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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Appraisal Committee Meeting – 4 February 2021
1st Committee meeting

The following documents are made available to the Committee:

The **final scope and final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from Novartis

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. MS Society
   b. MS Trust
   c. Association of British Neurologists

4. **Expert personal perspectives** from:
   a. Malcolm Qualie – commissioning expert, nominated by NHS England

5. **Evidence Review Group report** prepared by Warwick Evidence

6. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents
NB: the technical engagement is now based on the ERG report. A technical report will not be produced

7. **Technical engagement response from company**
   a. Company response form
   b. Appendix

8. **Technical engagement responses from experts:**
   a. Emma Meadows – patient expert, nominated by the MS Trust

9. **Technical engagement responses from consultees and commentators:**
   a. MS Trust
   b. Association of British Neurologists
   c. Biogen

10. **Evidence Review Group critique of company response to technical engagement** prepared by Warwick Evidence **–** to follow

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a. Critique

11. Appraisal Committee Meeting presentation slides

Please note that the full submission, appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Document A

Company evidence submission summary for committee

Novartis confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

August 2020

File name	Version	Contains confidential information	Date
NICE Ofatumumab Document A	Final_Updated ACIC	Yes	26th February 2021

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Instructions for companies

This is the template you should use to summarise your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

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

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Tables and figures

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List of Abbreviations

Abbreviation	Definition
ABN	Association of British Neurologists
ADCC	Antibody-dependent cytotoxicity
AE	Adverse event
ALEM	Alemtuzumab
ARR	Annualised relapse rate
BID	Twice a day
BSC	Best supportive care
BVL	Brain volume loss
CDC	Complement-dependent cytotoxicity
CDI-6	6-month confirmed disability improvement
CDW-3/6	3- / 6-month confirmed disability worsening
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLAD	Cladribine tablets
CrI	Credible interval
CSR	Clinical study report
DMF	Dimethyl fumerate
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End of study
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FAS	Full analysis set
FIN	Fingolimod
GA	Glatiramer acetate
HA	Highly active
HAHA	Human anti-human antibodies
HR	Hazard ratio
HRQoL	Health-related quality of life
HSU	Health state utility
ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G1
IM	Intramuscular
ITT	Intent-to-treat
IV	Intravenous
K-M	Kaplan-Meier
LYG	Life-years gained
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
NA	Not applicable

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NAT	Natalizumab
NEDA-4	No evidence of disease activity
NfL	Neurofilament light chain
NHS	National Health Service
NMA	Network meta-analysis
NMB	Net monetary benefit
OCR	Ocrelizumab
OMB	Ofatumumab
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PBO	Placebo
PO	Orally
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QD	Once daily
Q2D	Every 2 days
Q4W	Every 4 weeks
RCT	Randomised controlled trial
RES	Rapidly-evolving severe
RMS	Relapsing multiple sclerosis
RR	Rate ratio
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
s.c.	Subcutaneous
SE	Standard error
SPMS	Secondary progressive multiple sclerosis
TA	Technology appraisal
T25FW	Timed 25-Foot Walk Test
TEAE	Treatment-emergent adverse event
TER / TERI	Teriflunomide
TIW	Three times a week
WPAI:MS	Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis
WTP	Willingness-to-pay

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Submission summary

A.1 Health condition

Multiple sclerosis (MS) is a chronic, neurodegenerative autoimmune disorder in which the immune system attacks the myelin sheath of the nerve axons of the central nervous system.[1, 2] The effects of MS vary greatly between patients and from day to day; common symptoms include pain, muscle weakness or spasticity, chronic fatigue, unsteady gait or loss of balance, changes in vision, incontinence and cognitive impairment.[2-4]

MS is the most common cause of chronic neurologic disability, affects two to three times more women than men, and although it can develop at any age, most patients are diagnosed in early adulthood, typically between the ages of 20 and 40 years.[5, 6] It is estimated that approximately 130,000 people in the UK have MS, with nearly 7,000 new diagnoses every year.[7]

MS is a highly heterogenous disease and can present in one of several phenotypes.[8, 9] At the time of diagnosis, approximately 85% of patients exhibit a relapsing-remitting pattern.[10] During relapses, new symptoms present or old symptoms worsen, leading to acute deterioration in neurological function for at least 24 hours, although they typically last for 4–6 weeks.[11] Thereafter, there follows a period of remission in which symptoms improve, either partially or completely.[12] Over time, many patients with relapsing-remitting multiple sclerosis (RRMS) will experience a change in their disease presentation with fewer or no relapses but a progressive increase in disability and decline in neurological function, this is termed secondary progressive multiple sclerosis (SPMS).[13] This change from RRMS to SPMS is gradual, with no clearly defined clinical transition point.[8, 13]

Patients with MS have a significantly lower quality of life (QoL) as compared with the general population, and QoL worsens with increasing disease severity.[14] Patients with MS often eventually become unable to work and rely substantially on family and friends, often in assumed positions as unofficial carers, who also experience a reduced QoL due to high levels of stress and anxiety.[6, 15, 16]

A.2 Clinical pathway of care

There are currently 12 disease-modifying therapies (DMTs) recommended by NICE for use in patients with RRMS. Some patients with RRMS may be further classified as experiencing highly active (HA) disease, defined as ongoing disease activity on treatment, i.e. inadequate response to DMT, or rapidly-evolving severe (RES) RRMS, which can occur in both treatment-naïve and DMT-experienced patients and is defined as having two or more relapses within one year with magnetic resonance imaging (MRI) evidence of disease activity.[17] The current clinical pathway of care is summarised in Figure 1.

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. Section A.5 describes how this submission is targeting RRMS only.

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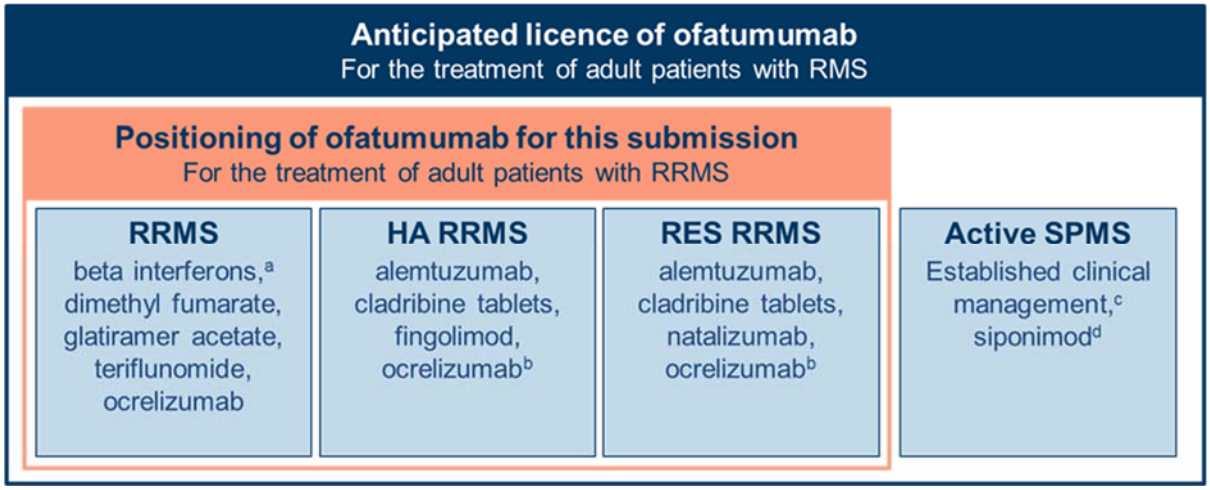
Figure 1: The anticipated positioning of ofatumumab in the clinical pathway of care in the treatment of RRMS – Document B, B.1.3.2, Figure 1 (page 20)



Ozanimod has not been included as a relevant comparator as its use is not established clinical practice at the time of submission.
[a] Including interferon β-1a, interferon β-1b and peginterferon β-1a.
[b] Recommended only if alemtuzumab is contraindicated or otherwise unsuitable.
[c] Established clinical management includes interferon β-1b or other DMTs used outside their marketing authorisations.[18]
[d] Subject to ongoing NICE appraisal.
Abbreviations: DMT: disease-modifying therapy; HA: highly active; RES: rapidly-evolving severe; RMS: relapsing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

A.3 Equality considerations

The technology is unlikely to raise any equality concerns. Introduction of ofatumumab is not likely to lead to recommendations which differentially impact patients protected by the equality legislation or disabled persons.

However, as a self-administered subcutaneous therapy, the introduction of ofatumumab has the potential to increase access to high efficacy treatment. With the currently available DMTs, some patients experience issues in accessing high-efficacy treatments administered as IV infusions, due to long waiting times for infusion appointments, which can considerably delay the start of an effective treatment, or an inability to travel to infusion clinics, owing to disabilities and/or patients living far from hospitals.[19, 20] Ofatumumab would allow timely access to a high-efficacy treatment that patients or carers, after being trained by a healthcare professional at the first injection, can administer at home, and thus reduce potential inequalities in access for patients living in rural areas or being unable to travel to infusions clinics due to disabilities. During the ongoing COVID-19 pandemic at the time of this submission, the possibility to administer ofatumumab at home may further enable patients with MS to access a high-efficacy treatment without subjecting them to increased risk of infection both on the journey to the infusion clinic and in the clinic itself.

