rates obtained from Pokorski et al. (1997).[54] Due to the paucity of information, it was assumed that the mortality for people with RRMS is the same as those with SPMS.

Information about resource use and unit costs were obtained from various sources (literature, British National Formulary, Personal Social Service Research Unit [PSSRU], NHS reference costs). The analysis was undertaken from the NHS and PSS perspective. The clinical outcomes reported were life-years gained, quality-adjusted life years (QALYs) gained, carers' disutility, adverse event disutility and relapse disutility over a lifetime horizon. Cost outcomes included drug acquisition, administration and monitoring, health state costs, costs for treating AE, relapse costs, and retreatment costs. The results were presented as an incremental cost effectiveness ratio (ICER), expressed as cost per QALY gained. Both costs and

benefits were discounted at 3.5% per annum. The company undertook several sensitivity and scenario analyses, and probabilistic sensitivity analysis (PSA) to assess the robustness of the base-case results to making changes to model inputs/assumptions. Also, results were presented for the highly active, and rapidly-evolving severe RRMS populations.

For the RRMS population, the base-case pairwise results showed that treatment with ofatumumab was [redacted] against dimethyl fumarate and teriflunomide, and was [redacted] against IFNβ-1a, glatiramer acetate and IFNβ-1a 44 mcg, and against ocrelizumab was [redacted]. Results from the one-way sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the HR for disability worsening efficacy, which had the greatest impact. The probabilistic sensitivity analysis suggested that at a £30,000 willingness-to-pay threshold for a QALY, ofatumumab had a [redacted] probability of being cost-effective.

4.2 ERG comment on company's review of cost-effectiveness evidence

CS document Appendices G, H and I provide detailed reports of three SLRs, aimed at identifying: a) literature published on economic analyses of treatments for patients with RMS; b) health-related quality of life (HRQoL) information and preference-based health state utility data for adults with MS and their caregivers, collected in the UK or using UK tariffs; c) healthcare resource use and costs associated with MS. The purpose of conducting these SLRs was for developing an economic model that could be used to assess the cost-effectiveness of ofatumumab versus other DMTs for people with RRMS. In summary, these systematic reviews were undertaken to:

- Identify economic models, resource use and costs, and utility information
- Summarise economic evidence reported in studies identified in the systematic reviews
- Critically appraise economic analyses, health state utility and costing studies

- Extract relevant information regarding resource use, costs and utility that could be used in the economic analysis.

4.2.1 Search strategy

Searches in an appropriate set of bibliographic databases were undertaken in December 2019, from database inception, with an update in March 2020 (CS document Appendices, Appendix G, section G.1.1). Searches combined terms for RMS and a reasonably comprehensive search filter for economic evaluations aimed at identifying particular types of study. Appropriately, no intervention terms are included. Searches in multiple databases were conducted simultaneously via Ovid (Ovid and Wiley in the update), which is not an ideal approach for the reasons described in Section 3.1.1. However, care has been taken to include terms from all relevant thesauruses, some term mapping will have occurred, and no limits have been applied to the original searches. Although MEDLINE records are included in Embase, it is advisable to search them separately[55] and therefore, it is worth noting that the main MEDLINE database does not appear to have been searched independently for the update, which ERG testing suggests may have had a small impact on the number of records retrieved. It is also unclear whether or not it was searched independently in the original SLR: the text under Electronic databases and Electronic databases searches (CS document Appendices, Appendix G, section G1.1) states that it was searched independently in the original SLR, although the heading of CS document Appendices, Appendix G, Table 49 contradicts this, only listing MEDLINE Daily, MEDLINE In-Process, Epub Ahead of Print. Some conference abstract, grey literature and HTA agency searches were undertaken.

Section H.1.1 of the CS document Appendix reports the search strategy for the SLR of HRQoL studies, which was performed on 18th January 2019, and subsequently updated on the 19th November 2019 and 14th April 2020. The MEDLINE and Embase databases were searched simultaneously via the embase.com interface in the original and first update SLRs and were searched separately via Ovid in the second update SLR. The ERG is unable to test the embase.com interface but assume that some mapping between MeSH and EMTREE has occurred. Terms from both thesauruses are present. Searches combined terms for MS of any type with a comprehensive search filter for HRQoL in the large databases and were limited to

the English language. Appropriately, no intervention terms are included. Some conference abstract, grey literature and HTA agency searches were undertaken.

The search strategy for the SLR of cost and resource use is reported in CS document Appendices, Appendix I, section I.1.1. Broad searches took place on 15th November 2018 and were updated on both 19th November 2019 and 14th April 2020. In a similar way to the other SLRs, MEDLINE and Embase were searched simultaneously via embase.com in the original SLR and first update. The company reports that MEDLINE and Embase were searched separately via Ovid in the second update SLR. The ERG is unable to test the embase.com interface but assume that mapping between MeSH and EMTREE has occurred. Searches combined terms for MS of any type with a wide range of terms for cost and resource use, and economics in general. No intervention terms were included, which was appropriate. The search is limited to English language. Some conference abstract, grey literature and HTA agency searches and checks of references of relevant reviews were performed. Grey literature searches are clearly reported with details being provided of the search approach, terms used, and numbers screened/included.

4.2.2 Inclusion/exclusion criteria

Identified studies were assessed against predetermined inclusion and exclusion criteria for the economic evaluations SLR. These are given in Table 19 (obtained from CS document, Appendix G, Table 56).

Table 19. Eligibility criteria for the original and updated economic evaluations SLR (obtained from CS document Appendices, Appendix G, Table 56)

Domain	***Inclusion Criteria***	***Exclusion Criteria***
Population	• *Adults (aged ≥18 years) with RRMS or active SPMS (RMS)*	• *Adults without RMS* • *Adults with CIS or PPMS* • *Patients <18 years* • *Studies assessing mixed populations of adult (≥18 years) and paediatric (<18 years) patients, where subgroup data for adult patients only are not reported, were excluded*
Intervention(s)	• *Alemtuzumab* • *Cladribine* • *Dimethyl Fumarate* • *Fingolimod* • *Glatiramer acetate*	• *Studies not assessing at least one of the relevant interventions*

Domain	Inclusion Criteria	Exclusion Criteria
	• *Interferon β-1a* • *Interferon β-1b* • *Mitoxantrone* • *Natalizumab* • *Ocrelizumab* • *Peginterferon β-1a* • *Siponimod* • *Teriflunomide* • *Emerging disease modifying therapies*	
Comparator(s)	• *Any of the interventions listed above* • *Placebo* • *Best supportive care*	• *Any other comparator*
Study design	*Economic evaluations:* • *Cost-effectiveness analyses* • *Cost-utility analyses* • *Cost-benefit analyses* • *Cost-minimisation analyses* • *Budget impact models* • *Cost-consequence studies*	• *Any study types other than economic evaluations*
Outcomes	• *ICERs* • *Cost per clinical outcome* • *Total QALYs* • *Total LYGs* • *Total costs* • *Incremental costs and QALYs*	• *Studies not presenting relevant outcomes for the population of interest* • *No outcome data (data not reported/qualitative data reported)*
Other considerations	• *Publications with full texts in the English language* • *Studies in humans* • *Conference abstracts published from 2017 onwards* • *No geographical restrictions* • ***During SLR update**: Records published after 24th December 2019*	• *Publications without full texts in the English language* • *Conference abstracts published before 2017* • ***During SLR update**: Records published before 24th December 2019*

[a] While this SLR took a broader geographical perspective, ultimately the studies considered for this submission are those from a UK perspective, which are most relevant to the submission.
***Abbreviations**: CIS: clinically-isolated syndrome; ICER, incremental cost-effectiveness ratio; LYGs, life-years gained; PPMS: primary progressive multiple sclerosis; QALYs, Quality adjusted life years; RMS, relapsing multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis*

As anticipated, certain selection criteria (such as those related to population, comparators, publication type and language) were similar between the clinical effectiveness and cost-effectiveness SLRs. No concerns are raised by the ERG in relation to these criteria, though of note is the exclusion of studies published in

languages other than English. However, this is a common practice grounded in practical reasons.

Separate sets of inclusion and exclusion criteria were used for conducting SLRs regarding HRQoL and health care resource use and costs. While some criteria such as the ones related to population and language were similar to those used in identifying relevant economic evaluations (presented in Table 20), some criteria were appropriately different and tailored to capture evidence specific to HRQoL and resource use (e.g. criteria related to outcomes and study design) (Table 20 and Table 21).

Table 20. Eligibility criteria for the HRQoL SLR (obtained from CS document Appendices, Appendix H, Table 79)

Domain	***Inclusion Criteria***	***Exclusion Criteria***
Population	• *Adults (aged ≥18 years) with MS of any race*	• *Studies in CIS/PPMS patients only* • *MS patients <18 years* *or mixed populations of adult (≥18 years) and paediatric (<18 years), patients where subgroup data for adult patients only is not reported*
Intervention(s)	*Any or none*	*NA*
Comparator(s)	*Any or none*	*NA*
Outcomes	• *Utility estimates for health states* • *Mapping algorithms from HRQoL to utilities* • *HRQoL associated with MS and caregiver burden* • *Impact of disease symptoms, medication adherence, employment status, education level on HRQoL*	• *Assessment of cognitive/symptom burden* • *Psychometry study of different PROs* • *Studies assessing impact of other variables on QoL or relation between QoL and other variables (e.g. symptoms, cognition, regression studies)*
Study design	*Any study reporting relevant outcomes, unless interventional by nature*	*Interventional studies*
Other considerations	• *Health state utility values from the UK or using UK tariffs* • *Publications with full texts in the English language* • ***During first SLR update**: Records published after 18th January 2019* • ***During second SLR update**:*	• *Publications without full texts in the English language* • ***During first SLR update**: Records published before 18th January 2019* • ***During second SLR update**: Records published before 19th*

Domain	Inclusion Criteria	Exclusion Criteria
	Records published after 19th November 2019	*November 2019*

***Abbreviations**: CIS: clinically isolated syndrome; HRQoL: health-related quality of life; MS: multiple sclerosis; NA: not applicable; PPMS: primary progressive multiple sclerosis; PRO: patient-reported outcome; SLR: systematic literature review.*

Table 21. Eligibility criteria for the healthcare cost and resource use SLR (obtained from CS document Appendices, Appendix I, Table 95)

Domain	Inclusion Criteria	Exclusion Criteria
Population	• *Adult patients (≥18 years) with MS of any race*	• *Patients without MS* • *Studies in CIS/PPMS patients only* • *MS patients <18 years* • *Mixed populations of adult (≥18 years) and paediatric (<18 years), patients where subgroup data for adult patients only is not reported*
Intervention(s)	*Any or none*	*NA*
Comparator(s)	*Any or none*	*NA*
Study design	• *Any study reporting novel cost and resource use data, such as:* • *Cost studies/surveys/analyses* • *Database studies collecting novel cost data* • *Burden of illness* • *Resource surveys*	• *Narrative reviews* • *Case reports* • *Case series* • *Case report* • *Editorials* • *Pharmacokinetic studies* *Systematic reviews/meta-analyses[a]*
Outcomes	• *Novel costs (direct and indirect)* • *Resource use (e.g. emergency room visits, neurologist visits, hospitalisations, outpatient visits, specialty clinic visits, nursing visits)*	• *Secondary cost and resource use data from another source* • *Comparison of cost/HRU among different types of disease cohorts i.e. treatment or insurance type, comorbidities, adherence*
Other considerations	• *Cost and resource use data from the UK* • *Publications in the English language*	• *Cost and resource use data from outside the UK* • *Publications not in the English language*

Domain	*Inclusion Criteria*	*Exclusion Criteria*
	• *Conference abstracts after 2019* • *During first SLR update: Records published after 15th November 2018* • *During second SLR update: Records published after 19th November 2019*	• *Conference abstracts before 2019* • *During first SLR update: Records published before 15th November 2018* • *During second SLR update: Records published before 19th November 2019*
[a]SLRs and NMAs were included at the abstract stage but subsequently excluded at the full text stage and their bibliographies hand searched for additional articles of relevance to this review. ***Abbreviations****: CIS: clinically isolated syndrome; HRU: healthcare resource utilisation; MS: multiple sclerosis; NA: not applicable; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis.*		

Overall, the selection criteria employed are deemed suitable and appropriate for the purposes of the undertaken reviews.

4.2.3 Identified studies

The company identified 136 economic evaluation studies in the original SLR for cost-effectiveness data. Supplementary searching retrieved a further 11 publications and 30 HTA submissions. Twenty-five publications and 22 HTAs from a UK setting were included and summarised for this submission. Relevant information from these studies was extracted and summarised in Tables 57 and 58 in Appendix G of the CS document Appendices. In total, 18 economic evaluations from 25 UK publications and 22 HTAs from a UK setting were identified in the original SLR. The results and critical appraisals of these studies were presented in Tables 63, 64, 65 and 66 in Appendix G of the CS document Appendices. One HTA submission (TA624)[5] from a UK setting was identified in the SLR update. The results and critical appraisal of this study were presented in Tables 67 and 68 in Appendix G of the CS document Appendices. The company provided information regarding the objective, country, perspective, summary of model, patient population, QALYs, costs, and ICER of the studies. Quality appraisals of each published economic evaluation included in the SLR were undertaken using the Drummond et al. (1996)[56] checklist as recommended by NICE.

The original SLR for HRQoL data carried out by the company identified 73 studies from 74 publications for inclusion. Of these studies, 53 provided information on HRQoL, and 57 publications on 56 studies provided information on health state utility

(HSU) value for either people with MS in the UK or using UK tariffs for utility elicitation. Included UK HSU value records and the results of these published utility studies were presented in Tables 80 and 84 respectively in Appendix H of the CS document Appendices. Records only reporting HRQoL information were not considered further in this submission. One study reporting data on HSU value, using a UK value set, was identified in the SLR updates. The results of this publication were presented in Table 85 in Appendix H of the CS document Appendices. The company provided information regarding the participants' characteristics, recruitment methods, country, sample size and response rates, health states and adverse events, methods (questionnaires) used to elicit values, the tariffs used to value health states, and the overall results of the studies. Results were mainly either presented as an overall mean utility (with standard deviation), utility by each EDSS or categorised (mild, moderate or severe) by severity of MS. Although a formal critique of the health state utility studies was not presented, the company provided information regarding consistency with the reference standard, as well as relevance to the decision problem.

The original SLR for healthcare resource use and costs data carried out by the company identified ten studies from 15 publications for inclusion. Included UK resource use and costs records and the results of these published studies were presented in Tables 96 and 99 respectively in Appendix I of the CS document Appendices. Three studies reporting data on resource use and costs were identified in the SLR updates. The results of these publications were presented in Tables 100 and 101 in Appendix I of the CS document Appendices. The company provided information regarding the objective, patient population, country, price year, valuation methods, and costs and resource use data of the studies. In general, little critique of resource use and costs studies was provided by the company.

In response to ERG clarification question C2, the company provided one reference in the CS document clarification responses for Tables 80 and 81 of the CS document Appendices, Appendix H, to resolve the inconsistency between CS documents. In summary, a small number of the studies identified by the SLRs were used in the CS economic analysis. Information on health state utilities, and resource use and costs sourced from the available literature was used in the form of inputs to different components of the economic model. For example, estimation of health state utilities,

where data was not available for specific EDSS states (EDSS 7–9), were taken from Orme et al (2007),[7] and calculations of relapse costs were obtained and inflated from Hawton and Green (2016).[57] As expected, the development of the economic model for this submission was informed by previous NICE appraisals in RRMS.[6, 17-20, 58-60] The appropriateness and suitability of using specific pieces of information in respective parts of the economic analysis is critiqued in Section 4.2.

4.2.4 Interpretation of the review

The company's SLR of the cost-effectiveness evidence that compared various DMTs for treating people with RRMS identified studies undertaken in a UK setting. Two other SLRs identified studies which reported data on (a) HSU value for either people with MS in the UK or using UK tariffs for utility elicitation and (b) UK resource use and costs. The ERG is satisfied with the company's SLR searches and that all key studies used for inputs have been reported.

However, the ERG testing suggests that the fact that the company did not independently search the main MEDLINE database for the update of the SLR of economic analyses of treatments for patients with RMS, may have had a small impact on the number of records retrieved. The ERG believes that using existing published evidence (e.g. in peer-reviewed studies and previous NICE appraisals) serves as useful input to the submitted economic model. However, the ERG would have welcomed further critique of the identified studies regarding the resource use and costs, and health state utility studies.

4.3 Summary and critique of the company's submitted economic evaluation by the ERG

In this section, the ERG appraises the company's economic analysis against the NICE reference case for technology assessment.[51] The ERG provide a summary of the company's illustrative model structure, as well as the clinical (treatment effect on confirmed disability worsening, ARR, treatment discontinuation and mortality) and economic evidence (DMT acquisition costs, monitoring costs, health state management costs for RRMS and SPMS, and treatment of AE) used to parameterised the economic model. Along with the summary, the ERG provides a

critique of methods and inputs used in the economic analysis in the following sections.