A.4 The technology

Table 1: Technology being appraised – Document B, B.1.2, Table 2 (page 16)

UK approved name and brand name	Ofatumumab (Kesimpta®)

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Mechanism of action	Ofatumumab is the first 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. B lymphocytes are cells of the immune system understood to contribute to the pathogenesis of MS in several distinct ways: they secrete cytokines to modulate the inflammatory environment, present antigens for the activation of T lymphocytes and, when mature, secrete antibodies which may contribute to the destruction of the myelin sheath.[21] The expression of CD20, a transmembrane protein understood to function as a calcium channel, is specific to B lymphocytes. Ofatumumab specifically binds to CD20 on the cell surface of B lymphocytes to target these cells for immune destruction via complement-dependent cytotoxicity (CDC) and antibody-dependent cytotoxicity (ADCC).[22] [23] The reduction in circulating B lymphocyte number is associated with lower MS activity and disease burden, which is underpinned by a reduction in the overall pro-inflammatory state of multiple sclerosis.[24]
Marketing authorisation/CE mark status	A marketing authorisation application for ofatumumab in RMS was submitted to the European Medicines Agency (EMA) in [redacted] 2020. Committee for Medicinal Products for Human Use (CHMP) opinion is expected in [redacted]. Marketing authorisation is expected in [redacted] 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated EU marketing authorisation wording for ofatumumab is "for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS)". Ofatumumab has the following contraindications: [redacted]
Method of administration and dosage	Ofatumumab is intended for patient self-administration by subcutaneous injection and will be provided in autoinjector pens pre-filled with the recommended dose (20 mg in 0.4 mL solution). The first injection should be performed under the guidance of a healthcare professional. It is recommended that ofatumumab is administered at Weeks 0, 1 and 2 followed by monthly dosing starting at Week 4.
Additional tests or investigations	Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment.[a]
List price and average cost of a course of treatment	The list price of ofatumumab is [redacted] (exc. VAT) per 1-unit pack (pre-filled autoinjector pen), equating to the following annual costs: Year 1: [redacted] Year 2+: [redacted]
Patient access scheme (if applicable)	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: Year 1: [redacted] Year 2+: [redacted] [redacted]

[a] This screening is also required for other DMTs (ocrelizumab and cladribine) and these costs have been considered in the economic model.

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Abbreviations: ADCC: antibody-dependent cytotoxicity; CD20: cluster of differentiation 20; CDC: complement-dependent cytotoxicity; CHMP: Committee for Medicinal Products for Human Use; DMT: disease-modifying therapy; EMA: European Medicines Agency; HBV: hepatitis B virus; IgG1: immunoglobulin G1; MS: multiple sclerosis; NICE: National Institute for Health and Care Excellence; PAS: Patient Access Scheme; RMS: relapsing multiple sclerosis; VAT: value-added tax.

A.5 Decision problem and NICE reference case

This submission focuses on part of the technology's full marketing authorisation. The full anticipated marketing authorisation for ofatumumab is for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS), however, this submission focuses on patients with RRMS only. The proposed population is narrower than the marketing authorisation because the evidence base for ofatumumab within an active SPMS population is limited (only 108 patients [5.7%] across both treatment arms of both of the pivotal phase III trials for ofatumumab, ASCLEPIOS I and II, were defined as having SPMS at baseline).[25] Therefore, the trials do not provide sufficient subgroup data to perform meaningful indirect comparisons or allow robust cost-effectiveness analyses in an active SPMS population.

As such, the company submission differs slightly from the final NICE scope in terms of the population considered. The decision problem addressed by this submission is summarised in Table 2.

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Table 2: The decision problem – Document B, B.1.1, Table 1 (page 13)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with RMS	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 (5.7%) in the pivotal phase III trials (ASCLEPIOS I and II),[25] and as such does not provide sufficient subgroup data to perform meaningful indirect comparisons or allow robust cost-effectiveness analyses in active SPMS.
Intervention	Ofatumumab	Ofatumumab	NA – in line with the NICE final scope
Comparator(s)	For people with active RRMS: • beta interferon • dimethyl fumarate • glatiramer acetate • teriflunomide • ocrelizumab • peginterferon beta-1a • ozanimod (subject to ongoing NICE appraisal) For people with HA RRMS despite previous treatment: • alemtuzumab • cladribine • fingolimod • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	For people with RRMS: • beta interferon • 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)	Some of the comparators listed under "active RRMS" have not been restricted by NICE to "active" RRMS (e.g. glatiramer acetate). This 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.

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	• ozanimod (subject to ongoing NICE appraisal) For people with RES RRMS: • alemtuzumab • cladribine • natalizumab • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) For people with active SPMS (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)	For people with RES RRMS: • alemtuzumab • cladribine tablets • natalizumab • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	This submission does not consider comparators for active SPMS due to its focus on an RRMS population (see Population section above).
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, 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 symptoms of MS: 6-month CDW by T25FW • Measures of freedom from disease activity: number of T1 Gd-enhancing	NA – in line with the NICE final scope

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		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	
Subgroups to be considered	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.[17] The population of 'people who could not tolerate previous treatment' is included in 'For people with RRMS' (see Comparators row above).

Abbreviations: AE: adverse event; ARR: annualised relapse rate; BVL: brain volume loss; CDI: confirmed disability improvement; CDW: confirmed disability worsening; DMT: disease-modifying therapy; EDSS: Extended Disability Status Scale; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels; Gd: gadolinium; HA: highly active; MRI: magnetic resonance imaging; MS: multiple sclerosis; MSIS-29: Multiple Sclerosis Impact Scale; NA: not applicable; NEDA-4: no evidence of disease activity; NHS: National Health Service; RES: rapidly-evolving severe; RMS: relapsing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SAE: serious adverse event; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk test; WPAI:MS: work productivity and impairment questionnaire for multiple sclerosis.

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A.6 Clinical effectiveness evidence

The clinical evidence base for ofatumumab in RRMS relevant to this submission comprises two identical, parallel, phase 3 trials (ASCLEPIOS I and II). The ASCLEPIOS trials collectively enrolled 1,882 patients across 37 countries, with patients randomised 1:1 to ofatumumab or teriflunomide.[26] Evidence from the ASCLEPIOS trials was used to inform the cost-effectiveness model presented in Section A.10

Table 3: Clinical effectiveness evidence – Document B, B.2.2, Table 3 (page 23)

Study	ASCLEPIOS I[27]	ASCLEPIOS II[28]
Study design	An international phase 3, multicentre, randomised, parallel, double-blinded, double-dummy, active comparator-controlled trial (N=927)	An international phase 3, multicentre, randomised, parallel, double-blinded, double-dummy, active comparator-controlled trial (N=955)
Population	Adult patients diagnosed with MS as per the 2010 Revised McDonald criteria.[29] Patients had to have RRMS or active SPMS with a disability status at screening of EDSS 0–5.5 and documentation of at least one of the following: • One relapse during the previous year • Two relapses during the previous two years prior to screening • A positive Gd-enhancing MRI scan within a year of randomisation[a]	
Intervention(s)	Ofatumumab 20 mg administered via s.c. injection on Days 1, 7, 14, Week 4 (Study month 1) and every four weeks thereafter, with teriflunomide-matching placebo capsules administered orally once daily	
Comparator(s)	Teriflunomide 14 mg administered orally once daily, with ofatumumab-matching placebo s.c. injections on Days 1, 7, 14, Week 4 (Study month 1) and every four weeks thereafter	
Outcomes specified in the decision problem	Primary outcome: • **ARR** Key disability-related secondary outcomes determined by EDSS: • CDW-3 • **CDW-6** • CDI-6 Key MRI-related secondary outcomes: • Number of T1 Gd-enhancing lesions • Number of new or enlarging T2 lesions per year (annualised T2 lesion rate) • Rate of brain volume loss Other key secondary outcomes: • Serum NfL concentrations Other non-key secondary and exploratory outcomes:[b] • Time to first relapse • Time to CDW-6 of at least 20% in the T25FW • NEDA-4 • MSIS-29 • WPAI:MS HRQoL:	

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	• **EQ-5D-5L** **Safety outcomes**: • TEAEs • SAEs • AEs leading to study drug discontinuation
Reference to section in submission	Document B, B.2.2 (page 23)

Outcomes in **bold** indicate those used in the economic model.
[a] Screening MRI could have been used if no positive Gd-enhancing scan existed from the prior year.
[b] This list is not exhaustive. The full list of non-key secondary outcomes is provided in Appendix L of Document B.
Abbreviations: AE: adverse event; ARR: annualised relapse rate; CDI-6: 6-month confirmed disability improvement; CDW-3/-6: 3-month/6-month confirmed disability worsening; EDSS: Expanded Disability Status Scale; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels; Gd: gadolinium; HRQoL: health-related quality of life; MRI: magnetic resonance imaging; MS: multiple sclerosis; MSIS-29: Multiple Sclerosis Impact Scale; NEDA-4: no evidence of disease activity; NfL: neurofilament light chain; RRMS: relapsing-remitting multiple sclerosis; SAE: serious adverse event; s.c.: subcutaneous; SPMS: secondary progressive multiple sclerosis; T25FW: Timed 25-Foot Walk test; TEAE: treatment-emergent adverse event; WPAI:MS: work productivity and impact impairment questionnaire for multiple sclerosis.
Sources: ASCLEPIOS I Clinical Study Report, 9th December 2019,[27] ASCLEPIOS II Clinical Study Report, 9th December 2019.[28]

A.7 Key results of the clinical effectiveness evidence

The ASCLEPIOS studies met their primary and almost all key secondary efficacy endpoints, demonstrating a statistically significant and clinically meaningful reduction in annualised relapse rate (ARR) and delaying the time to confirmed disability worsening (CDW) compared with teriflunomide.

Clinical effectiveness results for the ASCLEPIOS studies are presented below.

A.7.1 Annualised relapse rate

The primary endpoint of the ASCLEPIOS trials was adjusted ARR, summarised in Table 4. In both trials, the ofatumumab treatment group demonstrated a significantly lower ARR versus the teriflunomide treatment group.

Table 4: ARR for confirmed relapses in patients in the ASCLEPIOS trials (FAS) – Document B, Section B.2.6.1, Table 11 (page 38)

	ASCLEPIOS I[27]		ASCLEPIOS II[28]	
	20 mg OMB (N=454)	14 mg TER (N=452)	20 mg OMB (N=469)	14 mg TER (N=469)
Confirmed relapses	90	177	95	198
Exposure, patient-years	769	741	768	750
Adjusted ARR (95% CI)	0.11 (0.09, 0.14)	0.22 (0.18, 0.26)	0.10 (0.08, 0.13)	0.25 (0.21, 0.30)
Rate vs TER	−50.5%	NA	−58.5%	NA
ARR ratio vs TER (95% CI)	0.50 (0.37, 0.65)	NA	0.42 (0.31, 0.56)	NA
p-value vs TER	<0.001	NA	<0.001	NA

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Confirmed relapses are those accompanied by a clinically relevant change in the EDSS. Treatment comparison results obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. The natural log of the time-in-study was used as offset to annualise the relapse rate.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Extended Disability Status Scale; FAS: full analysis set; Gd: gadolinium; NA: not applicable; OMB: ofatumumab; TER: teriflunomide.

A.7.2 Confirmed disability worsening

It was pre-planned that analyses pooled across both ASCLEPIOS trials would be used to assess all disability-related secondary outcomes: 3-month and 6-month confirmed disability worsening (CDW-3 and CDW-6) and 6-month confirmed disability improvement (CDI-6).

Treatment with ofatumumab significantly reduced the risk of both CDW-3 and CDW-6 as compared with teriflunomide treatment in the combined analyses from the ASCLEPIOS trials. Across both trials, 9.3% and 7.5% of patients in the ofatumumab group experienced CDW-3 and CDW-6, respectively, as compared with 13.4% and 10.6% in the teriflunomide group, demonstrating a statistically significant reduction in risk of 34.4% (hazard ratio [HR] 0.66 [95% CI: 0.50, 0.86], p=0.002) for CDW-3 and 32.5% (HR: 0.68 [95% CI: 0.50, 0.92], p=0.012) for CDW-6 (Table 5). As well as reducing risk of CDW-3 and CDW-6, ofatumumab treatment delayed the time to first CDW-3 and CDW-6 as shown in Figure 2 and Figure 3.

Table 5: 3- and 6-month confirmed disability worsening in the ASCLEPIOS trials (FAS) – Document B, Section B.2.6.2, Tables 12 and 13 (pages 39 and 40)

	CDW-3		CDW-6	
	20 mg OMB (N=944)	**14 mg TER (N=931)**	**20 mg OMB (N=944)**	**14 mg TER (N=931)**
Number of CDW-3 events, n (%)	88 (9.3)	125 (13.4)	71 (7.5)	99 (10.6)
HR vs TER (95% CI)	0.66 (0.50, 0.86)	NA	0.68 (0.50, 0.92)	NA
Risk vs TER	−34.4%	NA	−32.5%	NA
p-value	0.002	NA	0.012	NA

Abbreviations: CDW-3: 3-month confirmed disability worsening; CDW-6: 6-month confirmed disability worsening; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; NA: not applicable; OMB: ofatumumab; TER: teriflunomide.
Source: Novartis Data on File (Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials).[25]

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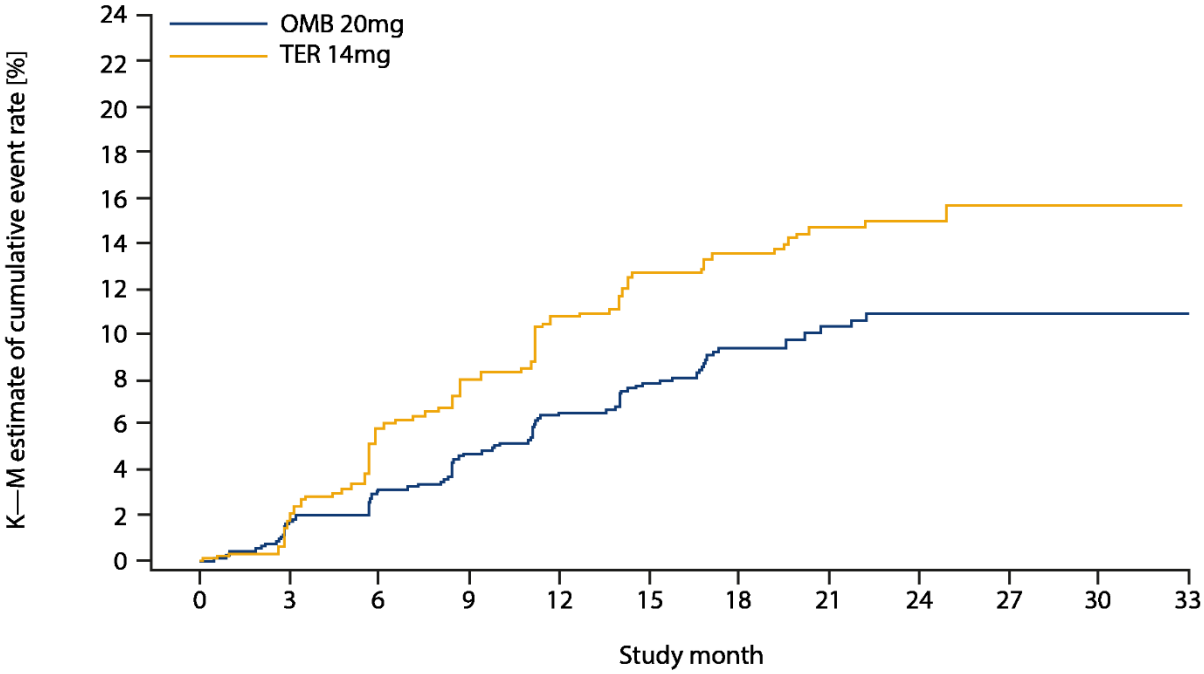
Figure 2: Time to first 3-month confirmed disability worsening during Treatment epoch in teriflunomide and ofatumumab treated patients in the ASCLEPIOS trials (FAS) – Document B, Section B.2.6.2, Figure 3 (page 40)

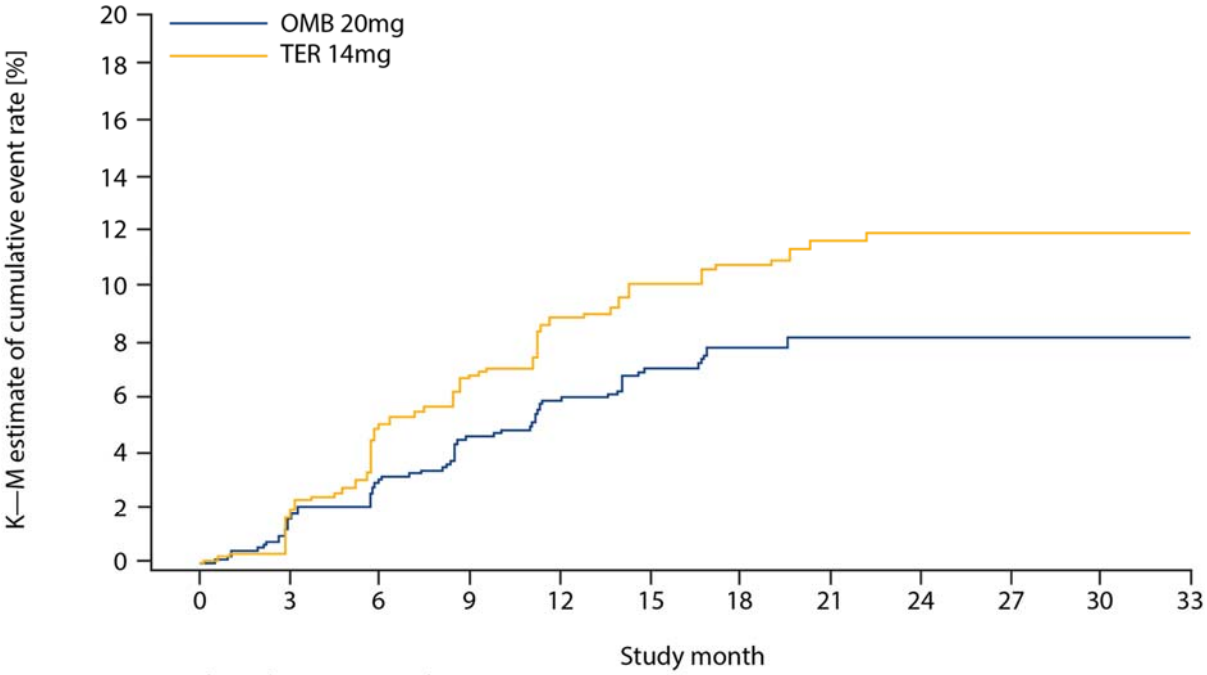


Number of patients at risk

OMB 20mg	944	908	878	844	810	784	534	319	176	49	1	0
TER 14mg	932	901	841	804	756	718	478	298	146	41	1	0

Abbreviations: FAS: full analysis set; K-M: Kaplan–Meier; OMB: ofatumumab; TER: teriflunomide.
Source: Novartis Data on File (Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials)[25]

Figure 3: Time to first 6-month confirmed disability worsening during Treatment epoch in teriflunomide and ofatumumab treated patients in the ASCLEPIOS trials (FAS) – Document B, Section B.2.6.2, Figure 4 (page 41)



Number of patients at risk

OMB 20mg	944	908	878	845	815	791	544	324	180	50	1	0
TER 14mg	932	902	849	812	769	734	487	305	151	43	1	0

Abbreviations: FAS: full analysis set; K-M: Kaplan–Meier; OMB: ofatumumab; TER: teriflunomide.

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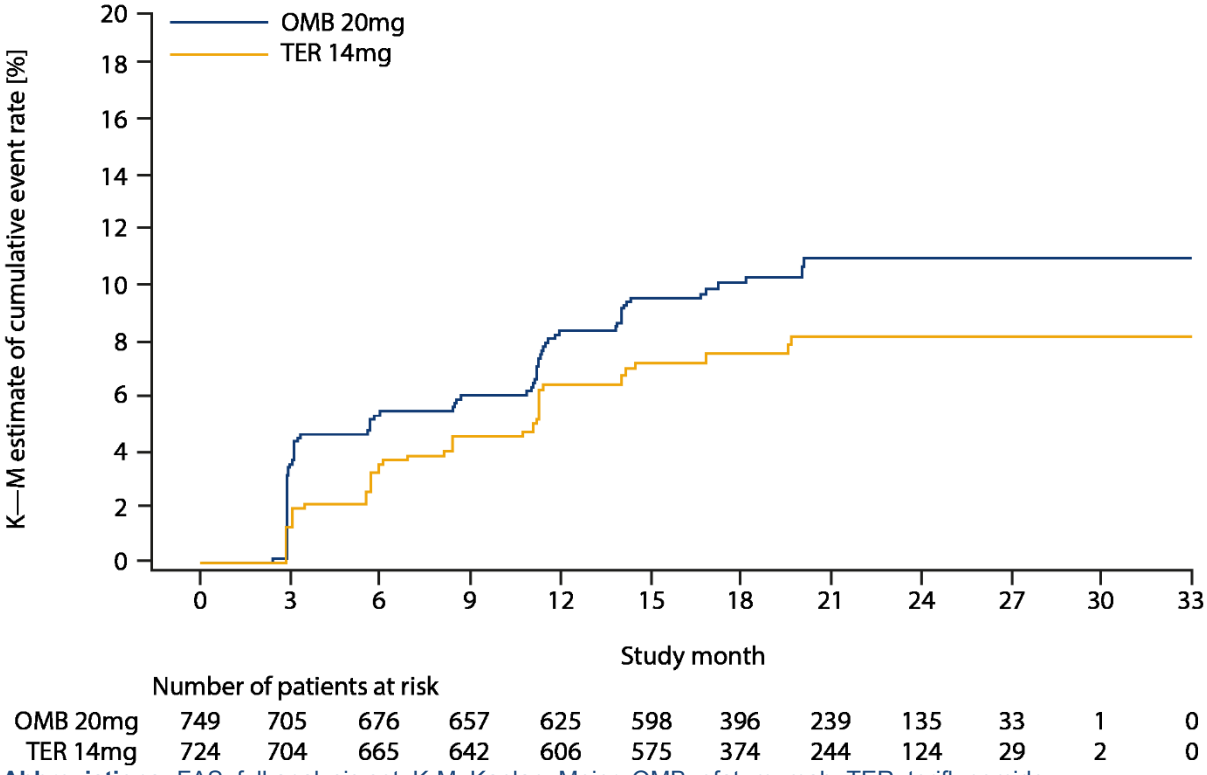
Source: Novartis Data on File (Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials).[25]

In total, [redacted] events of 6-month CDI-6 were observed across both ASCLEPIOS trials while [redacted] events were stipulated by the clinical study protocol for 80% power. Thus, statistical analysis of CDI-6 was [redacted] at the end of study (EOS).