4.3.1 NICE reference case checklist

The ERG has undertaken an evaluation of the company's submission in relation to the NICE reference case.[51] Our findings are summarised in Table 22.

Table 22: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (lifetime horizon)
Synthesis of evidence on health effects	Based on systematic review	Yes. Systematic review was conducted by the company
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes. Results reported in terms of quality adjusted life-years
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	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
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

Element of health technology assessment	Reference case	ERG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

4.3.2 Model structure

The company used a discrete-time cohort Markov model to evaluate the cost-effectiveness of ofatumumab against other DMTs in people with RRMS. The model simulated disability worsening and improvement between EDSS levels, progression from RRMS to SPMS, the relapse events, and treatment-related AEs. Patients with RRMS or SPMS could occupy one health-state at any given time, which ranged from 0 to 9 (the 0.5 EDSS scores were rounded down and combined with the lower EDSS score). In total, the model included 21 health states: RRMS EDSS levels 0, 1, 2, …, 9; SPMS EDSS levels 0, 1, 2, …, 9; and death. The company's representation of the model structure is given in Figure 4 (reproduced from CS document B, Figure 36, pg.118).

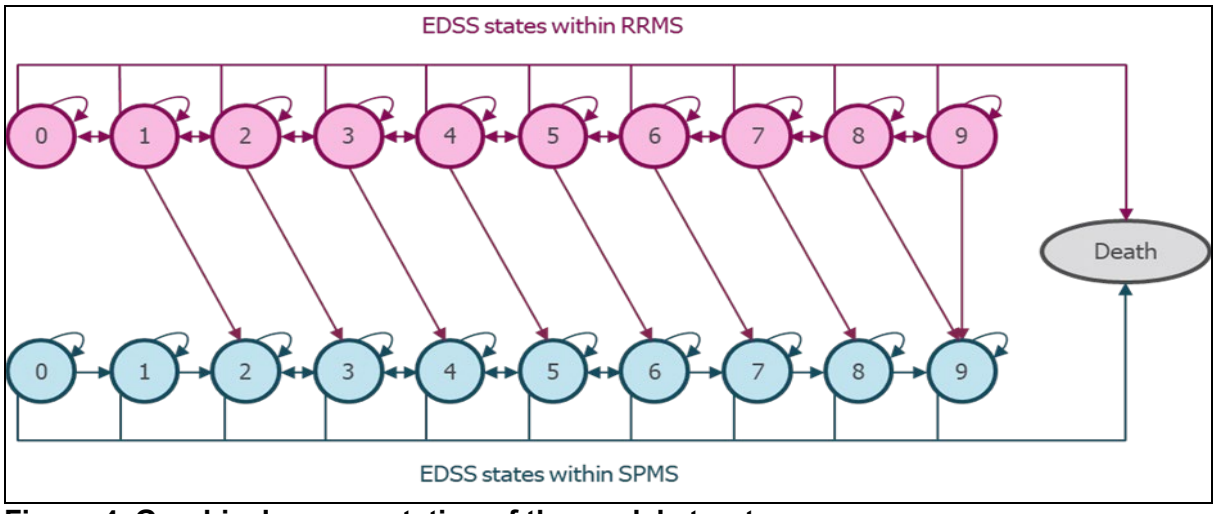

Figure 4. Graphical representation of the model structure

The model initiated from a cohort of people with RRMS, distributed across EDSS levels <7 (see Table 23) according to the baseline distribution of participants in the ASCLEPIOS trials. The starting mean age of the population was [redacted] years, with [redacted]

male and [redacted] female. In the HA RRMS or RES RRMS subgroups analyses, the relevant subgroup baseline characteristics were used. During each annual cycle of the model, people with RRMS experienced one of the following:

- Disability worsening, disability improvement or remained at their same level of disability.
- Progressed from RRMS to SPMS (always modelled to occur alongside an increase in EDSS).
- Patients discontinued receiving DMTs due to progressing to EDSS scores ≥7 and were switched to receive best supportive care (BSC).
- Discontinuation due to any cause (patients discontinued from DMTs and received BSC).
- Relapse event.
- AE.
- Mortality event and moved to the death state.

People with SPMS were assumed to receive BSC. During each cycle of the model, they experienced one of the following:

- Disability worsening, disability improvement (moved to lower EDSS state; this only applied to EDSS states 3–6) or remained at their same level of disability.
- Relapse event.
- Mortality event and move to the death state.

The model used a lifetime horizon. The number of model cycles varied by cohort baseline age and, in the base-case RRMS population, benefits (QALYs) accrued and costs incurred for 62 annual cycles.

Table 23. Baseline distribution of people by EDSS

EDSS		0	1	2	3	4	5	6	7	8	9
RRMS	Percentage (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HA RRMS		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RES RRMS		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EDSS: expanded disability status scale; HA: highly active; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis

ERG summary

There were some inconsistencies between the CS document B and the CS Excel model (Structure worksheet) in terms of the model structure and its statements. These were corrected in the company's responses to ERG clarification questions B1, B2, B3, and B5. In general, the ERG considers that the type and structure of the submitted model is appropriate for the purposes of the MS condition investigated and suitable for the decision problem in this appraisal. The discrete-time cohort Markov model appears to capture the key main features (movement between EDSS levels and progression from RRMS to SPMS) for patients living with RRMS. However, it should be noted that the model does not capture subsequent DMT costs/benefits following discontinuation of ofatumumab or its comparators. Instead, it is assumed that once treatment is discontinued, people follow the British Columbia natural history cohort; thus, not receiving any residual benefit from the DMT.

4.3.3 Population

The company submission differs slightly from the final NICE scope in terms of the population considered (see Section 2.3). This submission considers patients with RRMS only and excludes patients with active SPMS. The company's justification is that the evidence base for ofatumumab in patients with active SPMS is based on only a small proportion of patients (108 patients, 5.7%) in the pivotal phase III trials (ASCLEPIOS I and II), and as such does not provide sufficient subgroup data to perform meaningful indirect comparisons or allow robust cost-effectiveness analyses in active SPMS. The ERG's clinical expert considers this exclusion of patient group appropriate.

The patient characteristics used in the economic analysis were generated from patients' baseline values in the ASCLEPIOS trials ([redacted] female and [redacted] male, with a

mean age of [redacted] years). The starting distribution of people in each EDSS level is presented in Table 23.

The company stated that NMAs were not feasible in the HA and RES RRMS subgroups. Also, it stated that no subgroup-specific natural history data are available. Therefore, analyses for the HA and RES RRMS subgroups were undertaken using baseline data for these subgroups from the ASCLEPIOS trials, efficacy data from the ITT NMAs, and the same natural history data as for the full RRMS population. This was done to estimate ICERs versus relevant comparators in these subgroups. The ERG considers this conservative assumption/approach of sub-group analysis appropriate as the company's approach is unlikely to introduce substantial bias in favour of ofatumumab. The company's approach might under-estimate the uncertainties. However, this is unlikely to change any conclusions.

4.3.4 Interventions and comparators

The cost-effectiveness analysis compared ofatumumab with other DMTs which, as treatment comparators, are in line with the NHS England treatment algorithm for the use of DMTs in MS.[16] Table 24 shows the comparators included in the cost-effectiveness analyses for the RRMS population and HA and RES RRMS subgroups. The company excluded some of the DMTs, from the economic analysis although they were in the appraisal scope. These DMTs alongside a reason for their exclusion, are presented in Table 25.

Table 24. Comparators included in the economic model results (obtained from CS document B, Table 54)

RRMS	*HA RRMS*	*RES RRMS*

• *β-interferons:*
  ○ *Interferon β-1a (Avonex®)*
  ○ *Interferon β-1a (Rebif® 44)*
• *Dimethyl fumarate (Tecfidera®)*
• *Glatiramer acetate (Copaxone®, Brabio®)*
• *Teriflunomide (Aubagio®)*
• *Ocrelizumab (Ocrevus®)*
	• *Alemtuzumab (Lemtrada®)*
	• *Cladribine (Mavenclad®)*
	• *Fingolimod (Gilenya®)*
	• *Ocrelizumab (Ocrevus®)*
		• *Alemtuzumab (Lemtrada®)*
		• *Cladribine (Mavenclad®)*
		• *Natalizumab (Tysabri®)*
		• *Ocrelizumab (Ocrevus®)*

Abbreviations: *HA: highly active; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis*

Table 25. Comparators excluded from the economic results with reason for exclusion (reproduced from CS document B, Table 55)

Disease modifying therapy	Reason for exclusion from economic results
Interferon β-1a (Rebif® 22)	No CDW-6 data were available; this product is a step-down dose from Interferon β-1a (Rebif® 44) when patients cannot tolerate the higher dose and is therefore of limited relevance to the appraisal.[61]
Interferon β-1b (Extavia®)	No CDW-6 data were available; [redacted] (Novartis product).
Peginterferon β-1a (Plegridy®)	No CDW-6 data were available due to its exclusion from the base case NMA as an outlier (see Section B.2.9 in company submission document B), in line with NICE appraisal committee-preferred approach in TA533;[19] pegIFNβ-1a was also excluded from TA527 as an outlier.[6]
CDW-6, six-month confirmed disability worsening; NMA, network meta-analysis; TA, technology appraisal	

The ERG considered that the DMTs included in the economic analysis are in line with the NICE scope.[8] The company included a scenario NMA for pegIFNβ-1a (Plegridy®). However, in the economic analysis this comparator was excluded and there is no functionality for this comparison to be made. The ERG agrees that, based on the company's reasons, it was appropriate to exclude IFNβ-1a (Rebif® 22 mcg) and IFNβ-1b (Extavia®) mentioned in Table 26 from the economic analysis. However, the ERG deem that pegIFNβ-1a (Plegridy®) should have been considered for inclusion in the economic analysis as a scenario analysis, to align to the sensitivity analyses performed as part of the clinical effectiveness assessment described in Section 3.3.3.2. To our knowledge pegIFNβ-1a (Plegridy®) was excluded from TA527[6] because it was not included in the risk sharing scheme (RSS) and hence was appraised separately (TA624).[5]

4.3.5 Perspective, time horizon and discounting

The analysis was conducted from the NHS and PSS perspective, in line with the NICE Guide to the Methods of Technology Appraisal.[51] The model considered a lifetime horizon to capture the long-term costs and benefits of DMTs. In the base-case, both costs and benefits were discounted at the annual rate of 3.5%.

4.3.6 Treatment effectiveness and extrapolation

4.3.6.1 Transitions probabilities

To reflect the natural history of MS, information in the form of probabilities was required to show how people moved between the different health states in the model, information was required for the transitions between RRMS health states, progression from RRMS to SPMS and transitions between SPMS health states.

4.3.6.2 Transition probabilities within RRMS

Disability progression was based on a 10 x 10 transition matrix covering EDSS 0-9, which was derived from the natural history cohort from the British Columbia dataset. The British Columbia multiple sclerosis (BCMS) database is a population-based database established in the 1980s that captured about 80% of people with MS in British Columbia, Canada. EDSS scores were recorded by an MS specialist during face-to-face consultation with patients and this usually occurred at their annual visit to the MS clinic. This database is considered to be large (by 2004 the BCMS database included > 5900 participants), with prospectively collected information (e.g. EDSS scores, relapses, AE) and a long-term follow-up (> 25,000 cumulative years), and the database covers a relatively recent time period. Death (EDSS 10) was accounted for separately (see Section 4.3.6.7). Table 26 shows the transitions between the EDSS health states for people ≥ 28 years. In Table 26, people can remain, progress to more severe EDSS states, or regress to less severe health states.

Table 26. Natural history matrix based on information from the British Columbia dataset for people ≥ 28 years

EDSS From/to		EDSS state (to)											
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
EDSS state (from)	**0**	0.6954	0.2029	0.0725	0.0217	0.0042	0.0014	0.0018	0.0001	0.0000	0.0000	0.0000	1.0000
	1	0.0583	0.6950	0.1578	0.0609	0.0164	0.0046	0.0064	0.0005	0.0001	0.0000	0.0000	1.0000
	2	0.0159	0.1213	0.6079	0.1680	0.0446	0.0185	0.0216	0.0017	0.0005	0.0000	0.0000	1.0000
	3	0.0059	0.0496	0.1201	0.5442	0.0911	0.0585	0.1165	0.0103	0.0036	0.0003	0.0000	1.0000
	4	0.0017	0.0221	0.0666	0.1152	0.4894	0.1039	0.1681	0.0258	0.0067	0.0006	0.0000	1.0000
	5	0.0005	0.0053	0.0294	0.0587	0.0874	0.4870	0.2731	0.0388	0.0188	0.0010	0.0000	1.0000
	6	0.0001	0.0013	0.0044	0.0250	0.0307	0.0408	0.7407	0.1090	0.0438	0.0042	0.0000	1.0000
	7	0.0000	0.0002	0.0005	0.0025	0.0073	0.0039	0.1168	0.6927	0.1606	0.0156	0.0000	1.0000
	8	0.0000	0.0000	0.0000	0.0003	0.0006	0.0005	0.0188	0.0557	0.9034	0.0207	0.0000	1.0000
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0018	0.0057	0.1741	0.8183	0.000	1.0000
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.000	1.000

EDSS, expanded disability status scale

4.3.6.3 Transition probabilities from RRMS to SPMS

The probability of progressing from RRMS to SPMS in each cycle was based on information obtained from TA254.[17] These probabilities were applied to the RRMS population to generate the number of people expected to progress to SPMS over the model time horizon. Here, it was assumed that people who progressed from RRMS to SPMS had a one-unit increase in EDSS score. For example, people with RRMS with an EDSS of 5 would progress to SPMS with an EDSS of 6. Table 27 presents the probabilities of transitioning from RRMS to SPMS.

Table 27. Transition probabilities from RRMS to SPMS obtained from previous appraisals

EDSS	Probabilities	
	TA254[17] (Base-case)	**TA624[5] (ERG exploratory analysis)**
0	0	0.0040
1	0.0452	0.0020
2	0.0737	0.0290
3	0.0939	0.0970
4	0.1192	0.1810
5	0.1508	0.2250
6	0.1898	0.1680
7	0.2374	0.2110
8	0.2945	0.0640
9	1.0000	0.1540
10	0.0000	0.0000

EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal

4.3.6.4 Transition probabilities within SPMS

To reflect the natural history of people with SPMS, transitions were based on data from the placebo-arm of the EXPAND trial, and supplemented with information obtained from the London Ontario dataset, where transitions were not available in the EXPAND trial. Table 28 shows the transition matrix for people with SPMS. In scenario analysis (Table 29) the company used the transition matrix derived from the London Ontario dataset alone to explore the impact on the base-case results. Briefly, the MS Clinic at the University Hospital London, Canada was established in 1972 to

provide long-term care for patients with multiple sclerosis from its referral area of Southern Ontario. Information (inclusive of disability status scale) was collected annually for the 1,099 consecutive MS patients, between 1972 and 1984.[62] The London, Ontario dataset was analysed using the retrospectively smoothed disability status scale data, which censored improvements in patients' disability; this shows that participants cannot regress to less severe health states. Transition matrices based on the London Ontario dataset are available for people with RRMS and SPMS, separately.

ERG summary

The ERG agrees with the company's choice of datasets used to derive the transition matrices to reflect the natural history of people with RRMS and SPMS. These databases have been commonly used in NICE MS appraisals, but may be becoming dated, as the dataset may not represent current MS populations due to differences in diagnostics, as well as treatment practices.[63]

With respect to the RRMS-SPMS transition probabilities, the company provided the source as TA254,[17] but little information was provided about how these were derived. The ERG is aware of other RRMS-SPMS transition probabilities that have been used in previous appraisals[5] (see Table 29).

Table 28. Natural history transition probability matrix based on information from the EXPAND placebo group and London Ontario database (base-case)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	2	0.0000	0.0000	0.4550	0.3750	0.0991	0.0412	0.0270	0.0020	0.0007	0.0000	0.0000
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0019	0.0000	0.0000
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0061	0.0000	0.0000
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0228	0.0002	0.0000
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0484	0.0005	0.0000
	7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.6446	0.3490	0.0064	0.0000
	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084	0.0000
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

EDSS, expanded disability status scale

Table 29. Natural history transition probability matrix based on information from the London Ontario database alone (scenario analysis)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.3400	0.2300	0.3200	0.0800	0.0300	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	1	0.0000	0.7898	0.1423	0.0534	0.0057	0.0021	0.0055	0.0008	0.0004	0.0000	0.0000
	2	0.0000	0.0000	0.8168	0.1497	0.0150	0.0067	0.0106	0.0006	0.0005	0.0000	0.0000
	3	0.0000	0.0000	0.0000	0.8390	0.0702	0.0196	0.0624	0.0048	0.0039	0.0000	0.0000
	4	0.0000	0.0000	0.0000	0.0000	0.6524	0.1778	0.1524	0.0104	0.0069	0.0001	0.0000
	5	0.0000	0.0000	0.0000	0.0000	0.0000	0.5374	0.4090	0.0300	0.0234	0.0002	0.0000
	6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8883	0.0562	0.0547	0.0007	0.0000
	7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.7919	0.2039	0.0042	0.0000
	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9945	0.0055	0.0000
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

EDSS, expanded disability status scale

4.3.6.5 Calculation of patient disposition

Each cycle of the model requires information about patient disposition to attach costs incurred and benefits (LY and QALY) accrued over time for people occupying a specific EDSS health state.

For patients on treatment, the sequence in which the above events occur is the following:

1. *People who have discontinued treatment are moved to off-treatment*
2. *Mortality rates are applied, and people who die move to a death state. The mortality rates are applied to the people remaining on treatment after patients have been removed in step one*
3. *The transition probability matrix is applied. The matrix is applied to the people remaining on treatment after patients have been removed in steps one and two*
4. *People who discontinue due to progressing to EDSS ≥7 are moved to off-treatment. Simultaneously, people who discontinue due to progression to secondary progressive multiple sclerosis (SPMS) are moved to off-treatment*
5. *Relapses are calculated, based on half-cycle corrected EDSS state occupancies. These state occupancies are calculated by adding half the difference in state occupancy between the end of the given cycle and the beginning of the given cycle, to the state occupancy at the beginning of the given cycle.*

4.3.6.6 Discontinuation

Table 30 presents the all-cause discontinuation hazard ratios and annual probability of discontinuing treatment due to intolerance, lack of efficacy or other reasons. The probability of treatment discontinuation was based on the all-cause discontinuation hazard ratios derived from the studies included in the network meta-analysis, with the annualised all-cause discontinuation probability for people randomised to ofatumumab used as the reference.

Parametric models were fitted to the all-cause discontinuation data of people randomised to ofatumumab of the ASCLEPIOS I and II trials, and extrapolated beyond the trial horizon. In the base-case, the company chose the exponential parametric model. The exponential rate parameter was used with the treatment-specific hazard ratios to derive the annual all-cause discontinuation for each treatment. In scenario analyses, all-cause discontinuation was based other parametric models.

Table 30 Annualised probability of discontinuation

Disease modifying therapy	Hazard ratio vs ofatumumab (reference)	Annual discontinuation probability (%)
Ofatumumab	1.00	[redacted]
Ocrelizumab	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
IFN β-1a (Avonex®)	[redacted]	[redacted]
IFN β-1a (Rebif® 44)	[redacted]	[redacted]

IFN, interferon

4.3.6.7 Mortality

Mortality rates were required to estimate the rate at which people died within in each model cycle. People with RRMS and SPMS are at increased risk of death compared to the general population. Mortality was accounted for in the model by using age- and gender-specific all-cause mortality risks, and adjusted with different relative risks, independent of RRMS or SPMS. Age- and gender-specific mortality risks from the general population were obtained from mortality rates for England and Wales for 2016 to 2018, with all–cause mortality risk adjusted by risks obtained from Pokorski et al. (1997),[54] as used in the base-case. The company justified their choice of relative risks used and considered alternative sources in scenario analyses (Jick et al., 2014).[64] Table 31 shows the relative risks applied to general population mortality.

Table 31. Relative risks for RRMS and SPMS mortality

EDSS	Mortality multipliers		
	Pokorski et al., 1997[54] (base-case)	Jick et al., 2014[64] (ERG scenario analysis)	Kingwell et al., 2012[65] (ERG scenario analysis)
0	1.00	1.70	2.88
1	1.43	1.70	2.88
2	1.60	1.70	2.88
3	1.64	1.70	2.88
4	1.67	1.70	2.88
5	1.84	1.70	2.88
6	2.27	1.70	2.88
7	3.10	1.70	2.88
8	4.45	1.70	2.88
9	6.45	1.70	2.88
10	1.00	1.00	1.00
EDSS, expanded disability status scale			

These multipliers are based on an interpolation of the relative mortality risks obtained from Pokorski et al (1997).[54] Relative risks increase as severity of MS increases. In scenario analysis, the company considered a single relative risk of mortality of 1.70 obtained from Jick et al (2014)[64] and applied this to general population mortality.

Several assumptions were made with respect to mortality. It was assumed in the model that people with RRMS and SPMS had the same increased risk of mortality. Additionally, it was assumed that people could live to a maximum of 100 years. Furthermore, it was assumed that there is no direct effect on mortality associated with treatment. However, there is indirect benefit on mortality because DMTs delay progression to more severe EDSS health states, which are associated with a higher risk of dying.

ERG summary

The ERG considers it appropriate to use the mortality multipliers derived from Pokorski et al.[54] to reflect the increase in mortality in people living with MS compared to the general population.

4.3.6.8 Stopping rules

People in the model stopped DMTs upon progressing to EDSS ≥7 or progressing to SPMS. Other reasons for discontinuing treatment are discussed in Section 3.2.3. After discontinuing treatment, disability progression was based on the transition matrix derived from the British Columbia natural history cohort for people with RRMS. Disability progression for people who progressed to SPMS was based on the transition matrix derived from the EXPAND trial[53] and supplemented with information from the London, Ontario natural history cohort.[9] When people stopped treatment, costs and benefits of subsequent DMTs were not considered and people followed the transition matrix of a natural history cohort.

The company provided other transition matrices to reflect transitions within SPMS, derived from the British Columbia dataset, and the London Ontario dataset alone.[17] The model does not allow scenario analyses to be undertaken around the stopping rule.

ERG summary

The ERG considers that stopping treatment on progression to EDSS ≥7 is in line with the ABN guidelines. Additionally, on progression to SPMS the ERG agrees that it is appropriate to assume that people follow natural history transitions.

4.3.6.9 Treatment effectiveness and extrapolation

In the model, DMTs were considered to have direct impact on disability worsening and relapse frequency. However, there is an indirect treatment effect on mortality, as DMTs delay/reduce worsening to more severe EDSS health states.

4.3.6.10 Disability worsening

Treatment specific HRs were derived from the company's NMA for each DMT compared with best supportive care (BSC). These HRs were then applied to the forward transition matrix for the British Columbia natural history cohort to determine disease worsening for each treatment specific DMT. DMTs were assumed not to have any direct impact on the backward transition matrix (i.e., no direct impact to people who regress/improve to less severe EDSS states). Table 32 presents the HRs derived, based on the aligned criteria for ASCLEPIOS data (base-case), the

pre-defined criteria for ASCLEPIOS data (scenario analysis), and OPERA-aligned criteria for ASCLEPIOS data (scenario analysis).

Table 32. Hazard ratios for confirmed disability worsening for all DMTs compared to BSC for time to CDW-6

Disease modifying therapy	Time to CDW-6 (aligned criteria for ASCLEPIOS data) [base-case] HR (95% CrI)	Time to CDW-6 (pre-defined criteria for ASCLEPIOS data) [scenario analysis] HR (95% CrI)	Time to CDW-6 (OPERA-aligned criteria for ASCLEPIOS data) [scenario analysis] HR (95% CrI)
Ofatumumab	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
IFN β-1a (Avonex®)	[redacted]	[redacted]	[redacted]
IFN β-1a (Rebif® 44)	[redacted]	[redacted]	[redacted]

BSC, best supportive care; CDW, confirmed disability worsening; CrI, credible interval; DMTs, disease modifying therapies; HR, hazard ratio

People who transitioned to an SPMS health state followed a transition matrix, derived from the people randomised to placebo in the EXPAND trial, supplemented with information from the London Ontario Dataset.

In the model, treatment efficacy remains for the duration on treatment. When people in the model discontinue treatment, treatment benefit is stopped, and people follow disease progression for the natural history cohort. Here, the underlying assumption is that there is no residual benefit from taking DMTs and disease worsening would be at the same rate as people not treated with a DMT.

4.3.6.11 Relapse

The treatment effect of DMTs on reducing the annualised relapse rates (ARRs) required information about relapse rates in the absence of DMTs (i.e., relapse rates from people randomised to placebo in a trial and/or from a natural history cohort), and the treatment effect of each DMT compared to placebo. In Table 33, the natural

history annualised relapse rates used in the base-case were derived using information from the UK MS Survey and Patzold and Pocklington (1982)[18, 66] for RRMS, and from the UK MS Survey, Patzold and Pocklington (1982)[18, 66] and EXPAND trial data[9, 18, 66] for SPMS. To these off-treatment ARRs, on-treatment ARRs were derived in the model by applying the rate ratio for ARRs for each DMT compared to best supportive care obtained from the NMA (see Table 34).

Table 33. Annualised relapse rates for a natural history cohort, using UK MS Survey, Patzold and Pocklington 1982 and EXPAND; and values from alternative sources

EDSS	ARR, using MS Survey and Patzold and Pocklington (Patzold and Pocklington, 1982)[18, 66] (base-case)	ARR, using MS Survey, Patzold and Pocklington (Patzold and Pocklington, 1982) and EXPAND [9, 18, 66] (base-case)	ARR, using TA527 assessment[6] (ERG exploratory analysis)	
	RRMS	SPMS	RRMS	SPMS
0	0.71	0.00	0.8895	0.0000
1	0.73	0.00	0.7885	0.0000
2	0.68	0.47	0.6478	0.6049
3	0.72	[redacted]	0.6155	0.5154
4	0.71	[redacted]	0.5532	0.4867
5	0.59	[redacted]	0.5249	0.4226
6	0.49	[redacted]	0.5146	0.3595
7	0.51	[redacted]	0.4482	0.3025
8	0.51	[redacted]	0.3665	0.2510
9	0.51	[redacted]	0.2964	0.2172

ARR, annualised relapse rates; EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 34. Rate ratio on annualised relapse rates for each DMT compared to best supportive care

Disease modifying therapy	ARR (95%CrI)
Ofatumumab	[redacted]
Ocrelizumab	[redacted]
Alemtuzumab	[redacted]
Cladribine	[redacted]
Natalizumab	[redacted]
Fingolimod	[redacted]
Teriflunomide	[redacted]
Dimethyl fumarate	[redacted]

Disease modifying therapy	ARR (95%CrI)
Glatiramer acetate	[redacted]
IFN β-1a (Avonex®)	[redacted]
IFN β-1a (Rebif® 44)	[redacted]
ARR, annualised relapse rates; CrI, credible intervals; DMT, disease modifying therapy; IFN, interferon	

The ARRs from UK MS survey and Patzold and Pocklington (1982)[66] ranged from 0.49 to 0.72 across EDSS levels. Across both MS types, it appears that people in more severe EDSS states experienced more relapses than those in less severe health states. In Table 33, the ERG has provided ARRs and have noted the clear differences between the ARRs provided by the company and those obtained from TA527 assessment.[6]

In a scenario analysis, the company provided an alternative method that applied treatment specific rate ratios to declining relapse rates irrespective/independent of EDSS. Rate ratios were derived from the studies included in the company's NMA for ARR. This approach considers that relapse rates are independent of EDSS. It is assumed that the baseline relapse rate decreases over the model time horizon.

ERG summary

The base-case applied ARR rate ratios to natural history relapse rates derived depending on EDSS. In scenario analysis, the company provided an alternative method that applied treatment specific rate ratios to declining relapse rates irrespective/independent of EDSS to show the treatment effect of DMTs compared to best supportive care in reducing relapse rates. The ERG considers the approach taken in the base-case to be appropriate. However, our concerns relate to the seemingly low ARRs in people with SPMS, as well as the stable ARRs from EDSS 5 onwards for people with RRMS. The alternative ARRs obtained from the TA527 assessment[6] show that relapses decrease with EDSS severity across both types of MS; hence, we consider these values more appropriate.

4.3.6.12 Waning of the treatment effect

In the company's base-case results it was assumed that the treatment effect with ofatumumab and all comparators was constant and was not expected to wane over time, and that waning is already captured within the model via all-cause discontinuation which accounts for patients discontinuing for any reason, including perceived lack of efficacy. In response to the ERG's clarification question to consider including scenarios with waning of the treatment effect, the company stated that there is no evidence to support an assumption that the effectiveness of ofatumumab wanes over time. The company undertook further analyses on current data and concluded that *'CDW-6 treatment effect of ofatumumab as compared to teriflunomide does not appear to wane over time.'*

Additionally, the company undertook exploratory analyses around the ARR, another key clinical parameter in the economic model. Based on the 27-month data, the analysis of the cumulative ARR by time interval did not show that there was evidence of waning of the treatment effect with regards to the relapse rates. The company further stated that should the efficacy wane over time, people would not remain on the same DMT. The company further supported their argument, by stating that in the ASCLEPIOS trials, none of the participants developed neutralising antibodies.

In scenario analyses, the company provided results based on conservative assumptions that waning of the treatment effect existed.

ERG summary

The ERG considers that the exploratory analyses reported in ofatumumab ERG clarification questions company response to be appropriate to support that there is no evidence of treatment waning. However, given the short-term nature of the data used for these analyses and to be in line with previous MS appraisals, it would be appropriate to assume a waning of the treatment effect applied to all DMTs.

4.3.7 Health related quality of life

In each cycle, people accrue benefits according to the EDSS health state they occupy. Benefits were measured in terms of quality adjusted life years (QALYs). A preference-based valuation of the health-related quality of life (HRQoL) is required to derive health state utility values to generate QALYs. HRQoL information was

collected in the ASCLEPIOS trials using the EQ-5D-5L questionnaire and these data were pooled across trials as though they were collected from a single study. EDSS health state utility values were derived using a crosswalk algorithm. Where there was insufficient information (EDSS ≥7), the company supplemented missing health state values with values obtained from Orme et al. (2007).[7] Table 35 shows the health state utility values in the base-case and scenario analyses.

Table 35. Summary of the health state utility values used in company's cost-effectiveness analysis

EDSS	ASCLEPIOS trials and Orme et al., 2007[7] (base-case)		ASCLEPIOS trials and Orme et al., 2007[7]	Orme et al., 2007[7] (ERG exploratory analysis)
	RRMS	SPMS	RRMS	SPMS
0	[redacted]	[redacted]	[redacted]	0.825
1	[redacted]	[redacted]	[redacted]	0.754
2	[redacted]	[redacted]	[redacted]	0.660
3	[redacted]	[redacted]	[redacted]	0.529
4	[redacted]	[redacted]	[redacted]	0.565
5	[redacted]	[redacted]	[redacted]	0.473
6	[redacted]	[redacted]	[redacted]	0.413
7	0.297	0.252	0.297	0.252
8	−0.049	−0.094	−0.049	−0.094
9	−0.195	−0.240	−0.195	−0.240
10	0.000	0.000	0.000	0.000

EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

In the model, QALYs were accrued for each DMT, by improving the quality of life, by reducing/delaying disability progression, reducing the number of relapses, reducing caregivers' disutility and increasing the length of life (reducing/delaying progression avoids the increase risk of mortality associated with more severe EDSS health states). QALYs yielded over the model time horizon were discounted at an annual rate of 3.5%.

Across both types of MS (RRMS and SPMS), the health state values derived from the ASCLEPIOS trials were higher than those obtained from Orme et al., 2007

alone.[7] We noted that the utility values for EDSS 0-6 were the same for RRMS and SPMS. However, our clinical advisor stated that they would expect utility values to be lower in people with more progressive forms of MS (i.e. SPMS).

Utility coefficients of [redacted] per year since diagnosis and of [redacted] per year for males were derived from a regression model applied to the ASCLEPIOS trial data. These utility modifiers were not applied in the model for any patients (RRMS or SPMS) in the base case (see below) and the results of a scenario analysis including these utility modifiers were presented in response to ERG clarification question B10[redacted].

On clarification, the company stated that the base-case economic analysis had not incorporated these coefficients. However, in a scenario analysis that used the utility values from Orme et al. (2007)[7] these coefficients had been applied. At clarification, the company stated that the regression coefficients in the Orme et al. scenario were incorrectly applied using the ASCLEPIOS coefficients, where the Orme coefficients should have been applied instead. The company provided the correct values and re-ran the analyses.

ERG summary

Based on the information submitted at clarification stage, the ERG considers the methods used to derive health state utility values for people with RRMS to be appropriate. However, given the small number of participants in the trials with SPMS, we consider that these values may not be representative of people living with SPMS. Also, based on clinical expert opinion, using the same values for RRMS and SPMS is not appropriate; hence, the ERG consider using the health state values from Orme et al (2007)[7] for SPMS.

4.3.7.1 Relapse disutility

In the model people experience relapses. The company applied a disutility of [redacted] for each relapse experienced, regardless of severity (mild, moderate or severe) and MS type. This disutility was derived from the ASCLEPIOS trials and assumed to apply for three months of the annual model cycle.

4.3.7.1.1 Caregivers' disutilities

The model captures the disutility associated with providing care for people with MS. Caregivers' disutilities used in the base-case were obtained from TA127,[18] originally obtained from Gani et al.[67] Alternative disutilities from Acaster et al. (2013)[68] were available in the company's model. Table 36 shows the caregivers' disutility by EDSS.