The risk of CDI-6 was not statistically significantly different between the ofatumumab and teriflunomide groups in the ASCLEPIOS trials. Across both trials, 9.9% of patients in the ofatumumab group experienced CDI-6 as compared with 7.3% in the teriflunomide group, demonstrating an increased risk of 35.2% (HR: 1.35 [95% CI: 0.95, 1.92], p=0.094). As displayed in Figure 4, ofatumumab treatment provided greater numerical improvements in the time to first CDI-6 compared with teriflunomide treatment from approximately Month 3 onwards, but statistical significance was not reached.

Figure 4: Time to first 6-month confirmed disability improvement during Treatment epoch in teriflunomide and ofatumumab treated patients in the ASCLEPIOS trials (FAS) – Document B, Section B.2.6.2, Figure 5 (page 42)



Abbreviations: FAS: full analysis set; K-M: Kaplan–Meier; OMB: ofatumumab; TER: teriflunomide.
Source: Novartis Data on File (Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials)[25]

A.7.3 Gd-enhancing T1 lesions

Treatment with ofatumumab significantly reduced the mean number of Gd-enhancing T1 lesions per scan as compared with teriflunomide treatment in both ASCLEPIOS trials.

In ASCLEPIOS I, the mean adjusted number of Gd-enhancing lesions per scan was 0.01 (95% CI: 0.01, 0.02) in the ofatumumab group as compared with 0.45 (95% CI: 0.36, 0.58) in the teriflunomide group. This corresponded to a statistically significant reduction of 97.5%, with a rate ratio (RR) of 0.03 (95% CI: 0.01, 0.05) (p<0.001).

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In ASCLEPIOS II, the mean adjusted number of Gd-enhancing lesions per scan was 0.03 (95% CI: 0.02, 0.05) in the ofatumumab group as compared with 0.51 (95% CI: 0.40, 0.66) in the teriflunomide group. This corresponded to a statistically significant reduction of 93.8%, with an RR of 0.06 (95% CI: 0.04, 0.10) (p<0.001).

A.7.4 New and enlarging T2 lesions

Treatment with ofatumumab significantly reduced the mean adjusted annualised rate of new or enlarging T2 lesions as compared with teriflunomide treatment in both ASCLEPIOS trials.

In ASCLEPIOS I, the mean adjusted annualised rate of new or enlarging T2 lesions was 0.72 (95% CI: 0.61, 0.85) in the ofatumumab group as compared with 4.00 (95% CI: 3.47, 4.61) in the teriflunomide group. This corresponded to a statistically significant reduction of 82.0%, with an RR of 0.18 (95% CI: 0.15, 0.22) (p<0.001).

In ASCLEPIOS II, the mean adjusted annualised rate of new or enlarging T2 lesions was 0.64 (95% CI: 0.55, 0.75) in the ofatumumab group as compared with 4.15 (95% CI: 3.64, 4.74) in the teriflunomide group. This corresponded to a statistically significant reduction of 84.5%, with an RR of 0.15 (95% CI: 0.13, 0.19) (p<0.001).

In both trials, the total T2 lesion volume [redacted] from baseline to Month 12 and from baseline to Month 24 in ofatumumab-treated patients while it [redacted] in teriflunomide patients in the same time period. In both trials at both timepoints, this difference was statistically significant (all p[redacted]).

A.7.5 Neurofilament light chain (NfL) serum concentration

NfL has been identified as a biomarker to indicate treatment response and predict disability worsening in patients with MS. Blood serum NfL levels have been shown to correlate positively with disease activity and brain volume loss in patients with MS.[30] Treatment with ofatumumab significantly reduced the adjusted geometric mean concentration of NfL in serum as compared with teriflunomide treatment in both ASCLEPIOS trials at Months 3, 12 and 24.

In ASCLEPIOS I, patients in the ofatumumab group demonstrated a statistically significantly lower mean serum NfL concentration than the teriflunomide group at Month 3 (adjusted geometric mean ratio: 0.93 [95% CI: 0.89, 0.98], p=0.011), Month 12 (adjusted geometric mean ratio: [redacted] [95% CI: [redacted], [redacted], p[redacted]) and Month 24 (adjusted geometric mean ratio: [redacted] [95% CI: [redacted], [redacted], p[redacted]).

In ASCLEPIOS II, patients in the ofatumumab group demonstrated a statistically significantly lower mean serum NfL concentration than the teriflunomide group at Month 3 (adjusted geometric mean ratio: 0.89 [95% CI: 0.85, 0.93], p<0.001), Month 12 (adjusted geometric mean ratio: [redacted] [95% CI: [redacted], [redacted], p[redacted]) and Month 24 (adjusted geometric mean ratio: [redacted] [95% CI: [redacted], [redacted], p[redacted]).

A.7.6 Annual rate of brain volume loss (BVL)

The annual rate of brain volume change, estimated as the slope in BVL between Months 12 and 24, was not statistically significantly different between the ofatumumab and teriflunomide groups in either of the ASCLEPIOS trials. Therefore, this key secondary endpoint was not met.

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A.7.7 Time to confirmed relapse

Treatment with ofatumumab significantly [redacted] the time to first confirmed relapse as compared with teriflunomide treatment in ASCLEPIOS I and II. Ofatumumab treatment significantly [redacted] the risk of a confirmed relapse by Month 24 as compared with teriflunomide treatment in both ASCLEPIOS trials.

In ASCLEPIOS I, [redacted]% of patients in the ofatumumab group experienced a confirmed relapse by Month 24 as compared with [redacted]% in the teriflunomide group, demonstrating a 24-month Kaplan–Meier estimate of [redacted]% (95% CI: [redacted], [redacted]) as compared with [redacted]% (95% CI: [redacted], [redacted]). This [redacted]% [redacted] in risk (RR: [redacted], 95% CI: [redacted], [redacted]) was statistically significant (p[redacted]).

In ASCLEPIOS II, [redacted]% of patients in the ofatumumab group experienced a confirmed relapse by Month 24 as compared with [redacted]% in the teriflunomide group, demonstrating a Kaplan–Meier estimate of [redacted]% (95% CI: [redacted], [redacted]) as compared with [redacted]% (95% CI: [redacted], [redacted]). This [redacted]% [redacted] in risk (RR: [redacted], 95% CI: [redacted], [redacted]) was statistically significant (p[redacted]).

A.7.8 Subgroup analysis

Additional *post-hoc* analyses were conducted to explore the efficacy of ofatumumab within both the HA RRMS and RES RRMS subgroups. Due to the *post-hoc* nature of these analyses, each subgroup contains a relatively small sample size such that few events were observed for analysis, leaving them underpowered. In spite of the limitations inherent in subgroup analyses, the results suggest ofatumumab has favourable efficacy as compared with teriflunomide in each of these subgroups, as determined by ARR, CDW-3 and CDW-6 outcomes. This conclusion is consistent with the conclusions drawn from the intent-to-treat (ITT) analysis comprising the full study population.

HA RRMS

The HA RRMS subgroup was defined as RRMS patients in the ASCLEPIOS ITT population previously treated with any DMT who discontinued their last DMT due to lack of efficacy (comprising [redacted]% [n=[redacted]] of the ITT population).

Pooled across both trials, the ofatumumab group demonstrated an ARR estimate of [redacted] (95% CI: [redacted]) as compared with an ARR estimate of [redacted] (95% CI: [redacted]) in the teriflunomide group. This corresponded to [redacted]% in ARR estimates, with an ARR ratio of [redacted] (95% CI: [redacted], [redacted]) (p[redacted]).

Across both trials, [redacted]% of patients in the ofatumumab group experienced CDW-3 as compared with [redacted]% in the teriflunomide group, demonstrating an HR of [redacted] (95% CI: [redacted], [redacted]). This corresponded to [redacted]% in risk (p=[redacted]).

A [redacted] proportion of ofatumumab-treated patients experienced CDW-6 ([redacted]%) as compared with the teriflunomide group ([redacted]%), demonstrating an HR of [redacted] (95% CI: [redacted], [redacted]) and a [redacted]% [redacted] in risk (p=[redacted]).

Ofatumumab [redacted] the time to both first CDW-3 and first CDW-6 in the HA RRMS subgroup.

RES RRMS

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The RES RRMS subgroup was defined as RRMS patients in the ASCLEPIOS ITT population with ≥2 relapses in the previous year and ≥1 T1 Gd-enhancing lesions on baseline brain MRI (comprising [redacted]% [n=[redacted]] of the ITT population). Increase in T2 lesions compared with a previous MRI was not available at baseline which precluded inclusion of patients in the subgroup analysis based on T2 lesion criteria.

Pooled across both trials, the ofatumumab group demonstrated an ARR estimate of [redacted] (95% CI: [redacted]) as compared with an ARR estimate of [redacted] (95% CI: [redacted]) in the teriflunomide group. This corresponded to [redacted]% in ARR estimates, with an ARR ratio of [redacted] (95% CI: [redacted], [redacted]) (p[redacted]).