Table 36. Caregivers' disutilities by EDSS

EDSS	TA127[18] (base-case)	RRMS/SPMS obtained from Acaster et al., (2013)[68] (ERG scenario analysis)
0	0.000	-0.0020
1	-0.001	-0.0020
2	-0.003	-0.0020
3	-0.009	-0.0020
4	-0.009	-0.0450
5	-0.020	-0.1420
6	-0.027	-0.1670
7	-0.053	-0.0630
8	-0.107	-0.0950
9	-0.140	-0.0950

EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

It was unclear to the ERG if these utility decrements were applied to caregivers of people with SPMS. On clarification, the company confirmed that the same utility decrements were applied to caregivers in SPMS.

The model also captures the impact of adverse events on quality of life. Disutilities associated with AE are presented in CS Document B, Table 74, page 141 and are reproduced Table 37. These disutilities were obtained from TA533.[19] The severity of AEs included in the model was based on the average proportion of severe adverse events that occurred in the treatment arms of the ASCLEPIOS trials (see Table 38). These averages were applied for each cycle while people remained on treatment. It was assumed that for each AE, 89.87% were non-serious and 10.13% were serious events.

Table 37. Disutility and duration associated with serious adverse events and non-serious adverse events

Adverse event	Non-serious		Serious		Average utility decrement
	Utility decrement	Duration (days)	Utility decrement	Duration (days)	
Arthralgia	0.2500	10.50	0.2500	24.50	0.0082
Back pain	0.2500	10.50	0.5000	24.50	0.0099
Bronchitis	0.0100	14.00	0.0100	14.00	0.0004
Depression	0.1650	75.00	0.5600	365.25	0.0872
Fatigue	0.0000	182.63	0.0000	182.63	0.0000
Headache	0.1400	10.50	0.4930	24.50	0.0070
Influenza-like illness	0.0800	1.00	0.0800	1.00	0.0002
Infusion related reaction	0.0002	1.00	0.0002	1.00	0.0000
Injection site pain	0.0000	7.00	0.0000	7.00	0.0000
Insomnia	0.0002	1.00	0.0002	1.00	0.0000
Nasopharyngitis	0.0000	7.00	0.0000	14.00	0.0000
PML	0.3000	365.25	0.3000	365.25	0.2917
Sinusitis	0.0000	1.00	0.0000	1.00	0.0000
URTI	0.2000	7.00	0.2000	14.00	0.0042
UTI	0.1000	5.00	0.1000	5.00	0.0014

PML, progressive multifocal leukoencephalopathy; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Table 38. Adverse events observed in the ASCLEPIOS trials

Adverse events	Ofatumumab		Average	Teriflunomide		Average
	ASCLEPIOS I	ASCLEPIOS II		ASCLEPIOS I	ASCLEPIOS II	
Any adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events	Ofatumumab		Average	Teriflunomide		Average
	ASCLEPIOS I	ASCLEPIOS II		ASCLEPIOS I	ASCLEPIOS II	
Injection site pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PML, progressive multifocal leukoencephalopathy; URTI, upper respiratory tract infection; UTI, urinary tract infection.

4.3.8 Resources and costs

The following key categories of resource use and costs for ofatumumab and the comparators have been included in the company's analysis: (i) intervention and comparator costs (including treatment acquisition, administration and monitoring costs), (ii) health-state costs (including disease management and relapse costs), and (iii) treatment of AE costs, all from the perspective of the NHS and PSS.

4.3.8.1 Treatment acquisition costs

An overview of the treatment regimens for each of the DMTs considered in the economic model, as well as the drug acquisition cost (per dose and per annum) are presented in Table 39 (reproduced from the company submission document Appendices, Appendix M, Table 157). Annual costs presented are based on the list price for each DMT. Ofatumumab, fingolimod and IFNβ-1b are Novartis products, hence the PAS discount is known and provided by the company as well. Annual costs were derived from the annual dosage per year of each DMT (for year 1 and subsequent years) multiplied by the price per dose. All costs for each of the DMTs were obtained from the British National Formulary (BNF) online database[69] using the standard doses represented in the treatments' respective summary of product characteristics (SmPC). The posology for each comparator was also sourced from the BNF. Alemtuzumab retreatment costs were considered in a scenario analysis (see Section 3.5.1 in the CS document B for further detail).

In response to ERG clarification question B17 regarding cost of treatment discontinuation, the company stated that *"for alemtuzumab and cladribine, the full costs are incurred for those who discontinue treatment part way through the model cycle since these treatments are administered at the start of each treatment year. For all other DMTs, costs are calculated based on the half-cycle corrected state occupancies in the usual fashion; in effect this means half the annual cost is applied"* in the CS document clarification responses. All costs for each of the DMTs were checked by the ERG using the BNF online database[69] and previous MS appraisals (e.g. TA624[5], ongoing NICE appraisal of siponimod [ID1304][9]) and in general, the annual costs were believed to have been derived appropriately.

Table 39 Drug costs used in the economic model (reproduced from CS document Appendices, Appendix M, Table 157)

Drug	Posology	Annual doses		Cost per dose, £	Drug Cost Year 1, £	Drug Cost Year 2+, £
		Year 1	Year 2			
Ofatumumab ([redacted] 20 mg/0.4 mL solution for injection pre-filled autoinjector	20 mg administered at Weeks 0, 1 and 2, followed by monthly dosing starting at Week 4.	15.00	12.00	[redacted]	[redacted]	[redacted]
PAS Price				[redacted]	[redacted]	[redacted]
ocrelizumab (Ocrevus®)[a] 300 mg/10 ml concentrate for solution for infusion vials	Initially 300 mg, then 300 mg after 2 weeks; maintenance 600 mg every 6 months, the first maintenance dose should be given 6 months after the first initial dose.	4.00	4.00	£4,790.00	£19,160.00	£19,160.00
Alemtuzumab (Lemtrada®) 12 mg/1.2 ml concentrate for solution for infusion vials	Initial treatment of two courses: First treatment course: 12 mg/day on 5 consecutive days (60 mg total dose). Second treatment course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course. Up to two additional treatment courses, as needed, may be considered: Third or fourth course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the prior treatment course.	5.00	3.00	£7,045.00	£35,225.00	£21,135.00[d]
Cladribine (Mavenclad®)[b] 10 mg tablets	The recommended cumulative dose of Mavenclad is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a	1.00	1.00	£28,661.36	£28,661.36	£28,661.36[d]

	patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. The price is based on the number of tablets recommended for the model baseline weight in accordance with Table 1 in the cladribine SmPC.[70]					
Natalizumab (Tysabri®) 300 mg/15 ml concentrate for solution for infusion vials	Tysabri 300 mg is administered by intravenous infusion once every 4 weeks.	13.04	13.04	£1,130.00	£14,740.45	£14,740.45
Fingolimod (Gilenya®)[c] 0.5 mg capsules	0.5 mg once daily.	365.25	365.25	£52.50	£19,175.63	£19,175.63
PAS Price				[redacted]	[redacted]	[redacted]
Teriflunomide (Aubagio®)[a] 14 mg tablets	14 mg once daily.	365.25	365.25	£37.07	£13,538.25	£13,538.25
Dimethyl fumerate (Tecfidera®)[a] 240 mg	Initially 120 mg twice daily for 7 days, then increased to 240 mg twice daily.	730.50	730.50	£24.52	£17,910.29	£17,910.29
Glatiramer acetate (Brabio®)[a] 20 mg/1 ml solution for injection pre-filled syringes	20 mg once daily, alternatively 40 mg 3 times a week, doses to be separated by an interval of at least 48 hours.	365.25	365.25	£16.52	£6,033.93	£6,033.93
IFN β-1a (Avonex®)[a] 30 µg	30 µg once a week.	52.18	52.18	£163.50	£8,531.20	£8,531.20
IFN β-1a (Rebif® 22)[a,e] 22 µg/0.5 ml (6million units) solution for injection pre-filled pen	A lower dose of 22 µg, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.	156.54	156.54	£51.13	£8,003.15	£8,003.15
IFN β-1a (Rebif® 44)[a] 44 µg/0.5 ml (12million units) solution for injection 1.5 ml cartridges	The recommended posology of IFN β-1a (Rebif®) is 44 µg give three times per week by subcutaneous injection.	156.54	156.54	£67.77	£10,608.03	£10,608.03

IFN β-1b (Extavia®)[c,e] 300 µg powder and solvent for solution for injection vials[f]	The recommended dose of IFN β-1b (Extavia®) is 250 µg (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected subcutaneously every other day.	182.63	182.63	£39.78	£7,263.97	£7,263.97
PAS Price				[redacted]	[redacted]	[redacted]
Pegylated IFN β-1a (Plegridy®)[e] 125 µg/0.5 mL solution for injection pre-filled pens	The recommended dose of Pegylated IFN β-1a (Plegridy®) is 125 µg injected subcutaneously every 2 weeks (14 days).	52.18	52.18	£163.50	£8,531.20	£8,531.20

[a] A PAS agreement is known to apply to these treatments but the discounts are not considered in these analyses as they are confidential.
[b] Drug acquisition cost is based on the number of tablets recommended for the model baseline weight in accordance with Table 1 in the cladribine SmPC.[70]
[c] Fingolimod (Gilenya®) and Extavia® are Novartis products, hence the PAS discount is known.
[d] Drug acquisition cost only applies to Year 2. No further treatment is administered in Year 3+ (unless patients are retreated).
[e] No cost-effectiveness results presented as CDW-6 results were not available.
[f] After reconstitution, each millilitre contains 250 mg Extavia®.[71]
Abbreviations: CDW-6: 6 month confirmed disability worsening; IFN: interferon; PAS: Patient Access Scheme; SmPC: Summary of Product Characteristics.

4.3.8.2 Administration and monitoring costs

Resource use and costs associated with administration and monitoring were clearly reported in CS document Appendices, Appendix M. Annual administration and monitoring costs were reported for first year of DMT, and subsequent years are calculated by multiplying the expected annual resource use or the frequency of each required resource use per year by their respective unit cost (CS document Appendices, Appendix M, Tables 158; and 159). The assumptions for calculating administration costs were similar to those presented in the recent submission to NICE for ocrelizumab in RRMS and the unit costs were sourced from the BNF, the NHS and PSSRU.[19, 69, 72, 73] The assumptions for calculating monitoring costs were informed from the SmPC of the relevant treatments, and the unit costs were sourced from the NHS and PSSRU.[72, 73] Resource use for monitoring included visits to health care professionals (Neurology, MS nurse and ophthalmology visits) and undergoing tests (including full blood count, liver function test, urinalysis, renal function test, thyroid function test, Varicella zoster virus test, herpes papillomavirus test, Tuberculin skin test, Hepatitis B virus test and MRI). Table 40 reports the annual administration and monitoring costs for the first year and subsequent years by DMT.

The ERG notes that there are no subsequent administration costs following training for self-administration of ofatumumab or other subcutaneous treatments considered in the model in the first year. The ERG's clinical expert confirmed that in the first year, patients would require initial training regarding the self-administration of subcutaneous DMTs and that no further training would be required in subsequent years. The ERG notes the higher costs associated with monitoring patients on alemtuzumab. Although not explicitly stated by the company, this may reflect the mandatory monitoring for patients taking this treatment.[74] In general, the ERG considers the methods and assumptions employed in calculating administration and monitoring resource use and costs to be appropriate.

Table 40. Annual drug administration and monitoring costs used in the cost-effectiveness model (reproduced from CS document B, Table 78)

Drug name	Administration costs, £		Monitoring costs, £	
	Year 1	Year 2+	Year 1	Year 2+
Ofatumumab	46.00	0.00	371.11	306.65
Ocrelizumab	1,870.79	1,256.17	371.11	306.65
Alemtuzumab	3,157.03	1,927.80[a]	1,111.98	1,052.80
Cladribine	0.00	0.00	559.70	196.79
Natalizumab	7,990.03	7,990.03	653.07	459.00[b]
Fingolimod	614.62	0.00	604.63	306.06
Teriflunomide	0.00	0.00	384.95	248.22
Dimethyl fumarate	132.23	0.00	517.87	250.50
Glatiramer acetate (Brabio®)	46.00	0.00	352.48	301.07
IFN β-1a (Avonex®)	46.00	0.00	372.42	311.04
IFN β-1a (Rebif® 22)	46.00	0.00	373.52	311.04
IFN β-1a (Rebif® 44)	46.00	0.00	373.52	311.04
IFN β-1b (Extavia®)	46.00	0.00	372.42	311.04
Peginterferon β-1a (Plegridy®)	46.00	0.00	372.42	311.04

[a] In the base case, administration costs do not apply after Year 2.

[b] In response to ERG clarification question B6, the company stated in the CS document clarification responses that natalizumab monitoring costs are different for Year 2 (£459.00) and Years 3+ (£601.68) (see CS document clarification responses, page 23 and Table 15 for further detail). **Abbreviations:** IFN: interferon

4.3.8.3 Disease management costs

Disease management costs by EDSS health states were considered in the economic model. The inputs for each EDSS health state were obtained from the UK MS survey,[6] in line with previous NICE appraisals.[6, 17, 18, 59] This data was inflated to 2014–2015 values using the Pay and Price Index, and subsequently inflated for the remaining years to 2018–2019 values using the NHS Cost Inflation Index (see CS document Appendices, Appendix M for details on the inflation process). Only direct medical costs were considered in the model. The first two columns of Table 41 presents the company's disease management costs by EDSS health state.

Table 41. Disease management costs considered in the model (reproduced from CS document B, Table 80)

EDSS	Direct medical costs, inflated to 2018–2019 (base-case)	Management costs for SPMS (TA320)[59] and inflated to the 2018-2019 cost year (ERG exploratory analysis)
0	£994	£1,339
1	£1,033	£1,380
2	£757	£1,103
3	£4,143	£4,489
4	£2,007	£2,353
5	£3,405	£3,751
6	£4,545	£4,890
7	£11,963	£12,308
8	£29,137	£29,483
9	£23,314	£23,661
10	£0	£0
EDSS, expanded disability status scale; ERG, evidence review group; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal		

In response to ERG clarification question B14, the company confirmed that the same disease management costs for the various EDSS health states were used for both people with RRMS and SPMS in the economic model. The company stated that their approach aligns with the final committee-preferred cost source and model used in NICE TA527[75] and also TA533.[76] All costs have been inflated to current prices using appropriate indexes. The ERG conducted a search of the NICE website for recent (within the last two years) NICE technology appraisals of DMTs used to treat MS.

We identified alternative SPMS specific health state management costs that are available and have been used in TA624[5] and the ongoing NICE appraisal of siponimod [ID1304].[9] Original costs for SPMS health states were from TA320.[59] These were uprated to current price costs and were used in TA624[5] and the ongoing NICE appraisal of siponimod [ID1304][9] (see the third column of Table 41). The ERG will use these SPMS costs to explore the impact of these on the ICER in a base-case analysis. The company's use of the lower disease management costs for SPMS may have resulted in an underestimate of mean total costs.

4.3.8.4 Relapse costs

An overview of relapse management costs for each severity level considered in the economic model is presented in Table 42. These costs were £100, £823 and £3,560 for mild, moderate and severe relapses respectively. The total costs caused by relapses are calculated from the number of relapses in each relapse severity category multiplied by the associated relapse management costs. These relapse costs were obtained and inflated from Hawton and Green (2016)[57] identified by the systematic review. The standard error was assumed to be 20% of the mean value as it was not possible to calculate the standard errors for these cost items. Relapse treatment costs are the same for people with RRMS or SPMS on/off treatment. The ERG is satisfied with the approach that was taken and to our knowledge these costs have been used in the model.

Table 42. Relapse management costs used in the model base case (obtained from CS document B, Table 81)

Relapse severity	***Direct medical cost (SE)***	***Assumption***
Mild	*£100 (£20)*	*Relapse not treated with steroids minus the cost of no relapse*
Moderate	*£823 (£165)*	*Weighted average of relapse requiring oral steroids and relapse resulting in IV steroids minus the cost of no relapse*
Severe	*£3,560 (£712)*	*Relapse resulting in hospital admission minus the cost of no relapse*
Source: *Hawton and Green, 2016.[57]* ***Abbreviations****: SE: standard error.*		

4.3.8.5 Cost of treating adverse events

Resource use and costs associated with the management of AE were included in the economic analysis (see CS document Appendices, Appendix M, Table 161).

Separate costs were considered for non-serious and serious AE. These were subsequently weighted by the proportion of serious AE and AE that occurred in the treatment arms of the ASCLEPIOS trials (10.13% of people who experienced an AE, experienced a SAE) to provide an average annual cost per adverse event in the model. Annual costs associated with the treatment of AE are presented in Table 43. The most costly adverse effects to treat were depression and progressive multifocal leukoencephalopathy (PML), with average treatment costs of £1,077.72 and £13,258.28, respectively.

Table 43. Annual AE management costs (obtained from CS document B, Table 82)

Adverse event	*Non-serious*	*Serious*	*Average cost*[a]
Arthralgia	*£3.72*	*£451.24*	*£49.07*
Back pain	*£0.00*	*£689.29*	*£69.85*
Bronchitis	*£78.91*	*£79.91*	*£79.01*
Depression	*£849.56*	*£3,101.16*	*£1,077.72*
Fatigue	*£0.00*	*£54.39*	*£5.51*
Headache	*£0.00*	*£220.24*	*£22.32*
Influenza-like illness	*£0.00*	*£0.00*	*£0.00*
Infusion related reaction	*£0.00*	*£0.00*	*£0.00*
Injection site pain	*£0.00*	*£39.23*	*£3.98*
Insomnia	*£0.00*	*£0.00*	*£0.00*
Nasopharyngitis	*£0.00*	*£39.23*	*£3.98*
PML	*£13,258.28*	*£13,258.28*	*£13,258.28*
Sinusitis	*£0.00*	*£0.00*	*£0.00*
URTI	*£39.23*	*£39.23*	*£39.23*
UTI	*£2.11*	*£738.21*	*£76.70*

[a] Based on the average proportion of SAEs in both treatment arms of the pooled ASCLEPIOS trials, it was assumed that for each AE, 89.87% of the events were non-serious and 10.13% were serious.

Abbreviations: AE: adverse event; PML: progressive multifocal leukoencephalopathy; SAE: serious adverse event; URTI: upper respiratory tract infection; UTI: urinary tract infection.

There were some AE e.g. gastroenteritis, hypertension, pneumonia, neoplasms (breast/skin), liver disturbance (clinical or biochemical i.e. alanine aminotransferase (ALT) or other liver function change), or pyrexia which were excluded from the annual adverse event probabilities for each DMT included in the economic model. In response to ERG clarification question B15, the company provided justification for these exclusions. They stated that prior experience has suggested that AE are not usually model drivers when comparing DMTs for RRMS. Therefore, the company

aligned with the approach taken in the ocrelizumab appraisal (TA533).[19] The ERG are satisfied with the approach taken and that the excluded adverse events do not seem to be the key drivers of the economic model and that they do not have much impact on the ICER. The ERG notes that the company has not derived the probability of events based on the incidence. If the company had used the incidence of events, they could have derived a probability of events that occurred in each cycle. However, the ERG accepts the methodology and the assumptions used to derive AE average annual costs.

ERG summary

The ERG considers the methodology applied to identify and inflate costs taken from the literature to be reasonable and appropriate for analysing the data. However, the company submission could further benefit in terms of a critique of the resource use and cost studies, which could provide a stronger justification for choosing inputs for the base-case analysis. Also, alternative SPMS specific health state management costs could be considered.

4.3.8.6 Overview of model assumptions and ERG critique

In Table 44, we present the company's modelling assumptions with comments from the ERG.

Table 44. Model assumptions with ERG's comments

Base-case assumption	ERG's comment
The patient population in ASCLEPIOS is representative of the NHS population eligible for treatment with ofatumumab	The ERG agrees with these assumptions.
EDSS health state is the primary determinant of health state costs and utilities	
Patients who discontinue treatment receive BSC	
Patients who reach the EDSS treatment threshold of 7 (i.e. patients in EDSS 7 or above) are automatically assumed to discontinue treatment and receive BSC	
Patients who transition from RRMS to SPMS are assumed to discontinue treatment and receive BSC	
BSC is assumed to incur zero cost	The economic analysis includes disease management costs.
Treatment benefits are accrued only during the treatment period and no residual treatment effect is modelled for patients who discontinue to BSC	The ERG agrees with these assumptions.
Treatment effects are not applied to backwards transitions (i.e. disability improvement) nor to the probability of transitioning to SPMS	In the model, DMTs were considered to have direct impact on disability worsening and relapse frequency.

	However, there is an indirect treatment effect on mortality, as DMTs delay/reduce worsening to more severe EDSS health states, which are associated with higher risk of dying. There is also an indirect effect on the risk of progression to SPMS. Delaying progression avoids higher probability of progression to SPMS.
Any long-term treatment effect waning is captured in all-cause discontinuation	The ERG is unaware of any long-term follow-up evidence for ofatumumab. The ERG supports a precautionary approach to use a conservative assumption of waning of the treatment effect.
AEs are assumed to occur at a constant rate in patients receiving DMTs and are assumed to stop after discontinuing DMTs in alignment with the assumption in TA533	The ERG considers this a plausible assumption.
AE, adverse event; BSC, best supportive care; DMTs, disease modifying therapies; EDSS, expanded disability status scale; NHS, National Health Service; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis, TA, technology appraisal	

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The following section presents the company's cost-effectiveness results reported in the CS, Document B and the economic model. Results are presented based on the PAS agreements for ofatumumab and fingolimod and for all other DMTs at list prices.

5.1.1 Cost-effectiveness base-case results: ofatumumab versus comparators

The pairwise deterministic results are presented in Table 45 for ofatumumab versus all included comparators for the RRMS population. Results are reported based on the PAS price for ofatumumab and fingolimod and list prices for all other comparators. These results show that there were modest gains in QALYs across all DMTs. Ofatumumab was [redacted] against two alternative treatment strategies (dimethyl fumarate and teriflunomide) and was [redacted] against three treatment strategies (IFN β-1a (Avonex), IFN β-1a (Rebif® 44 mcg) and glatiramer acetate), but it is [redacted] ocrelizumab. Incremental results were obtained from the company's economic model (see Table 46). These results showed that ofatumumab [redacted] dimethyl fumarate and teriflunomide. When compared to

glatiramer acetate the ICER was approximately [redacted] per QALY. Ocrelizumab was [redacted] treatment strategy, with an ICER of approximately [redacted] per QALY when compared to ofatumumab.

In Table 47 and Table 48, the results of the pairwise comparisons for the highly active and rapidly-evolving severe RRMS populations are reported. In the highly active RRMS population, ofatumumab was [redacted] against cladribine and fingolimod treatment, and was [redacted] alemtuzumab and ocrelizumab. In people living with rapidly-evolving severe RRMS, ofatumumab [redacted] cladribine, and was [redacted] all other drugs. The ICER for the comparison between ofatumumab and alemtuzumab was approximately [redacted]. In the other comparisons except with cladribine, the ICERs were [redacted].

Table 45. Base-case results at ofatumumab PAS price, RRMS population (deterministic)

Comparator	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
IFN β-1a (Avonex®)	Avonex® (IFN β-1a)	£306,413	5.09	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£314,016	5.66	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	£337,849	5.15	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£314,016	5.66	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	£302,300	4.92	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£314,016	5.66	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	Ocrelizumab	£341,622	5.72	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£314,016	5.66	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a (Rebif® 44)	Rebif® 44 (IFN β-1a)	£308,816	5.05	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£314,016	5.66	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	Teriflunomide	£326,125	4.89	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£314,016	5.66	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis; WTP, willingness-to-pay

Table 46. Incremental cost-effectiveness results, RRMS population (deterministic) (extracted from the company's economic model)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis

Table 47. Pairwise results, highly active RRMS population (deterministic)

Comparator	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB of £30,000 WTP
Alemtuzumab	Alemtuzumab	£326,872	5.46				
	Ofatumumab	£319,141	5.12				
Cladribine	Cladribine	£327,349	5.00			-	-
	Ofatumumab	£319,141	5.12				
Fingolimod	Fingolimod	£329,031	4.60			-	-
	Ofatumumab	£319,141	5.12				
Ocrelizumab	Ocrelizumab	£345,465	5.19			-	-
	Ofatumumab	£319,141	5.12				
[redacted]							

ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis; WTP, willingness-to-pay

Table 48. Pairwise results, rapidly-evolving severe RRMS population (deterministic)

Comparator	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB of £30,000 WTP
Alemtuzumab	Alemtuzumab	£327,707	6.14				
	Ofatumumab	£322,832	5.78				
Cladribine	Cladribine	£328,806	5.66				
	Ofatumumab	£322,832	5.78				
Natalizumab	Natalizumab	£361,933	5.82				
	Ofatumumab	£322,832	5.78				
Ocrelizumab	Ocrelizumab	£350,803	5.84				
	Ofatumumab	£322,832	5.78				
[redacted]							

ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis; WTP, willingness-to-pay

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analysis

The company undertook several deterministic one-way sensitivity analyses for ofatumumab versus each comparator for RRMS, HA RRMS and RES RRMS to identify the key inputs of the economic model and important sources of uncertainty. Where possible, lower and upper bounds were used, according to confidence intervals, reported in the literature. In all other cases (e.g. where the standard errors or confidence intervals were missing), bounds were assumed to be ±20% of the input value. The results are presented in the from of tornado plots and these plots show the top ten parameters whose impact on the net monetary benefit (NMB) results is the greatest. It was seen, in each plot, that the estimates of effectiveness on disability worsening for each DMT had the greatest impact on the ICER and NMB results at a £30,000 threshold. Apart from disability worsening, results were largely robust to parameter uncertainty. Figure 5 and Figure 6 report the results for the comparison between ofatumumab and ocrelizumab in the RRMS population.

[redacted]

5 [redacted]

[redacted]

6 [redacted]

In summary, a comprehensive list of model input parameters was included by the company in their deterministic sensitivity analyses to show which inputs were the key drivers of the economic analysis. The ERG considers this analysis to be appropriately undertaken. However, the ERG believes that while, these deterministic one-way sensitivity analyses suggest indications on the influence of single parameters on the cost-effectiveness results, these should be seen as 'stress tests' where the lower and upper values substituting a parameter may not be realistic. In

addition, it should be noted that these types of sensitivity analyses do not account for interrelations between parameters or the fact that more than one of these parameters will be uncertain at the same time.

5.2.2 Probabilistic sensitivity analysis

Results of the probabilistic sensitivity analyses are presented in Table 49 to Table 51 for the RRMS, highly active and rapidly-evolving severe RRMS populations, respectively. In the RRMS population, the PSA results are in line with the deterministic results.

Table 49. Incremental cost-effectiveness results, RRMS population (PSA)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis

Likewise, the PSA results for the highly active and rapidly-evolving severe RRMS populations are similar to the deterministic results.

Table 50. Incremental cost-effectiveness results, highly active RRMS population (PSA)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis

Table 51. Incremental cost-effectiveness results, rapidly-evolving RRMS population (PSA)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis

The company reported the results of the PSA in the from of a scatterplot (comparing ofatumumab vs each comparator) (see Figure 7) and CEACs (see Figure 8), respectively.

[redacted]

Figure 7. Probabilistic scatterplot on an incremental cost-effectiveness plane, RRMS population

[redacted]

Figure 8. Cost-effectiveness acceptability curve, RRMS population (applying PAS to ofatumumab)

Table 52 reports the probability of each DMT being cost-effective at a willingness-to-pay threshold of £30,000 per QALY. These results show that ofatumumab has a [redacted] probability of being cost-effective.

Table 52. Probability of each DMT being cost-effective, RRMS population

Disease modifying therapy	Probability of being cost-effective at £30,000/QALY WTP threshold
IFN β-1a (Avonex®)	[redacted]
Dimethyl fumarate	[redacted]
Glatiramer acetate	[redacted]
Ocrelizumab	[redacted]
Ofatumumab	[redacted]

IFN β-1a (Rebif® 44)	[redacted]
Teriflunomide	[redacted]
DMT, disease modifying therapy; QALY, quality-adjusted life year; RRMS, relapsing remitting multiple sclerosis; WTP, willingness-to-pay.	

The company has provided CEACs for the highly active and rapidly-evolving severe RRMS populations, with ofatumumab having a [redacted] and a [redacted] probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

ERG summary

The probabilistic analysis was undertaken to determine the joint uncertainty in the input parameters on the outcome of cost per QALY. The PSA assigned a parametric distribution to chosen model input parameters and the incremental results were calculated by randomly selecting values from each distribution. The ERG notes that these results were remarkably close to the deterministic results.

In the ERG's re-run of the company's PSA, it was noted that the analysis returned the same results for teriflunomide and IFNβ-1b (Rebif®). Given that these drugs have different costs, effects, and discontinuation rates, we considered there to be a technical error when calculating the PSA results for these drugs. The ERG corrected this error (see Appendix G, Table 26) and re-ran the company's PSA. The ERG's re-run of the company's PSA returned similar results.

5.2.3 Scenario analyses results

The company conducted a range of deterministic scenario analyses to examine the impact of each change to the base-case results and to evaluate the robustness of the ICER estimates. Alternative values for various parameters were considered to perform the following scenario analyses (see Table 53):

Table 53. Description of the company's scenario analyses in comparison to the base-case

Scenario	Base-case analysis	Scenario analysis
1. **Efficacy outcome measurement**	CDW-6 aligned criteria NMA	CDW-6 pre-defined criteria NMA
2. **Efficacy outcome measurement**	CDW-6 aligned criteria NMA	CDW-6 OPERA-aligned criteria NMA
3. **Natural history**	The British Columbia matrix for RRMS,	The same British Columbia

Scenario	Base-case analysis	Scenario analysis
transition matrix	the SPMS matrix from EXPAND plus London Ontario from the ongoing NICE appraisal of siponimod [ID1304][9]	matrix for both RRMS and SPMS
4. **Natural history transition matrix**	The British Columbia matrix for RRMS, the SPMS matrix from EXPAND plus London Ontario from the ongoing NICE appraisal of siponimod [ID1304][9]	The London Ontario matrices for RRMS and SPMS in line with TA254[17]
5. **Relapse rate**	EDSS-dependent relapse rates	Relapse rate independent of EDSS
6. **Mortality multiplier**	An EDSS-dependent mortality multiplier from Pokorski (1997)[54]	An EDSS-independent mortality multiplier from Jick et al. (2014)[64]
7. **All-cause discontinuation rates**	Time-constant discontinuation	The Weibull distribution as the best-fitting time-dependent discontinuation extrapolation curve
8. **Health state utility values**	Health state utility values derived from the ASCLEPIOS trials (EDSS 0 – 6) supplemented with Orme et al. (2007)[7] (EDSS 7–9)	Health state utility values from Orme et al. (2007)[7]
9. **Alemtuzumab retreatment (HA and RES RRMS populations only)**	Alemtuzumab treatment to cease after Year 2	Inclusion of alemtuzumab retreatment in Years 3, 4 and 5
10. **Alemtuzumab and cladribine discontinuation rates (HA and RES RRMS populations only)**	All-cause discontinuation rates from the NMA	Alemtuzumab and cladribine annual discontinuation rates were set equal to ofatumumab

CDW-6, six-month confirmed disability worsening; EDSS, expanded disability status scale; HA, highly active; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RES, rapidly-evolving severe; RRMS. relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Scenario analyses suggested that ofatumumab remained cost-effective in all scenarios for the RRMS population (see Section 3.8.4 and Table 92 in the CS document B for further detail). The most significant effect on findings was from the NMA undertaken with the ASCLEPIOS pre-defined CDW-6 data (see Table 54). Analyses related to the HA and RES RRMS subgroup populations showed that ofatumumab was cost-effective versus all comparators apart from alemtuzumab. Also, in the additional scenarios allowing an additional course of alemtuzumab, and assuming equal annual discontinuation rates for ofatumumab as for alemtuzumab and cladribine, ofatumumab was cost-effective in all comparisons in the HA RRMS population and it was cost effective versus cladribine in the RES RRMS population (see Section 3.8.4 and Tables 93 and 94 in the CS Document B for further detail).

Table 54. Scenario analyses results at ofatumumab PAS price in the RRMS population (reproduced from CS document B, Table 92)

Comparator	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Efficacy estimate: CDW-6 (pre-defined criteria NMA)							
IFN β-1a (Avonex®)	IFN β-1a (Avonex®)	£306,413	5.09	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£316,564	5.51	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	£337,849	5.15	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£316,564	5.51	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	£302,300	4.92	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£316,564	5.51	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	Ocrelizumab	£342,057	5.69	[redacted]	[redacted]	-	-
	Ofatumumab	£316,564	5.51	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a (Rebif® 44)	IFN β-1a (Rebif® 44)	£308,816	5.05	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£316,564	5.51	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	Teriflunomide	£325,779	4.91	[redacted]	[redacted]	[redacted]	[redacted]
	Ofatumumab	£316,564	5.51	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] **Abbreviations**: CDW-6: 6-month confirmed disability worsening; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; NMB: net monetary benefit; PAS, patient access scheme; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay

Additional analyses run in response to the ERG's clarification questions included: (i) a scenario using the coefficient values from Orme et al.(2007)[7] for male sex and time since diagnosis (see the response to clarification question B10 including Tables 22-24 in the CS document clarification responses for further detail); (ii) a scenario applying the coefficients for sex and time since diagnosis from the ASCLEPIOS trials (see the response to clarification question B10 including Tables 25-27 in the CS document clarification responses for further detail); (iii) a scenario to explore the effect of AE incidence on the ICER.