A [redacted] proportion of ofatumumab-treated patients experienced CDW-3 ([redacted]%) as compared with the teriflunomide group ([redacted]%), demonstrating an HR of [redacted] (95% CI: [redacted], [redacted]) and a [redacted]% [redacted] in risk (p=[redacted]).

A [redacted] proportion of ofatumumab-treated patients experienced CDW-6 ([redacted]%) as compared with the teriflunomide group ([redacted]%), demonstrating an HR of [redacted] (95% CI: [redacted], [redacted]) and a [redacted]% [redacted] in risk (p=[redacted]).

Ofatumumab [redacted] the time to both first CDW-3 and first CDW-6 in the RES RRMS subgroup.

A.7.9 Adverse reactions

Across both ASCLEPIOS trials, no clinically meaningful difference in the overall frequencies of treatment-emergent adverse events (TEAEs) was observed between the teriflunomide and ofatumumab groups. Occurrence of all TEAEs and Grade 3–4 TEAEs was well-balanced across the ofatumumab and teriflunomide treatment arms of each trial with a slightly higher proportion of patients from both treatment arms of the ASCLEPIOS II trial reporting TEAEs as compared with the ASCLEPIOS I trial. Injection-related reactions and nasopharyngitis were the most common adverse events (AEs) in the ofatumumab arms in both ASCLEPIOS trials.

The proportion of patients that experienced AEs necessitating temporary or permanent study drug discontinuation was well-balanced across treatment groups in both trials despite a slightly higher proportion of serious adverse events (SAEs) in the ofatumumab treatment groups.

No deaths occurred in the ofatumumab or teriflunomide treatment groups during the Treatment epoch in either trial.

Overall, the ASCLEPIOS trials demonstrated ofatumumab to be well-tolerated with a safety profile similar to teriflunomide.

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.[31, 32] In the ASCLEPIOS studies [redacted] patients with neutralising anti-drug antibodies were identified (as discussed further in Document B, Section B.2.10.7). Consequently, long-term treatment effect waning due to formation of neutralising antibodies is considered unlikely with ofatumumab.

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A.8 Evidence synthesis

Network meta-analyses (NMAs) were conducted in order to synthesise the relative efficacy of ofatumumab versus other DMTs in the population of interest. The outcomes of interest were CDW-3, CDW-6, ARR and all-cause discontinuation.

The feasibility assessment identified differences between trials in the outcome definition of CDW (alternatively termed confirmed disability progression in some trials), mainly relating to the magnitude of increase in EDSS required to be considered as a disability worsening in an individual patient. For CDW-3 and CDW-6, all trials required an EDSS score increase of ≥1.0 if baseline EDSS was between 1 and 5. However, heterogeneity existed for baseline EDSS score 0 (required increase of ≥1.0 or ≥1.5) and baseline EDSS score 5.5 (required increase of ≥0.5 or ≥1.0). In the ASCLEPIOS trials, an increase in EDSS score of ≥1.5 points was required if baseline EDSS was 0, of ≥1 point if baseline EDSS was 1–5, or of ≥0.5 points if baseline EDSS was ≥5.5.

Within the context of an NMA, heterogeneity between trials is an important consideration for conducting a fair comparison. A UK-based treating Consultant Neurologist and seven additional UK neurologists at a recent advisory board acknowledged the importance of using consistent criteria in the NMA in order to create a less biased, more homogeneous comparison across treatments, particularly when considering the small absolute numbers of patients experiencing disability worsening events. An additional consideration in the NMA feasibility assessment was the intended use of the results in the economic model. The literature sources from which the natural history disability progression probabilities and health state unit costs and resource use for the economic model are derived, consider only whole number EDSS states. Therefore, the economic model presented in this submission considers whole number EDSS states, in alignment with previous economic models of MS DMTs in the UK. Based on this, a CDW definition only considering ≥1.0 increases in EDSS as disability worsening, which has commonly been used in other trials, was judged to have greater concordance with the model structure than the ASCLEPIOS CDW criteria.

In order to reduce heterogeneity between trials and increase concordance with the structure of the economic model, the base case NMA was conducted using ASCLEPIOS trial data reanalysed to align with this whole number CDW definition commonly used across MS trials. This “aligned criteria” definition of EDSS change required for disability worsening, used in the ocrelizumab pivotal RCTs OPERA I and II and in the teriflunomide trials TEMSO and TOWER which connect ofatumumab, via teriflunomide, to the rest of the CDW network, required an increase in EDSS score of ≥1.0 from any baseline (0–5.5) to be considered a disability worsening event.[33-35] NMA scenario analyses performed using the pre-defined criteria of the ASCLEPIOS trials and, due to the importance of ocrelizumab as a key comparator, criteria fully aligned with the CDW definition of the ocrelizumab OPERA trials (see Section B.2.9.2 of Document B for further details) are presented in Document B, Sections B.2.9.5 and B.2.9.6, respectively. The CDW-3 and CDW-6 results for the base case aligned criteria and the scenario analyses are presented in Table 6.

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Table 6: 3- and 6-month confirmed disability worsening in the ASCLEPIOS trials (FAS) – Document B, Sections B.2.6.2 and B.2.9.2, Tables 12–13 and 36–39 (pages 39–40 and 71–73)

	CDW-3		CDW-6	
	20 mg OMB (N=944)	14 mg TER (N=931)	20 mg OMB (N=944)	14 mg TER (N=931)
Aligned criteria [base case]				
Number of CDW events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR vs TER (95% CI)	[redacted]	NA	[redacted]	NA
Risk vs TER	[redacted]	NA	[redacted]	NA
p-value	[redacted]	NA	[redacted]	NA
Pre-defined criteria				
Number of CDW events, n (%)	88 (9.3)	125 (13.4)	71 (7.5)	99 (10.6)
HR vs TER (95% CI)	0.66 (0.50, 0.86)	NA	0.68 (0.50, 0.92)	NA
Risk vs TER	−34.4%	NA	−32.5%	NA
p-value	0.002	NA	0.012	NA
OPERA-aligned criteria				
Number of CDW events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR vs TER (95% CI)	[redacted]	NA	[redacted]	NA
Risk vs TER	[redacted]	NA	[redacted]	NA
p-value	[redacted]	NA	[redacted]	NA

Abbreviations: CDW-3: 3-month confirmed disability worsening; CDW-6: 6-month confirmed disability worsening; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; NA: not applicable; OMB: ofatumumab; TER: teriflunomide.
Source: Novartis Data on File (Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials);[25] Novartis Data on File: Additional ITT Analyses.[36]

A.8.1 ARR

The network diagram for ARR is displayed in Figure 5. The relative effectiveness of ofatumumab at reducing ARR versus other DMTs and placebo is summarised in the league table in Figure 6. Ofatumumab (HR: 0.30, 95% CrI: 0.22–0.40) was the second most effective treatment versus placebo after alemtuzumab (HR: [redacted], 95% CrI: 0.21–0.36).

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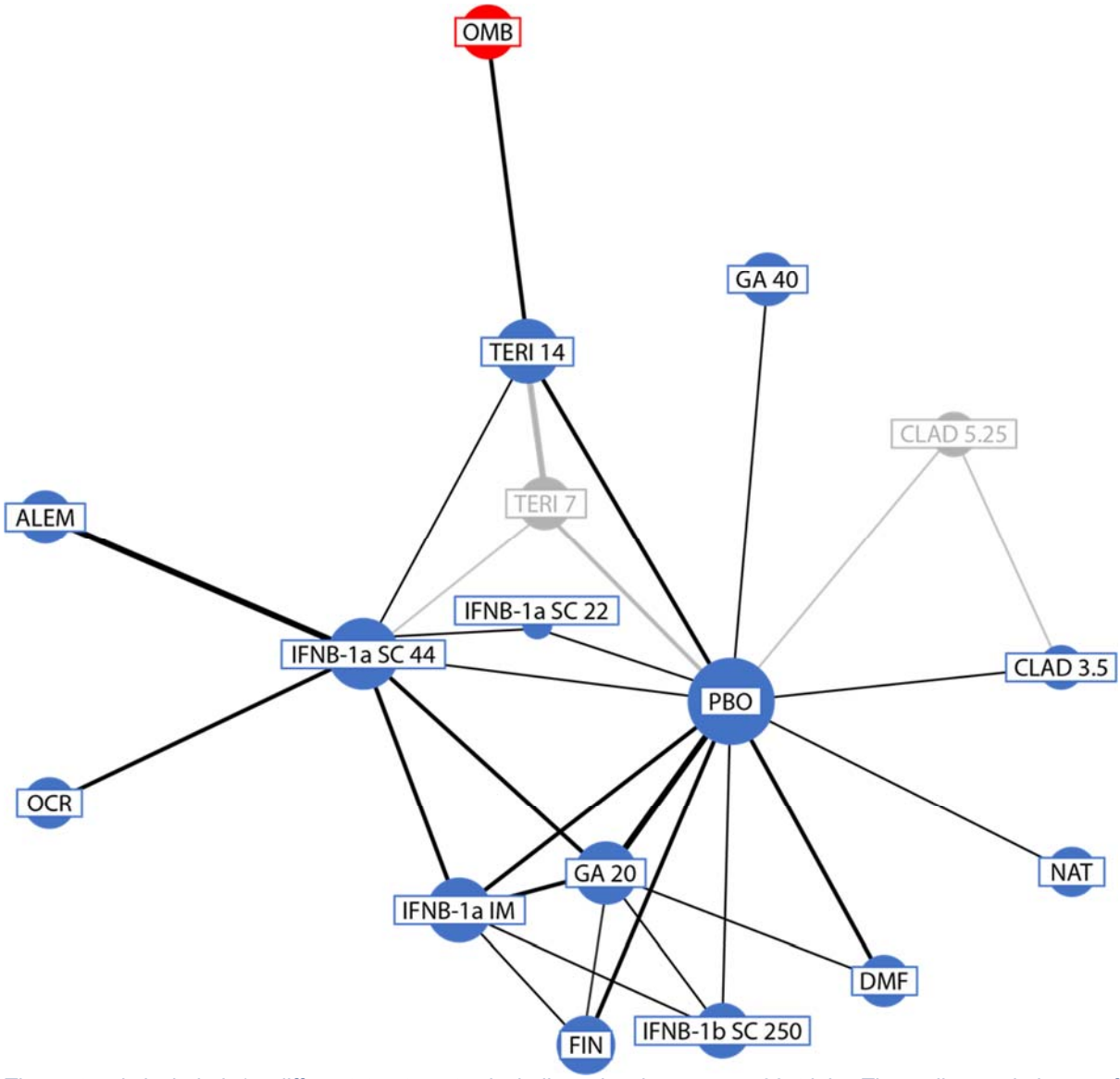
Figure 5: ARR network diagram – Document B, Section B.2.9.4, Figure 19 (page 83)



The network included 17 different treatments, including placebo, across 30 trials. The unlicensed doses of cladribine (5.25 mg/kg) and teriflunomide (7 mg) were run in the network, but results are not presented as these doses are 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; QD: once a day; Q2D: every 2 days; Q4W: every 4 weeks; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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Figure 6: ARR league table – Document B, Section B.2.9.4, Figure 20 (page 84)

All values displayed as HR (95% CrI). Pink denotes comparisons that exclude unity.