The AE incidence for ofatumumab was maintained as in the base case while the incidence of all AE in all comparators was set to zero (see the response to clarification question B15 including Tables 29-31 in the CS document clarification responses for further detail); and (iv) two scenarios to allow exploration of the impact of waning in the model on the ICERs. These were 1) an extremely conservative scenario: a precipitous 50% reduction in effectiveness was applied after 5 years; 2) a conservative scenario: a 25% reduction in effectiveness was applied after 5 years, then a 50% reduction after 8 years was used (see the response to clarification question B18 including Tables 34-36 in the CS document clarification responses for further detail). All scenarios were conducted for the RRMS, HA RRMS and RES RRMS populations. The effect of scenarios (i); (ii); (iii); and (iv) on the ICERs was negligible in all three populations and the changes did not affect any of the conclusions of cost-effectiveness drawn.

In general, the results accurately reflect the changes made in each scenario analysis. However, the ERG notes that no scenario analysis was conducted on management costs. Using alternative values might have resulted in a change to the base-case ICER.

5.3 Model validation and face validity check

Model validity comprised clinical and health economic opinion for the development of the model structure, inputs and assumptions. Additionally, the company sought guidance from previous NICE technology MS appraisals undertaken between 1999 and 2019. The company stated that cross validation of the outputs was not

undertaken due to the presence of confidential PAS discounts for various DMTs. Several tests on the model were undertaken for internal technical validation and quality assurance.

The ERG considers the steps taken for model validation and internal validation to be appropriate. However, with respect to model cross validation, the company could compare outcomes across models for DMTs, where possible, or present results based on list prices.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG provided a summary and critique of the company's economic model (see Section 4.2). Based on our critique we have made some changes to the inputs with justifications, to explore the impact of each change to the company's base-case results. Here we report the suggested change, provide our justification and cross-reference to the relevant section of this report where our concern was discussed.

- Disease management costs associated with SPMS from TA320[59] and inflated to 2018/19 cost year (Table 55)

Table 55. Disease management costs considered in the model (reproduced from CS document B, Table 80) and ERG preferred values

EDSS	Direct medical costs, inflated to 2018–2019 (base-case)	SPMS-specific management costs for SPMS[5] (ERG preferred values)	Justification
0	£994	£1,339	For consistency with other recent technology appraisals,[5] the ERG suggest that SPMS-specific disease management costs which differ from those associated with treating people with RRMS should have been included in the economic analysis. (see Section 4.3.8.3)
1	£1,033	£1,380	
2	£757	£1,103	
3	£4,143	£4,489	
4	£2,007	£2,353	
5	£3,405	£3,751	
6	£4,545	£4,890	
7	£11,963	£12,308	
8	£29,137	£29,483	
9	£23,314	£23,661	
10	£0	£0	
SPMS, secondary progressive multiple sclerosis			

- Transition probabilities from RRMS to SPMS obtained from TA624[5] (Table 56)

Table 56. Transition probabilities from RRMS to SPMS obtained from TA624[5]

EDSS	Probabilities		Justification
	TA254[17] (Base-case)	TA624[5] (ERG preferred values)	
0	0	0.0040	For consistency with a recent MS technology appraisal (TA624)[5] and a previous health technology assessment (TA527),[6] the ERG suggests that transition probabilities from RRMS to SPMS obtained from these previous appraisals are more appropriate to be used in the economic analysis. (see Section 4.3.6.3)
1	0.0452	0.0020	
2	0.0737	0.0290	
3	0.0939	0.0970	
4	0.1192	0.1810	
5	0.1508	0.2250	
6	0.1898	0.1680	
7	0.2374	0.2110	
8	0.2945	0.0640	
9	1.0000	0.1540	
10	0.0000	0.0000	

EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal

- Annualised relapse rates for a natural history cohort from TA527[6] (Table 57)

Table 57. Annualised relapse rates for a natural history cohort, using UK MS Survey, Patzold and Pocklington 1982 and EXPAND; and values from alternative sources

EDSS	ARR, using MS Survey and Patzold and Pocklington (Patzold and Pocklington, 1982)[18, 66] (base-case)	ARR, using MS Survey, Patzold and Pocklington (Patzold and Pocklington, 1982) and EXPAND[9, 18, 66] (base-case)	ARR, using TA527 assessment [6] (ERG preferred values)		Justification
	RRMS	SPMS	RRMS	SPMS	
0	0.71	0.00	0.8895	0.0000	Values shown here are for the annual relapse frequency by EDSS for a natural history cohort (i.e. in the absence of DMTs). The values used by the company for RRMS show that there is a steady decrease in the annual relapse rates. Those used for SPMS show that at more severe EDSS levels, there is a greater frequency of relapses when compared to less severe EDSS levels. The ERG is aware of other relapse
1	0.73	0.00	0.7885	0.0000	
2	0.68	0.47	0.6478	0.6049	
3	0.72	[redacted]	0.6155	0.5154	
4	0.71	[redacted]	0.5532	0.4867	
5	0.59	[redacted]	0.5249	0.4226	
6	0.49	[redacted]	0.5146	0.3595	
7	0.51	[redacted]	0.4482	0.3025	
8	0.51	[redacted]	0.3665	0.2510	
9	0.51	[redacted]	0.2964	0.2172	

					frequencies values reported in TA527[6] assessment, which are based on the British Columbia cohort. These values show that annual relapse rates decrease as EDSS levels increase. (see Section 4.3.6.11)

ARR, annualised relapse rates; EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

- Health state utility values from Orme et al. (2007)[7] for people living with SPMS (Table 58)

Table 58. Health state utility values, by EDSS

EDSS	ASCLEPIOS trials and Orme et al. 2007[7] (Base-case)		ASCLEPIOS trials and Orme et al. 2007[7] (ERG preferred values)	Orme et al. 2007[7] (ERG preferred values)	Justification
	RRMS	SPMS	RRMS	SPMS	Orme et al. (2007)[7] has shown that utility values are lower in people with more progressive (SPMS and PPMS) forms of MS, which concurs with the clinical experience of our clinical advisor. Additionally, given that there were only [redacted] of participants with active SPMS included in the ASCLEPIOS trials, the ERG consider that the utility values for the SPMS population may not be generalizable. Hence, using the utility values from Orme et al. (2007)[7] for SPMS may be more appropriate. (see Section 4.3.7)
0	[redacted]	[redacted]	[redacted]	0.8250	
1				0.7540	
2				0.6600	
3				0.5290	
4				0.5650	
5				0.4730	
6				0.4130	
7	0.297	0.252	0.297	0.2520	
8	-0.049	-0.094	-0.049	-0.0940	
9	-0.195	-0.240	-0.195	-0.2400	

EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)

The company provided justification to support no waning of the treatment effect (see Section 4.3.6.12). However, for consistency with other recent technology appraisals and the lack of long-term follow-up information, the ERG supports a precautionary approach of using a conservative assumption of waning of the treatment effect, which the effectiveness wanes with a 25% reduction after five years, then a 50% reduction after eight years.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Here we present the results following the ERG's suggested changes to the company's model inputs and the impact of each change to the company's base-case results for the RRMS population. Incremental results for the HA RRMS and RES RRMS populations are presented in Appendix E.

6.2.1 Relapsing-remitting multiple sclerosis population

- SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year (see Table 59)

Table 59. Exploratory analysis results, using SPMS-specific disease management costs from TA320[59]

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years; SPMS, secondary progressive multiple sclerosis

- Probability of progressing from RRMS to SPMS from TA624[5] (see Table 60)

Table 60. Exploratory analysis results, transition probability of progressing from RRMS to SPMS from TA624[5]

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)

ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

- Annualised relapse rates for a natural history cohort obtained from TA527[6] (see Table 61)

Table 61. Exploratory analysis results, using annualised relapse rates from TA527[6]

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)

ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

- Health state utility values from Orme et al. (2007)[7] for people living with SPMS (see Table 62)

Table 62. Exploratory analysis results, using health state utility values from Orme et al. (2007)[7] for people living with SPMS

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)

ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years; SPMS, secondary progressive multiple sclerosis

- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years) (see Table 63)

Table 63. Exploratory analysis results, using a waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

ERG Summary

In the majority of the exploratory analyses, the base-case model results were robust to each individual change made to the company's model inputs. In the RRMS population, ofatumumab compared to ocrelizumab continued being the [redacted] option. The assumption of a waning of the treatment effect (25% reduction after Year 5, then 50% reduction after Year 8) had the greatest impact to the ICER but remained [redacted].

In all other populations, results were robust to these individual changes.

6.3 ERG's preferred assumptions

The ERG's base-case analysis compares ofatumumab (inclusive of PAS) versus comparators (using PAS for company's comparator drug and list prices elsewhere) for people with RRMS. In Table 64, we present a summary of the ERG's preferred assumptions. In Table 65 to Table 66, we present, the deterministic results (pairwise and incremental) for the RRMS, HA and RES RRMS populations using the ERG's preferred assumptions.

Table 64. ERG's preferred model assumptions

Preferred assumption	Section in ERG report
Company base-case	
SPMS-specific disease management costs from TA320[59]	Section 4.3.8.3
Transitions from RRMS to SPMS from TA624[5]	Section 4.3.6.3
Annualised relapse rates for a natural history cohort from TA527[6]	Section 4.3.6.11
Health state utility values from Orme et al. (2007)[7] for people living with SPMS	Section 4.3.7
Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)	Section 4.3.6.12

6.3.1 ERG base-case deterministic results

In Table 65 we report the results of the pairwise comparison between ofatumumab versus all comparators for the RRMS. These results show that ofatumumab [redacted] dimethyl fumarate and teriflunomide, by [redacted]. For the comparison against ocrelizumab, ofatumumab was [redacted]. These results are mirrored in the NMB results, with these three comparisons [redacted]. Against all other comparators, ofatumumab was [redacted]. In Table 66 we report the incremental results for the RRMS, which shows that [redacted], ofatumumab compared to glatiramer acetate was [redacted].

Table 65. Pairwise results for the RRMS population, using the ERG preferred assumptions

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £20,000 WTP	NMB at £30,000 WTP
Ofatumumab	[redacted]						
IFN β-1a (Avonex®)							
Dimethyl fumarate							
Glatiramer acetate							
Ocrelizumab							
IFN β-1a (Rebif® 44)							
Teriflunomide							
[redacted]							

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; IFN, interferon; NMB, net monetary benefit; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis; WTP, willingness-to-pay

Table 66. ERG base-case deterministic results for people with RRMS (Incremental)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ERG, Evidence review group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

In Table 67 and Table 68, we present the deterministic results for the HA RRMS population using the ERG's preferred assumptions. In Table 67, we present the pairwise comparison between ofatumumab against all comparators, separately. These results show that ofatumumab is [redacted] against cladribine and fingolimod and is [redacted] against alemtuzumab and ocrelizumab. We also present the NMB results, assuming a £20,000 and £30,000 WTP per unit increase of effectiveness. Under both WTP thresholds, ofatumumab versus all parameters, individually, was [redacted]. In Table 68, we present the incremental results, and these show that

ofatumumab is [redacted] against [redacted] cladribine and fingolimod and, alemtuzumab [redacted] ocrelizumab. [redacted], alemtuzumab is approximately [redacted] ofatumumab and expected to yield [redacted] QALYs, which equates [redacted].

Table 67. Pairwise results for the HA RRMS population, using the ERG preferred assumptions

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £20,000 WTP	NMB at £30,000 WTP
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

ERG, Evidence review group; HA RRMS, highly active relapsing remitting multiple sclerosis, ICER, Incremental cost-effectiveness ratio; IFN, interferon; NMB, net monetary benefit; QALY, Quality adjusted life years; WTP, willingness-to-pay

Table 68. Incremental results for the HA RRMS population, using the ERG preferred assumptions

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; HA RRMS, highly active relapsing remitting multiple sclerosis; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

In Table 69 and Table 70, we present the deterministic results for the RES RRMS population using the ERG's preferred assumptions. In Table 69, we present the pairwise comparison between ofatumumab against all comparators, separately. These results show that ofatumumab [redacted] cladribine and is [redacted] all other comparators. We also present the NMB results, assuming a £20,000 and £30,000 WTP per unit increase of effectiveness. At a WTP threshold of £20,000 against all comparators, ofatumumab was [redacted]. In Table 70, we present the incremental results, and these show that ofatumumab [redacted] cladribine and, alemtuzumab [redacted] ocrelizumab and natalizumab. [redacted],

alemtuzumab was [redacted] ofatumumab, with [redacted].

Table 69. Pairwise results for the RES RRMS population, using the ERG preferred assumptions

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £20,000 WTP	NMB at £30,000 WTP
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

ERG, Evidence review group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; NMB, net monetary benefit; QALY, Quality adjusted life years; RES RRMS, rapidly-evolving severe relapsing remitting multiple sclerosis; WTP, willingness-to-pay

Table 70. Incremental results for the RES RRMS population, using the ERG preferred assumptions

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years; RES RRMS, rapidly-evolving severe relapsing remitting multiple sclerosis

6.4 ERG Sensitivity analyses

6.4.1 ERG Deterministic one-way sensitivity analysis results

We undertook one-way sensitivity analysis for the comparison between ofatumumab and ocrelizumab and report the results in the form of tornado diagrams based on the NMB and ICER (see Figure 9 and Figure 10). In both figures, results were robust to the key input parameters except for treatment efficacy.

[redacted]

[redacted]

[redacted]

[redacted]

6.4.2 ERG Probabilistic sensitivity analysis results

The probabilistic sensitivity analysis results are presented in Table 71. In addition, these results are presented in the form of a scatterplot on a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) in Figure 11 and Figure 12, respectively. In terms of the expected total costs and total QALYs, the probabilistic results in Table 71 are similar to the deterministic results presented in Table 66.

Table 71. ERG probabilistic results for people with RRMS (Incremental)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ERG, Evidence review group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

Each iteration of the incremental costs and incremental benefits of ofatumumab versus all comparators was plotted on an incremental cost-effectiveness plane as shown in Figure 11. These results show that there is some correlation between the costs and benefits. Additionally, a proportion of the iterations for the comparison between ofatumumab and ocrelizumab are in the [redacted] quadrant, indicating that ofatumumab is [redacted].

11 [redacted]

Figure 12 shows the results of the PSA in the form of a CEAC for all DMTs. The curves show the proportion of iterations in which treatments are cost-effective at different WTP thresholds for a QALY. These results show that at a WTP threshold of £30,000 per QALY ofatumumab has a [redacted] probability of being cost-effective.

12 [redacted]

6.4.3 ERG Scenario analyses

The ERG undertook further analyses to assess the impact to the ERG's base-case ICER by individually making changes to our assumptions. The following changes were made in scenario analyses for RRMS, HA RRMS, and RES RRMS. Results for the HA RRMS and RES RRMS populations are presented in Appendix F.

6.4.3.1 Relapsing remitting multiple sclerosis population

- Caregivers' disutilities obtained from Acaster et al. (2013)[68] (see Table 72)

Table 72. ERG scenario analysis results, using caregivers' disutilities from Acaster et al. (2013)[68]

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

- Mortality multipliers from Jick et al. (2014)[64] (see Table 73)

Table 73. ERG scenario analysis results, using mortality multipliers from Jick et al. (2014)[64]

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

- Mortality multipliers from Kingwell et al. (2012)[65] (see Table 74)

Table 74. ERG scenario analysis results, using mortality multipliers from Kingwell et al. (2012)[65]

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

- No waning of the treatment effect (see Table 75)

Table 75. ERG scenario analysis, applying a no waning of the treatment effect

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					

ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

- Waning of the treatment effect (50% reduction after 5 years) (see Table 76)

Table 76. ERG scenario analysis, applying a waning effect (50% reduction after 5 years)

Treatments	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ERG, Evidence Review Group; ICER, Incremental cost-effectiveness ratio; IFN, interferon; QALY, Quality adjusted life years

In summary, several scenario analyses of the ERG's base-case were undertaken to explore the impact to the ICER. In general, results were robust to these individual changes made to the ERG's preferred assumptions.

6.5 Conclusions of the cost effectiveness section

The company's economic analysis was based on a discrete-time cohort Markov model programmed in Microsoft Excel. The ERG considered that the type and structure of the submitted model was appropriate for the purposes of the MS condition investigated and suitable for the decision problem in this appraisal. The model captured the key features (movement between EDSS levels and progression from RRMS to SPMS) for patients living with RRMS. The intervention and outcomes included in the company submission were similar to those outlined by NICE. However, the ERG considered that the comparators described in the CS partially matched the comparators described in the NICE Final Scope[8] for treatment of people with RRMS. The anticipated MA for ofatumumab was for all RMS patients which is partially consistent with the evidence provided by the company. The company restricted the population, and therefore the comparators, to patients with RRMS only.