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; QD: once a day; Q2D: every 2 days; Q4W: every 4 weeks; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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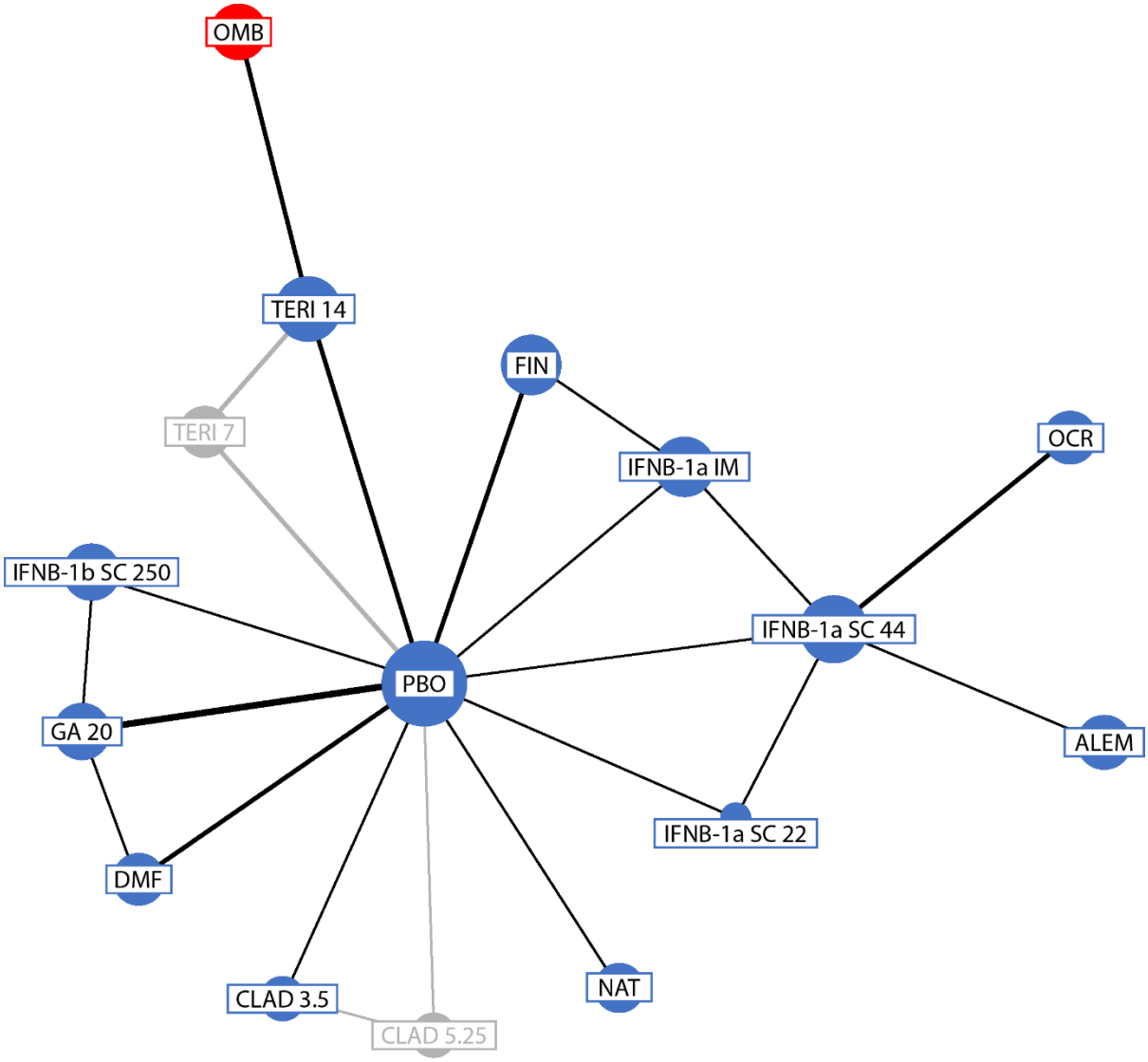
A.8.2 CDW-3

The network diagram for time to CDW-3 is displayed in Figure 7. The relative effectiveness of ofatumumab at delaying time to CDW-3 versus other DMTs and placebo is summarised in the league table in Figure 8. Ofatumumab (HR: [redacted], 95% CrI: [redacted]) was the second most effective treatment versus placebo after ocrelizumab (HR: [redacted], 95% CrI: [redacted]).

Figure 7: Time to CDW-3 network diagram – Document B, Section B.2.9.4, Figure 22 (page 86)



The network included 16 different treatments, including placebo, across 21 trials. The unlicensed doses of cladribine (5.25 mg/kg) and teriflunomide (7 mg) were run in the network, but results are not presented as these doses are 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; 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; QD: once a day; Q2D: every 2 days; Q4W: every 4 weeks; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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Figure 8: Time to CDW-3 league table using the aligned criteria – Document B, Section B.2.9.4, Figure 23 (page 87)

All values displayed as HR (95% CrI). Pink denotes comparisons that exclude unity.
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; 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; QD: once a day; Q2D: every 2 days; Q4W: every 4 weeks; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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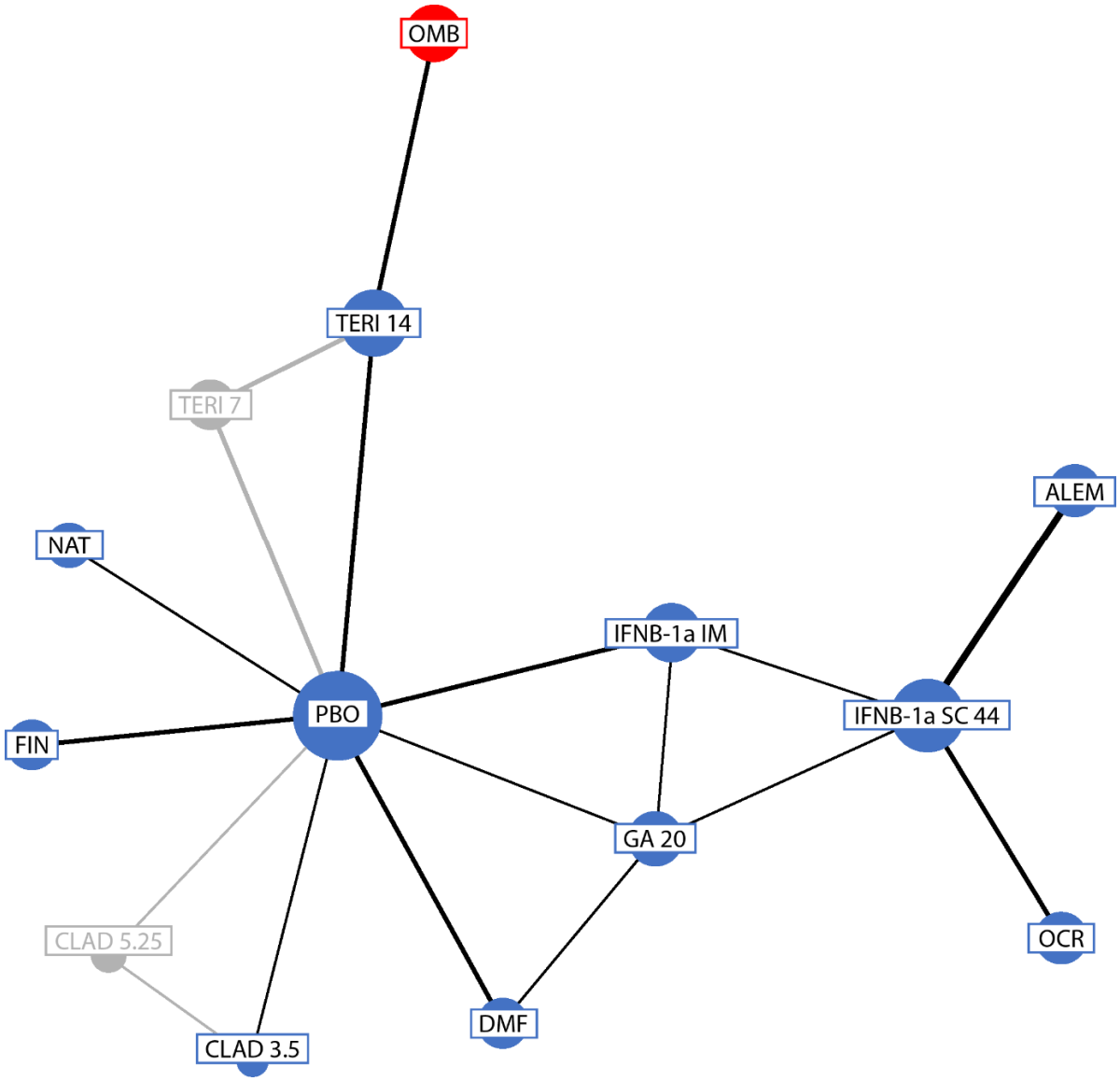
A.8.3 CDW-6

The network diagram for time to CDW-6 is displayed in Figure 9. The relative effectiveness of ofatumumab at delaying time to CDW-6 versus other DMTs and placebo is summarised in the league table in Figure 10. Ofatumumab (HR: [redacted], 95% CrI: [redacted]) the fourth most effective treatment versus placebo, with an HR similar to that of ocrelizumab (HR: [redacted], 95% CrI: [redacted]) and natalizumab (HR: [redacted], 95% CrI: [redacted]) and after alemtuzumab (HR: [redacted], 95% CrI: [redacted]).

Figure 9: Time to CDW-6 network diagram – Document B, Section B.2.9.4, Figure 25 (page 89)



The network included 14 different treatments, including placebo (PBO), across 20 trials. The unlicensed doses of cladribine (5.25 mg/kg) and teriflunomide (7 mg) were run in the network, but results are not presented as these doses are 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; IFNB-1a IM 30: IFN β-1a IM 30 µg QW; IFNB-1a SC 44: IFN β-1a SC 44 µg TIW; 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; QD: once a day; Q2D: every 2 days; Q4W: every 4 weeks; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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Figure 10: Time to CDW-6 league table using the aligned criteria – Document B, Section B.2.9.4, Figure 26 (page 90)

All values displayed as HR (95% CrI). Pink denotes comparisons that exclude unity.

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; IFNB-1a IM 30: IFN β-1a IM 30 µg QW; IFNB-1a SC 44: IFN β-1a SC 44 µg TIW; 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; QD: once a day; Q2D: every 2 days; Q4W: every 4 weeks; SC: subcutaneous; TERI 7: teriflunomide PO 7 mg QD; TERI 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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A.9 Key clinical issues

- Direct comparison of efficacy and safety of ofatumumab in a clinical trial setting is not available for all relevant comparators, necessitating an NMA to be performed. In the feasibility assessment, heterogeneity was identified in some patient baseline characteristics, notably time since first MS symptoms, T2 lesion volume and prior DMT use. Despite these differences between trials, an NMA was considered the most robust comparison option to make the best use of the available evidence.
- A substantial amount of heterogeneity exists in the definition of a disability worsening event across MS trials. Between-study differences in outcome definitions could partially be addressed in the NMA by recalculating ASCLEPIOS CDW data in line with a definition commonly used in other trials, which also had higher concordance with the structure of the economic model. Results for the CDW NMAs using the pre-defined criteria from ASCLEPIOS and using a definition fully in line with the definition used in the ocrelizumab OPERA trials are presented as scenario analyses in Document B, Section 2.9.5 (page 91) and Section 2.9.6 (page 95), respectively.
- Due to the *post-hoc* nature of subgroup analyses in HA RRMS and RES RRMS, each subgroup contains a relatively small sample size such that few events were observed for analysis, leaving them underpowered. Performing NMAs within the HA RRMS and RES RRMS subgroups was found to be unfeasible due to a lack of available data to connect all relevant comparators to form a network. Furthermore, the lack of available baseline characteristics for these subgroups reported in comparator trials prevents the population adjustments necessary for alternative methods such as matching-adjusted indirect comparisons or simulated treatment comparisons. Instead, the relative effectiveness estimates from the NMAs conducted in the ITT population were also used for the cost-effectiveness analyses in the HA RRMS and RES RRMS subgroups, thereby maintaining randomisation.

A.10 Overview of the economic analysis

A discrete-time cohort Markov model was employed to evaluate the cost-effectiveness of ofatumumab in patients with RRMS with annual cycles and a lifetime horizon. The model structure was based on 10 EDSS scores (where the half-point EDSS scores were rounded down and combined with the lower EDSS score, e.g. EDSS 4 comprised EDSS 4.0 and 4.5) with 21 states (10 states each [EDSS 0–9] for RRMS and SPMS, and a 'Death' state). These different health states reflect differences in disability worsening, QoL, treatment practices, and cost of disease management.[37-44] This is in line with the previous NICE appraisals in RRMS which informed the development of this economic model (TA127,[37] TA254,[38] TA303,[39] TA312,[40] TA320,[41] TA493 [now superseded by TA616],[42] TA527,[43] TA533[44]). A schematic representation of the model is presented in Figure 11.

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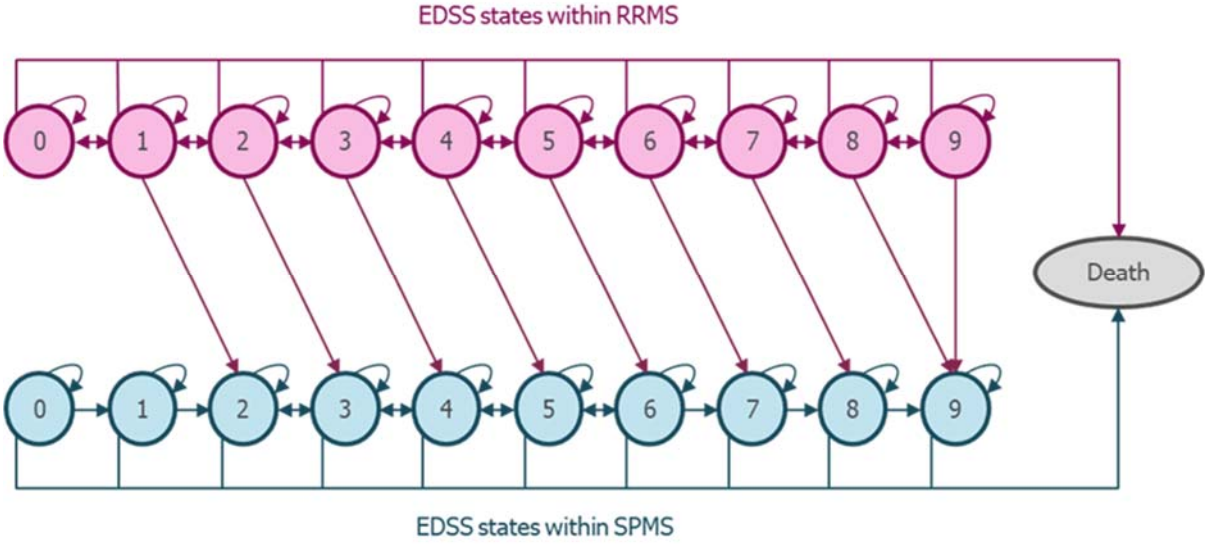
Figure 11: Schematic of the model structure – Document B, Section B.3.2.2, Figure 36 (page 118)



In the base case, improvement in EDSS state is possible in all EDSS states in RRMS and in EDSS states 3–6 in SPMS. Improvement from EDSS state 7 does not result in treatment restarting. It is possible for a patient to move between states that are more than one EDSS point apart. Transition arrows indicating movement between states more than one EDSS point apart in a single cycle have been omitted for clarity. Patients may transition to the death state from any EDSS state.
Abbreviations: EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Model characteristics:

- The major outcomes considered in the model were relative efficacy on disability worsening (CDW-6) and reduction in the frequency of relapses as assessed by ARR. These outcomes were applied to natural history data to capture EDSS state transitions and relapse event-associated costs and utility values within the model.
- All analyses were performed from a National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits, in line with the NICE Methods Guide.[45]
- An annual cycle length was employed in the model, in line with previous MS appraisals.[44] A lifetime time horizon was considered in the model.
- The Association of British Neurologists (ABN) clinical guideline and the NHS England Treatment Algorithm for MS DMTs state that treatment should be stopped if the patient has developed an inability to walk (EDSS 7.0), which is persistent for more than 6 months, due to MS.[17, 46] The economic analysis therefore applies a stopping rule at EDSS 7.0 (patients restricted to wheelchair).

A summary of the model characteristics is provided in Table 7.

Table 7: Features of the economic analysis – Document B, Section B.3.2.2, Table 53 (page 120)

Factor	Current appraisal	
	Chosen values	Justification
Time horizon	Lifetime	MS is a lifelong condition
Source of natural history EDSS	*RRMS health states:* British Columbia	*RRMS health states:* Consistent with previous NICE MS appraisals

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	SPMS health states: EXPAND and London Ontario SPMS dataset	*SPMS health states:* The British Columbia database does not provide a separate SPMS transition matrix and using a matrix which is predominantly RRMS is implausible for SPMS. Data from the placebo arm of a recent trial were available, supplemented by the SPMS-specific transitions from the London Ontario data set; this matrix was preferred by NICE in an ongoing appraisal (ID1304).[47]
Source of natural history relapse	*RRMS health states:* Patzold et al., 1982 combined with UK MS Survey data.[37, 48] *SPMS health states:* EXPAND, Patzold et al., 1982 and UK MS Survey data.[37, 48]	Consistent with previous and ongoing NICE MS appraisals
Source of MS mortality multiplier	Pokorski, 1997 extrapolated for EDSS states[49]	Consistent with previous NICE MS appraisals
Application of treatment effect	• CDW-6 (aligned criteria NMA) • ARR • No treatment effect applied to SPMS transition	CDW-6 is a longer-term outcome than CDW-3 and has been preferred over CDW-3 by NICE appraisal committees in previous MS appraisals. DMTs for which CDW-6 was not available were excluded. Both subgroups (HA and RES RRMS) used the main ITT NMA data as subgroup-specific NMAs were infeasible and no subgroup-specific natural history inputs are available.
Treatment effect waning	Not applied; all-cause treatment discontinuation acts as a proxy for waning	Consistent with TA533 in which the NICE appraisal committee accepted that treatment stopping could be considered a proxy for the treatment effect waning in the absence of evidence. Given the choice of other DMTs, patients are not likely to be maintained on a treatment that is ineffective. This approach was validated by a UK-based treating Consultant Neurologist.
Application of treatment discontinuation	Based on NMA; reference probability of discontinuation was ofatumumab (all-cause discontinuation), constant annualised rates	Applying the relative effects (i.e. discontinuation HRs) from the NMA allows for a consistent estimation of discontinuation probabilities
Stopping rule	EDSS ≥7.0 SPMS transition	Consistent with previous NICE MS appraisals

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Source of patient utilities	Pooled ASCLEPIOS trials (ITT; EDSS 0–6) and Orme et al., 2007 (EDSS 7–9)[50]	The ASCLEPIOS trials provide the most recent and relevant source of utility data, which is supplemented with literature data from Orme et al. in line with recent NICE MS appraisals.
Source of relapse disutility	Pooled ASCLEPIOS trials	Most up to date and relevant data available
Source of caregiver disutility	Natalizumab NICE appraisal [TA127][37]	Consistent with the majority of previous NICE MS appraisals[37-41, 44]
Source of EDSS cost	UK MS survey data with values inflated to current cost year.[43]	Consistent with NICE appraisal committee preferences of recent NICE MS appraisals[37, 38, 41]
Source of relapse cost	Hawton et al., 2016.[51]	Most up to date data available

Abbreviations: ARR: annualised relapse rate; CDW-3/6: 3-/6-month confirmed disability worsening; DMT: disease-modifying therapy; EDSS: Extended Disability Status Scale; HA: highly active; HR: hazard ratio; ITT: intent-to-treat; MS: multiple sclerosis; NMA: network meta-analysis; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; TA: technology appraisal.