Appropriate methods were used to identify information to populate the economic model, with the clinical information for ofatumumab obtained from the ASCLEPIOS trials, and treatment efficacy derived from an NMA, based on the aligned criteria for ASCLEPIOS I & II. The company stated that the pivotal trial evidence for patients with active SPMS represent only a small proportion of patients in the trial ([redacted]) and therefore, supplementary evidence from alternative SPMS populations was used in the cost-effectiveness analysis. The resource use and costs were in keeping with the viewpoint of the economic analysis, with information obtained from published sources and using current prices. To have a workable model the company made some simplifying assumptions, which were plausible.

Under the company's assumptions and the economic model used, the base-case pairwise deterministic results for RRMS showed that there were modest gains in QALYs across all DMTs. Ofatumumab was [redacted] against two alternative treatment strategies (dimethyl fumarate and teriflunomide) and was [redacted] against three treatment strategies (IFN β-1a [Avonex], IFN β-1a [Rebif® 44 mcg] and glatiramer acetate), but it was [redacted] ocrelizumab. The company's incremental results for RRMS showed that ofatumumab was [redacted] against dimethyl fumarate and teriflunomide. When compared to glatiramer acetate [redacted]. Ocrelizumab was [redacted] treatment strategy, [redacted] when compared to ofatumumab.

In the HA RRMS population, the company's pairwise deterministic results showed that ofatumumab was [redacted] against cladribine and fingolimod treatment, and was [redacted] alemtuzumab and ocrelizumab. The company pairwise deterministic results for the RES RRMS population showed that ofatumumab was [redacted] against cladribine, and was [redacted] all other drugs.

The company's PSA results for RRMS showed that ofatumumab has a [redacted] probability of being cost-effective at a WTP threshold of £30,000 per QALY. The ERG noted that the company's probabilistic sensitivity analysis results were remarkably close to the deterministic results.

The ERG made some amendments to the company's economic model inputs, which formed the basis for the ERG's base-case model. These changes resulted in

differences between the company's base-case results and those reported by the ERG. The company's results were presented based on using the PAS price for ofatumumab and fingolimod and list prices for all other comparators, and this was the basis/approach to the ERG's analysis.

The ERG's amendments using alternative sources of information are provided:

- SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year
- Transition probabilities from RRMS to SPMS obtained from TA624[5]
- Annualised relapse rates for a natural history cohort from TA527[6]
- Health state utility values from Orme et al.[7] for people living with SPMS
- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)

In general, the company's results were robust to individual changes made by the ERG, with the inclusion of waning of the treatment effect having the greatest impact to the ICER. Based on the changes made simultaneously, the ERG pairwise deterministic results for RRMS showed that ofatumumab [redacted] dimethyl fumarate and teriflunomide, by [redacted]. For the comparison against ocrelizumab, ofatumumab was [redacted]. These results were mirrored in the NMB results, with these three comparisons [redacted]. The ERG base-case incremental results for RRMS showed that [redacted], ofatumumab compared to glatiramer acetate was [redacted].

Using the ERG's preferred assumptions in the HA RRMS and RES RRMS populations, the results showed that ofatumumab and alemtuzumab were the [redacted] treatments, with [redacted], respectively.

The ERG PSA results for RRMS demonstrated that at a WTP threshold of £30,000 per QALY ofatumumab had a [redacted] probability of being cost-effective. However, it should be noted that these results were based on the PAS price for ofatumumab and fingolimod and list prices for all other comparators; hence the analysis does not incorporate commercial agreements between the companies and the Department of Health for the other comparators.

7 END OF LIFE

The intervention is not considered relevant to meet end of life criteria published by NICE.

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9 ERG Appendices

Appendix A: ERG quality assessment of the ASCLEPIOS trials using the Cochrane RoB tool

Appendix B: Flow-charts of participants through the ASCLEPIOS I & II trials

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ERG Clinical Effectiveness Appendices

9.1 Appendix A: ERG quality assessment of the ASCLEPIOS trials using the Cochrane RoB tool

Table 1. ERG quality appraisal of ASCLEPIOS trials using Cochrane RoB tool

Risk of Bias category	Judgement	Rationale
Randomisation	Low	A patient randomisation list was produced by the Interactive Response Technology provider using a validated system that automated the random assignment of patient numbers to randomisation numbers, which were then linked to the different treatment arms and to medication numbers. A separate medication list was produced by Novartis Drug Supply Management, using a validated system that automated the random assignment of medication numbers to packs containing each of the trial drugs[24]
Allocation concealment	Low	See rationale under 'randomisation'
Are participants blinded?	Low	Double-dummy design (i.e. appropriate matched placebo medication) was used
Are caregivers blinded?	Low	Double-dummy design ensured that all staff were blinded from the time of randomization[24]
Blinding of assessors	Low	MRI scans were analysed independently at a central reading centre by staff blinded to treatment group assignments. All EDSS scores were rated by independent evaluating physician who were unaware of treatment group assignments and not otherwise involved in the clinical management of the patient[24]
Incomplete outcome data	Moderate	Outcome analyses excluded patients who had missing values for covariates or completely missing values for post-baseline assessments (based on response to clarification priority question A2). However, sensitivity analyses included all patients randomised at baseline.
Selective reporting	Low	All specified outcomes were reported.

Risk of Bias category	Judgement	Rationale
Other biases	Low	The trials were conducted by the drug manufacturer, and although this introduces an unclear risk of bias, it is standard for this type of trial so the ERG has judged this to pose a low risk.
Overall risk of bias	Low	

9.2 Appendix B: Flow-charts of participants through the ASCLEPIOS I & II trials

Flow-charts of participants through the ASCLEPIOS I are provided in Figure 1.

Figure 1: Participant flow through ASCLEPIOS I trial[a]

OMB: ofatumumab; TER: teriflunomide
[a]From CS Appendix D, pg.141.

Flow-charts of participants through the ASCLEPIOS II are provided in Figure 2.

Figure 2: Participant flow through ASCLEPIOS II trial[a]

OMB: ofatumumab; TER: teriflunomide
[a]From CS Appendix D, pg.142.

9.3 Appendix C: OPERA-aligned criteria for CDW

The OPERA-aligned criteria for CDW uses the definition for confirmed disability worsening that was used in the OPERA trials which assessed the efficacy of ocrelizumab, as ocrelizumab was a key compactor in this submission.

Table 2 presents the scenario NMA results for ofatumumab versus each of the comparators, and the relative rankings of all of the DMTs.

For the CDW-3 outcome, [redacted] efficacy compared to ofatumumab. The HR was [redacted] to the base case NMA for alemtuzumab. In this scenario NMA, [redacted].

For the CDW-6 outcome, [redacted] efficacy compared to ofatumumab. The HRs was [redacted] to the base case NMA across all of the treatments, except for natalizumab and ocrelizumab where [redacted].

Table 2: Scenario NMA results using the OPERA-aligned criteria for CDW

OPERA-aligned	CDW-3		CDW-6	
	HR (95% CrI)	Rank	HR (95% CrI)	Rank
Ofatumumab vs:	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a IM	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 22	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 44	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1b SC 250	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14	[redacted]	[redacted]	[redacted]	[redacted]

* Calculated by inversing the HR and 95% CrI in Figure 32/34
Abbreviations: ARR: annualised relapse rate; CDW: confirmed disability worsening; IM: intramuscular; SC: subcutaneous; HR: hazard ratio; CrI: credible interval

9.4 Appendix D: Assessing the transitivity between ASCLEPIOS trials and other key trials in the NMA evidence networks

Findings of the detailed ERG assessment are presented in Table 3-5.

Table 3: Risk of bias (Low, Medium, High or Unclear RoB)

Item	TEMSO	TOWER	TENERE	OPERA I and II
Randomisation	*Judgement:* ***Low*** *Rationale: Eligible patients were randomly assigned to each arm of the study on 1:1:1 ratio. Randomisation was stratified by baseline EDSS (≤3.5 or >3.5) and trial site, with a block size of 6. No further information was provided on logistics of the randomisation.*	*Judgement:* ***Low*** *Rationale: Eligible patients were randomly assigned to each arm of the study on 1:1:1 ratio, stratified by baseline EDSS (≤3.5 or >3.5) and trial site. Randomisation was done centrally, via interactive voice recognition system that generated allocation sequence using permuted-block randomisation schedule.*	*Judgement:* ***Low*** *Rationale: Eligible patients were randomly assigned to each arm of the study on 1:1:1 ratio, stratified by baseline EDSS (≤3.5 or >3.5) and country. No further information was provided on logistics of the randomisation.*	*Judgement:* ***Low*** *Rationale: Eligible patients were randomly assigned to each arm of the study on 1:1 ratio. Randomisation was done centrally, via independent interactive web-response system.*
Allocation concealment	*Judgement:* ***Medium*** *Rationale: Randomisation was stratified by baseline EDSS (≤3.5 or >3.5) and trial site, with a block size of 6. The constant block size of 6 increases the risk of predicting which arms of the study a patient will be allocated.*	*Judgement:* ***Unclear*** *Rationale: Randomisation was done centrally, via interactive voice recognition system that generated allocation sequence using permuted-block randomisation schedule. It is unclear if the block sizes were known to investigators which would increase risk of unblinding.*	*Judgement:* ***Unclear*** *Rationale: Unclear what step was taken to ensure allocation concealment as details of randomisation process was not provided.*	*Judgement:* ***Low*** *Rationale: Randomisation was done centrally, via independent interactive web-response system.*
Are participants blinded?	*Judgement:* ***Low*** *Rationale: The study used double-blind, placebo-controlled study design (no further information was provided but ERG assumes appropriate matched placebo medication was used).*	*Judgement:* ***Low*** *Rationale: Patients, individuals administering interventions and those assessing the outcomes were masked to treatment allocation. Placebo and drugs given once-daily orally were identical in taste and appearance.*	*Judgement:* ***Unclear*** *Rationale: Patients were randomised 1:1:1 to Teriflunomide 7mg or* *14mg (double-blind) or IFNβ-1a (open-label) – suggesting that those in the IFNB-1a were known both to patients and investigator. ERG assumes that patients in Teriflunomide were blinded (double-blinded) to dose but no details of blinding was discussed in the trial paper.*	*Judgement:* ***Low*** *Rationale: Patients in each arm of the study received matching subcutaneous or intravenous placebo as appropriate and they all received the 100mg dose of methylprednisolone before each infusion.*

Are caregivers blinded?	*Judgement:* ***Low-medium*** *Rationale: Both treating and examining neurologists were unaware of treatment assignments. Although treating clinicians was aware of side effects that could potentially be related to active therapy, ERG consider the risk of unblinding from this to be low/medium*	*Judgement:* ***Low*** *Rationale: Patients, individuals administering interventions and those assessing the outcomes were masked to treatment allocation. Placebo and drugs given once-daily orally were identical in taste and appearance.*	*Judgement:* ***Medium*** *Rationale: Patients were randomised 1:1:1 to Teriflunomide 7mg or* *14mg (double-blind) or IFNβ-1a (open-label) –the treating neurologist who was responsible for patient selection, medication administration, managing AEs, and relapse and safety assessments appear not to be blinded to drug treatment.*	*Judgement:* ***Low*** *Rationale: Each site had a separate treating and examining investigators, all of whom were blinded to treatment allocation all through the study. MRI scans were analysed centrally by personnel who were blinded to treatment allocation.*
Blinding of assessors	*Judgement:* ***Low*** *Rationale: The independent examining neurologists who assessed EDSS scores and assessed functional systems was unaware of treatment assignments.*	*Judgement:* ***Low*** *Rationale: Patients, individuals administering interventions and those assessing the outcomes were masked to treatment allocation. Placebo and drugs given once-daily orally were identical in taste and appearance.*	*Judgement:* ***Low*** *Rationale: Patients were randomised 1:1:1 to teriflunomide 7mg or* *14mg (double-blind) or IFNβ-1a (open-label) – The examining neurologist (who scored the functional system and EDSS) remained blinded to treatment and* *associated AEs.*	*Judgement:* ***Low*** *Rationale: Each site had a separate treating and examining investigators, all of whom were blinded to treatment allocation all through the study. MRI scans were analysed centrally by personnel who were blinded to treatment allocation*
Incomplete outcome data	*Judgement:* ***Low*** *Rationale: All analyses were performed using a modified intention-to-treat principle, the modification included all patients randomised at baseline who were exposed to study medications for at least 1 day. This modification may have affected the effect of randomisation however only two patients were excluded because of this modification.*	*Judgement:* ***Low*** *Rationale: All analyses were performed using a modified intention-to-treat principle, the modification included all patients randomised at baseline, who were also exposed to study medications for at least 1 day. This modification may have affected the effect of randomisation however only four patients were excluded because of this modification.*	*Judgement:* ***Low*** *Rationale: All efficacy analyses were performed using intention-to-treat principle, which included all randomised* *Patients. The safety analysis included all randomised patients exposed to study medication.*	*Judgement:* ***Low*** *Rationale: All efficacy analyses were performed using intention-to-treat principle. Endpoint of no disease activity used modified ITT which excluded patients who withdrew from the trial for reasons other than death or efficacy failure and had no disease activity at the time of discontinuation.*
Selective	*Judgement:* ***Low***	*Judgement:* ***Low***	*Judgement:* ***Low***	*Judgement:* ***Low***

reporting	*Rationale: All specified outcomes were reported.*	*Rationale: All specified outcomes were reported.*	*Rationale: All specified outcomes were reported.*	*Rationale: All specified outcomes were reported.*
Other biases	*Judgement:* ***Unclear*** *Rationale: The trials data were analysed by the drug manufacturer and it is not clear if they were blinded.*	*Judgement:* ***Unclear*** *Rationale: The trials data were analysed by the drug manufacturer and it is not clear if they were blinded.*	*Judgement:* ***Unclear*** *Rationale: The trial was conducted by the drug manufacturer*	*Judgement:* ***Medium*** *Rationale: Adjustment to infusion rate and treatment of symptoms during infusion were permitted to manage infusion-related reactions. This could potentially have resulted in unblinding (for treating clinicians) especially as more patients in one arm of the treatment had more infusion-related reactions which could potentially be related to therapy. Also, the trial was conducted, and data analysed by the drug manufacturer.*
Overall RoB	*Low*	Low	Low	Low

Table 4: Comparability with ASCLEPIO trials (Identical, Comparable but some issues, Not comparable)

Item	TEMSO	TOWER	TENERE	OPERA I and II
Study overview	*RCT with 1,088 MS patients randomly assigned, in a 1:1:1 ratio, to placebo or 7mg Teriflunomide or 14mg Teriflunomide for 108 weeks.*	*RCT with 1,169 MS patients randomly assigned, in a 1:1:1 ratio, to placebo or 7mg Teriflunomide or 14mg Teriflunomide for 48 weeks.*	*RCT with 324 MS patients randomly assigned, in a 1:1:1 ratio, to 7mg Teriflunomide or 14mg Teriflunomide or 44µg IFNβ-1a for 48 weeks.*	*RCT with 1,656 MS patients randomly assigned, in a 1:1 ratio, to 600mg Ocrelizumab or 44µg IFNβ-1a for 96 weeks.*
Patient selection criteria	*Judgement:* ***Comparable but some issues*** *Rationale: The study has selected patients using same age (18-55), similar MS criteria (McDonald 2005 vs version 2010), same EDSS (0-5.5) and same number of previous relapses (1 relapse in 1 year and 2 relapses in 2 years prior) as ASCLEPIOS studies.* *However, neurologically clinically stable (no relapses) period before randomisation was 1 month for ASCLEPIOS and 2 months (60 days) for TEMSO* *ASCLEPIOS also excluded patients based on previous DMT and washout period, but this exclusion was not applied for TEMSO*	*Judgement:* ***Comparable*** *Rationale: The study has selected patients using same age (18-55), similar MS criteria (McDonald 2005 vs version 2010), same EDSS (0-5.5) and same number of previous relapses (1 relapse in 1 year and 2 relapses in 2 years prior) and same neurologically stable period (30 days) and similar exclusion based on previous DMT (3 months washout period was for TOWER whilst ASCLEPIOS varies washout depending on the DMT) as ASCLEPIOS studies.*	*Judgement:* ***Comparable but some issues*** *Rationale: The study has selected patients using similar age (18 and over vs 18-55), similar MS criteria (McDonald 2005 vs version 2010), same EDSS (0-5.5) and similar exclusion based on previous DMT (3 months washout period was used for TENERE whilst ASCLEPIOS varies washout depending on the DMT) as ASCLEPIOS studies.* *Both studies have specified same neurologically stable period of 30 days for relapses however ASCLEPIOS specified the number of previous relapses permitted (1 relapse in 1 year and 2 relapses in 2 years prior to screening) but TENERE did not.*	*Judgement:* ***Comparable but some issues*** *Rationale: The study has selected patients using same age (18-55), same MS criteria (McDonald 2010), same EDSS (0-5.5) and same number of previous relapses (1 relapse in 1 year and 2 relapses in 2 years prior) as ASCLEPIOS studies.* *However, OPERA excluded primary progressive MS, excluded only B-cell DMTs and had additional criteria of disease duration of 10 years with EDSS ≤2.0 at screening. Although the studies used the same neurologically stable period (30 days), OPERA studies was 30 days before screening and randomisation whilst ASCLEPIOS was randomisation only.*
Study Population	*Judgement:* ***Comparable but some issues*** *Rationale: The study population for TEMSO and ASCLEPIOS has similar age (37.4-38.4 vs 37.8-38.9 years), similar female proportion (69.7-75.8% vs 66.3%-68.6%), similar time since 1st*	*Judgement:* ***Comparable but some issues*** *Rationale: The study population for TOWER and ASCLEPIOS has similar age (37.4-38.2 vs 37.8-38.9 years), similar female proportion (69-74% vs 66.3%-68.6%), similar time since 1st*	*Judgement:* ***Comparable but some issues*** *Rationale: The study population for TENERE and ASCLEPIOS has similar age (35.2-37 vs 37.8-38.9 years), similar female proportion (64.2%-70.3% vs 66.3%-68.6%), similar baseline EDSS*	*Judgement:* ***Comparable but some issues*** *Rationale: The study population for OPERA and ASCLEPIOS has similar age (36.9-37.4 vs 37.8-38.9 years), similar female proportion (65-67% vs 66.3%-68.6%), similar baseline EDSS*