A.11 Incorporating clinical evidence into the model

A.11.1 Baseline patient characteristics

The baseline input parameters for defining patient characteristics considered in the model were generated from RRMS patients from both arms (ofatumumab and teriflunomide) from the pooled ASCLEPIOS trials. Baseline characteristics of the HA RRMS and RES RRMS subgroups were used in separate analyses of these populations.

A.11.2 Disability worsening

The transition of patients between each of the EDSS states was modelled using natural history data. Treatment benefits (HRs for disability worsening) were applied to the natural history disability worsening transition matrix to estimate the disability worsening of patients on DMT.

The British Columbia natural history dataset was used for the RRMS health states as it has been the preferred choice in prior NICE MS appraisals, and does not censor improvement in patients' disability. The placebo arm data from the EXPAND trial and the London Ontario dataset were used for the SPMS health states as they provide SPMS-specific data which are more appropriate to be used in these health states and their use was the preferred approach by NICE in the ongoing ID1304 appraisal.[47] This combination of using both the British Columbia and London Ontario datasets for RRMS and SPMS, respectively, is consistent with prior NICE MS appraisals.

The natural history transitions from RRMS to SPMS assume that the transition is always associated with an increase in EDSS of one. This assumption has been accepted in prior NICE MS appraisals and is in line with clinical practice, where an SPMS diagnosis will be associated with a worsening event.

The HRs of CDW-6 for each treatment applied in the model were available from the aligned criteria NMA, in which the ASCLEPIOS trial data were reanalysed with another definition of a worsening event commonly used across MS trials.

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In both the HA RRMS and RES RRMS subgroups, the main ITT NMA data were used, as subgroup-specific NMAs were infeasible (See Document B, Section B.2.9) and, in addition, no subgroup-specific natural history inputs are available.

A.11.3 Relapse rates

In the base case, relapse rates were considered to be dependent on EDSS; this approach was considered by a UK-based treating Consultant Neurologist to be more appropriate and relevant to patients in UK clinical practice than EDSS-independent rates and has previously been preferred by NICE appraisal committees.[43, 44] The natural history data for relapse rates were derived from previous appraisals where they had been calculated for each EDSS score using UK MS survey data and Patzold and Pocklington et al., 1982, for RRMS, and using EXPAND trial data (from the ongoing siponimod NICE appraisal [ID1304]), UK MS survey data and Patzold and Pocklington et al., 1982, for SPMS.[37, 48, 52] The relative effects of treatments were applied in the model by applying the RR obtained from the NMA to the natural history relapse rates.

A.11.4 Mortality

Rates for all-cause mortality for the general population were derived from age- and gender-specific mortality rates for England and Wales for 2016–2018.[53] Patients are assumed to live up to a maximum of 100 years.

A curve fit to data from Pokorski, 1997[49] is used in the base case analyses as an EDSS-dependent mortality multiplier in MS. Pokorski, 1997 assumes different EDSS scores have different mortality HRs and has been used in previous NICE MS appraisals.

A.11.5 Discontinuation

The all-cause discontinuation HRs were obtained from an NMA (described in Document B Appendix D). The discontinuation probability should be interpreted as the observed annual probability of discontinuing treatment for any reason, including intolerance, lack of efficacy or other. In order to calculate the probability of discontinuation (absolute effects) for each treatment using the relative effect estimates from the NMA, the annualised all-cause discontinuation probability from the ofatumumab arms of the ASCLEPIOS trials was used as the reference arm. The model assumes a time-constant rate of discontinuation from treatment derived by applying the HRs from the NMA to the ofatumumab discontinuation probability.

In the model, patients can discontinue treatment for any reason, including lack of efficacy. Therefore, any potential efficacy waning of individual DMTs is already captured within the model via all-cause discontinuations. Inclusion of a separate arbitrary waning of treatment effect in the model is considered to lack clinical plausibility since it would not reflect routine clinical practice of discontinuing current therapy if it becomes ineffective. The approach taken in this submission is consistent with the NICE appraisal committee preferences for the most relevant recent appraisal, TA533.[44] Consideration of discontinuation as a proxy for waning was also considered the most valid approach by a UK-based treating Consultant Neurologist consulted by Novartis. As described in Section A.7.9 , the overall risk of immunogenicity, and hence reduction of treatment effect, due to formation of neutralising anti-drug antibodies is considered unlikely with ofatumumab.

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A.11.6 Safety

The AE probabilities for ofatumumab and teriflunomide were derived from the ASCLEPIOS trial data. AE probabilities for cladribine were derived from the CLARITY trial,[54] while AE probability data for all other comparators were sourced from TA533.[44] Based on the average proportion of SAEs in the pooled ASCLEPIOS trials, it was assumed that for each AE, 89.87% of the events were non-serious and 10.13% were serious. Probabilities were assumed to remain constant across Year 1 and subsequent years of therapy.

A.11.7 Health state utilities (HSUs)

Health-related quality of life data were collected in the ASCLEPIOS trials using the EQ-5D-5L questionnaire and these data, pooled across both ASCLEPIOS trials, were cross-walked to a utility score based on the algorithm presented in van Hout et al., 2012, consistent with the NICE reference case.[55, 56] From these data, health state utilities (HSUs) could be derived for EDSS 0–6. HSUs for EDSS 7–9 were sourced from Orme et al., 2007.[50] In the base case, these trial data supplemented by Orme et al. values were utilised; this approach has been accepted in previous NICE appraisals, including TA533.[44] These utility values for RRMS and SPMS are presented in Table 8.

The disutilities associated with experiencing a relapse were derived from ASCLEPIOS trial data and are presented in Table 9. Disutilities for caregivers and AEs are also reported in Document B, Section B.3.4.

Table 8: HSUs derived from ASCLEPIOS trials and supplemented by Orme et al. 2007

EDSS	RRMS		SPMS	
	Patient utility	SE	Patient utility	SE
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	0.297	0.094	0.252	0.110
8	−0.049	0.095	−0.094	0.111
9	−0.195	0.119	−0.240	0.135

Abbreviations: EDSS: Expanded Disability Status Scale; HSU: health state utility; RRMS: relapsing-remitting multiple sclerosis; SE: standard error; SPMS: secondary progressive multiple sclerosis.

Table 9: Relapse disutility considered in the model derived from the ASCLEPIOS trials

Relapse severity	Disutility coefficient	SE
Mild	[redacted]	[redacted]
Moderate		
Severe		

These disutilities were assumed to apply for three months and have been calculated from the annual disutility associated with relapse (0.043).
Abbreviations: SE: standard error.

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A.12 Key model assumptions and inputs

The key model assumptions and inputs are summarised in Table 10.

Table 10: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Patient population [B.3.2.1, page 118]	The patient population in the ASCLEPIOS trials is representative of the NHS population eligible for treatment with ofatumumab	The model population was consistent with the population expected to be treated with ofatumumab in UK clinical practice.
Treatment discontinuation [B.3.2.2, page 118, and 3.2.3, page 122]	Patients who transition from RRMS to SPMS discontinue treatment	In line with current treatment recommendations in the UK that DMTs are stopped following transition to SPMS.
	Patients who reach the EDSS treatment threshold of 7 discontinue DMT and receive best supportive care (BSC)	In line with ABN guidelines that patients who reach EDSS 7.0 discontinue treatment.
	Treatment benefits of DMTs are accrued during the treatment period only	After discontinuing the DMT, patients will move to BSC and no residual treatment effect is modelled.
Waning of efficacy [B.3.3.5, page 133]	Any long-term treatment effect waning is captured in all-cause discontinuation	In line with the NICE appraisal committee preferences during the appraisal for ocrelizumab, TA533.[44]
Adverse events [B.3.3.6, page 136]	AEs are assumed to occur at a constant rate in patients receiving DMTs and are assumed to stop after discontinuing DMTs	A similar approach was used in previous NICE RRMS submissions.[44]

Abbreviations: ABN: Association of British Neurologists; AE: adverse events; BSC: best supportive care; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; NHS: National Health Service; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

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A.13 Base case ICER (deterministic)

The base case cost-effectiveness results are presented in Table 11. The cost-effectiveness results for ofatumumab versus the relevant comparators in the HA and RES RRMS subgroups are presented in Table 12 and Table 13, respectively. For all analyses, ofatumumab was considered at its PAS price. Since Fingolimod (Gilenya®) is a Novartis product, the PAS discount is known and was taken into account for these analyses. A PAS agreement is also known to apply to ocrelizumab, teriflunomide, dimethyl fumarate, glatiramer acetate (Brabio®), Avonex® and Rebif® but the discounts are not considered in these analyses as they are confidential and not known to Novartis.

In the RRMS population, ofatumumab was found to be cost effective versus all comparators: ofatumumab was [redacted] versus dimethyl fumarate and teriflunomide, [redacted] versus Avonex®, glatiramer acetate and Rebif®, and [redacted] versus ocrelizumab [redacted]

The HA RRMS subgroup was defined as patients with RRMS previously treated with any DMT who discontinued their last DMT due to lack of efficacy. The RES RRMS subgroup was defined as patients with RRMS with ≥2 relapses in the previous year and ≥1 T1 Gd-enhancing lesion on baseline brain MRI. In the HA RRMS subgroup, ofatumumab was [redacted] versus cladribine and fingolimod and was [redacted] versus ocrelizumab [redacted]. In the RES RRMS subgroup, ofatumumab was [redacted] versus cladribine and was [redacted] versus natalizumab and ocrelizumab [redacted]. Overall, ofatumumab was found to be cost-effective versus all comparators except alemtuzumab in HA and RES RRMS.

Table 11: Base case results at ofatumumab PAS price, RRMS population (deterministic) – Document B, Section B.3.7, Table 