	MS symptoms (8.6-8.8 vs 8.18-8.36 years), similar baseline EDSS (2.67-2.68 vs 2.86-2.97) and similar MS subgroups. *However, TEMSO has a higher mean number of relapses in previous 2 years (2.2-2.3 vs 0.7-0.9) and higher proportion with no previous DMTs (71.6% - 75.2% vs 38.2% to 41.1%)*	*MS symptoms (7.64- 8.18 vs 8.18-8.36 years), similar baseline EDSS (2.69-2.71 vs 2.86-2.97).* *TOWER has much fewer patients with SPMS (1% vs 5.1-6.1%) but has progressive relapsing MS patients which ASCELPIOS did not have. TOWER reported higher proportion with no previous DMTs in 2 years (65%-70% vs 38.2% to 41.1%) and a higher mean number of relapses in previous 2 years (2.1 vs 0.7-0.9)*	*(2.0-2.3 vs 2.86-2.97).* *TENERE has only one patient with SPMS (0.9% vs 5.1-6.1%) but has two progressive relapsing MS patients which ASCELPIOS does not have. TENERE reported lower time since 1st MS symptoms (6.6-7.7 years vs 8.18-8.36 years), higher mean number of relapses in previous 2 years (1.7 vs 0.7-0.9) and higher proportion with no previous DMTs in 2 years (76.0% to 88.3% vs 38.2% to 41.1%)*	*(2.75-2.86 vs 2.86-2.97) and similar mean number of relapses in previous 1 year (1.31-1.34 vs 1-2-1.3).* *OPERA has a lower time since 1st MS symptoms (6.25-6.74 vs 8.18-8.36 years), lower time since diagnosis (3.71-4.15 vs 5.48-5.77 years) and higher proportion with no previous DMTs in 2 years (71.4% to 75.3% vs 38.2% to 41.1%)*
Relapse Rate	*Judgement:* ***Identical*** *Rationale: TEMSO definition of ARR is identical to ASCLEPIOS studies based on clinical definition and change in EDSS. ARR was also the primary outcome in both studies and was powered appropriately. ARR was adjusted in both studies for varying treatment duration.*	*Judgement:* ***Comparable but some issues*** *Rationale: TOWER definition of ARR is similar to ASCLEPIOS studies based on clinical definition and change in EDSS. The only difference is that previous clinically stable period was not defined for TOWER but was 30 days for ASCELPIOS* *ARR was the primary outcome in both studies and was powered appropriately. ARR was adjusted in both studies for varying treatment duration.*	*Judgement:* ***Identical*** *Rationale: TENERE definition of ARR is identical to ASCLEPIOS study based on clinical definition and change in EDSS and were both adjusted for varying treatment duration. However, ARR was a secondary outcome in TENERE, powered to detect 36% relative reduction but both Teriflunomide doses saw an increase in ARR. The primary outcome used in TENERE was Time to failure (relapse or discontinuation).*	*Judgement:* ***Comparable but some issues*** *Rationale: OPERA definition of ARR is similar to ASCLEPIOS studies based on clinical definition and change in EDSS. However, ARR was not adjusted in OPERA studies for varying treatment duration as was specified in the protocol section 8.2.1).*
Sustained Disability progression	*Judgement:* ***Comparable but some issues*** *Rationale: TEMSO definition of sustained disability progression is similar to ASCLEPIOS studies, based on increase in EDSS score from baseline depending on the baseline score. The difference in TEMSO criteria*	*Judgement:* ***Comparable but some issues*** *Rationale: TOWER definition of sustained disability progression is similar to ASCLEPIOS studies, based on increase in EDSS score from baseline depending on the baseline score. The difference in TOWER*	*Judgement:* ***Not comparable*** *Rationale: Sustained disability progression was not reported in TENERE study*	*Judgement:* ***Comparable but some issues*** *Rationale: OPERA definition of sustained disability progression is similar to ASCLEPIOS study based on increase in EDSS score from baseline depending on the baseline score. The difference in OPERA criteria is that it*

	is that it required 1-point increase rather than 1.5-point increase for those with EDSS=0 at baseline. *ASCLEPIOS reported this measure at 3 months (12weeks) and at 24 months, but this was only reported at 3 months (12 weeks for TEMSO).*	*criteria is that it required 1-point increase rather than 1.5-point increase for those with EDSS=0 at baseline.*		*required 1-point increase rather than 1.5-point increase for those with EDSS=0 at baseline.* *OPERA also reported confirmed disability improvement at 12 weeks and this used a similar definition to ASCLEPIOS – the difference in OPERA is that it required a decrease of 0.5 points if the baseline EDSS was >5.5 compared with >6.5 for ASCLEPIOS*

Table 5: Outcome comparison with ASCLEPIOS trials

Item	ASCLEPIOS I	ASCLEPIOS II	TEMSO	TOWER	TENERE	OPERA I	OPERA II
Relapse rate							
Ofatumumab	0.11 ([redacted])	0.10 ([redacted])					
Teriflunomide 14 mg	0.22 ([redacted])	0.25 ([redacted])	0.37 (0.31, 0.44)	0.32 (0.27, 0.38)	0.26 (0.15, 0.44)		
Teriflunomide 7 mg			0.37 (0.32, 0.43)	0.39 (0.33, 0.46)	0.41 (0.27, 0.64)		
Interferon beta-1a					0.22 (0.11, 0.42)	0.29 (0.24, 0.36)	0.29 (0.23, 0.36)
Ocrelizumab						0.16 (0.12, 0.20)	0.16 (0.12, 0.20)
Placebo			0.54 (0.47, 0.62)	0.50 (0.43, 0.58)			
CDP-3 events at 96 weeks (24 months)							
Ofatumumab	10.9%						
Teriflunomide 14 mg	15.0%		20.2% (15.6, 24.7)	15.8% (11.2, 20.4)			
Teriflunomide 7 m g			21.7% (17.1, 26.3)	21.1% (16.1, 26.1)			
Interferon beta-1a						13.6%	
Ocrelizumab						9.1%	
Placebo			27.3% (22.3, 32.3)	19.7% (15.2, 24.1)			
CDP-6 events at 96 weeks (24 months)							
Ofatumumab	8.1%						
Teriflunomide 14 mg	12.0%						
Teriflunomide 7 mg							
Interferon beta-1a						10.5%	
Ocrelizumab						6.9%	
Placebo							

9.5 Appendix E: Impact of ERG's suggested changes on the company's base-case results

Here we present the results following the ERG's suggested changes to the company's model inputs and the impact of each change to the company's base-case results for HA RRMS and RES RRMS populations.

9.5.1 Highly active relapsing remitting multiple sclerosis population

- SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year (see Table 6)

Table 6: Exploratory analysis results, using SPMS-specific disease management costs from TA320[59]

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

- Transition probabilities from RRMS to SPMS obtained from TA624 (see Table 7)

Table 7. Exploratory analysis results, using transition probabilities from RRMS to SPMS obtained from TA624

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

- Annualised relapse rates for a natural history cohort from TA527 (see Table 8)

Table 8. Exploratory analysis results, using annualised relapse rates from TA527

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Health state utility values from (Orme et al., 2007) for people living with SPMS (see Table 9)

Table 9. Exploratory analysis results, using health state utility values from (Orme et al., 2007) for people living with SPMS

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years) (see Table 10)

Table 10. Exploratory analysis results, using waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

ERG summary

In the majority of the exploratory analyses for the HA RRMS population, the results were robust to each individual change made to the company's model inputs. Incremental results in Tables 6 to 9 show that treatment with alemtuzumab [redacted] cladribine, fingolimod and ocrelizumab. Incremental results in Table 10 show that ofatumumab [redacted] cladribine and fingolimod and, alemtuzumab [redacted] ocrelizumab. Alemtuzumab when compared to ofatumumab has an ICER of approximately [redacted] per QALY.

9.5.2 Rapidly-evolving severe relapsing remitting multiple sclerosis population

- SPMS-specific disease management costs from TA320[59] and inflated to 2018/19 cost year (see Table 11)

Table 11. Exploratory analysis results, using SPMS-specific disease management costs from TA320[59]

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

- Transition probabilities from RRMS to SPMS obtained from previous appraisals TA624 (see Table 12)

Table 12. Exploratory analysis results, using transition probabilities from RRMS to SPMS obtained from TA624

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

- Annualised relapse rates for a natural history cohort from TA527 (see Table 13)

Table 13. Exploratory analysis results, using annualised relapse rates from TA527

Treatment	Total costs	Total QALYs	Incremental	Incremental	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Health state utility values from (Orme et al., 2007) for people living with SPMS (see Table 14)

Table 14. Exploratory analysis results, using health state utility values from (Orme et al., 2007) for people living with SPMS

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

- Waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years) (see Table 15)

Table 15. Exploratory analysis results, using waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

ERG summary

In the majority of the exploratory analyses for the RES RRMS population, the results were robust to each individual change made to the company's model inputs. Incremental results in Tables 11 to 14 show that treatment with alemtuzumab [redacted] cladribine, ocrelizumab and natalizumab. Incremental results in Table 15 show that ofatumumab [redacted] cladribine and, alemtuzumab [redacted] ocrelizumab and natalizumab.

9.6 Appendix F: ERG scenario analyses

The ERG undertook further analyses to assess the impact to the ERG's base-case ICER by individually making changes to our assumptions. The following changes were made in scenario analyses for HA RRMS and RES RRMS populations:

9.6.1 Highly active relapsing remitting multiple sclerosis (HA RRMS) population

- Using caregiver disutility from Acaster et al.(2013) (see Table 16)

Table 16. ERG scenario analysis, using caregiver disutility from Acaster et al. (2013)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Using the mortality multipliers from Jick et al. (2014) (see Table 17)

Table 17. ERG scenario analysis, using the mortality multipliers from Jick et al. (2014)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Using the mortality multipliers from Kingwell et al. (2012) (see Table 18)

Table 18. ERG scenario analysis, using the mortality multipliers from Kingwell et al. (2012)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- No waning of the treatment effect (see Table 19)

Table 19. ERG scenario analysis, applying a no waning of the treatment effect

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Waning of the treatment effect (50% reduction after 5 years) (see Table 20)

Table 20. ERG scenario analysis, using waning of the treatment effect (50% reduction after 5 years)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

ERG summary

The ERG undertook several scenario analyses to assess the impact of these changes to our results for the HA RRMS population. In general, the results were robust to changes made to the assumptions. Incremental results in Tables 16, 17 and 18 show that ofatumumab dominates cladribine and fingolimod, alemtuzumab dominates fingolimod and ocrelizumab. Incremental results in Table 19 indicate that treatment with alemtuzumab dominates cladribine, fingolimod and ocrelizumab. Incremental results in Table 20 show that treatment with ofatumumab [redacted] cladribine and fingolimod and, alemtuzumab [redacted] ocrelizumab. [redacted]

9.6.2 2.2 Rapidly-evolving severe relapsing remitting multiple sclerosis (RES RRMS) population

- Using caregiver disutility from Acaster et al. (2013) (see Table 21)

Table 21. ERG scenario analysis, using caregiver disutility from Acaster et al. (2013)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Using the mortality multipliers from Jick et al. (2014) (see Table 22)

Table 22. ERG scenario analysis, using the mortality multipliers from Jick et al. (2014)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Using the mortality multipliers from Kingwell et al. (2012) (see Table 23)

Table 23. ERG scenario analysis, using the mortality multipliers from Kingwell et al. (2012)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- No waning of the treatment effect (see Table 24)

Table 24. ERG scenario analysis, applying a no waning of the treatment effect

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					

ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

- Waning of the treatment effect (50% reduction after 5 years) (see Table 25)

Table 25. ERG scenario analysis, using waning of the treatment effect (50% reduction after 5 years)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER (£/QALY)
[redacted]					

ERG, Evidence review group, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

ERG summary

The ERG undertook several scenario analyses to assess the impact of these changes to our results for the RES RRMS population. In general, the results were robust to changes made to the assumptions. Incremental results in Tables 21, 23 and 25 show that treatment with ofatumumab [redacted] cladribine and, alemtuzumab [redacted] ocrelizumab and natalizumab. Incremental results in Tables 22 and 24 show that alemtuzumab [redacted] cladribine, ocrelizumab and natalizumab.

9.7 Appendix G: Summary of ERG changes made in the economic model to implement the ERG preferred assumptions

Table 26 summarises the changes to the company's model to undertake the ERG's base-case analysis, scenario analyses and probabilistic sensitivity analysis. To undertake the ERG's base-case, changes should be made simultaneously before running the multiway analysis. For the scenario analyses, each change should be made individually before running the multiway analysis.

Table 26. Summary of ERG changes made in the economic model to implement the ERG preferred assumptions

Description of ERG change to economic model	Implementation of the change in the model
Base-case model	
Inclusion of SPMS-specific disease management costs obtained from TA320	Control worksheet, and include a row with the 'UK MS Survey costs (TA320) ERG option under the EDSS cost inputs (cell C79) Costs worksheet, in cells I220 and J220, enter costs from TA320 Costs worksheet, in cell D216 select the 'UK MS Survey costs (TA320) ERG from the dropdown box
Probability of progressing from RRMS to SPMS obtained from TA624	NH transitions worksheet, in cells D32 to D42 insert the probabilities from TA624
Annualised relapse	Control worksheet, and include a row with 'TA624' under the

rates for a natural history obtained from TA527	Relapse Rates SPMS (cell C41) Relapse worksheet, in cells J35 and K35, enter relapse rates and standard errors, respectively Relapse worksheet, in cell D31 select the 'TA624' from the dropdown box
Health state utility values from Orme et al., 2007 for people living with SPMS	Utilities worksheet, in cell D64 select 'Orme et al. 2007 (SPMS)' from the dropdown box
Addition of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)	Settings worksheet, in cell D42 select 'Yes' from the dropdown box Under the Relative Treatment Effect table, set full efficacy to 100% and onset 1, partial efficacy 75% and onset 6, partial efficacy 50% and onset 9
ERG's scenario analyses	
Caregivers' disutilities obtained from Acaster et al., 2013	Utilities worksheet, in cell D95, select 'Acaster et al 2013' from the dropdown box
Morality multipliers obtained from Jick et al., 2014	Mortality worksheet, in cell D11 select 'EDSS-independent mortality multiplier (Jick et al 2014)'
Morality multipliers obtained from Kingwell et al., 2012	Control worksheet, and include a row with 'EDSS-independent mortality multiplier (Kingwell et al 2012' under the Relative Mortality due to RRMS cell Mortality worksheet, in cells J35 and K35, enter the mortality multiplier Mortality worksheet, in cell D11 select EDSS-independent mortality multiplier (Kingwell et al 2012) from the dropdown box
No treatment waning	Settings worksheet, in cell D42 select 'No' from the dropdown box
Treatment waning (50% reduction after 5 years)	Settings worksheet, in cell D42 select 'Yes' from the dropdown box Under the Relative Treatment Effect table, set full efficacy to 100% and onset 1, partial efficacy 50% and onset 6
Technical error	
Same PSA results are returned for teriflunomide and IFNβ-1b (Rebif®)	1. Go to View 2. Click the Macros dropdown box to view Macros 3. Click (only once) on the Multiway_PSA_CEAC 4. Click Edit 5. Under the RRMS population, go to the 'Comparator 6', which is in green font 6. In this line of code (Sheets("Settings").Range("comp_tmnt").Value =

	Sheets("Multiway Analysis").Range("RRMS_PSA_comp5").Value, change the 5 to a 6 7. Save this change 8. Run the PSA
CEAC, cost-effectiveness acceptability curve; EDSS, expanded disability status scale; ERG, evidence review group; PSA, probabilistic sensitivity analysis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal	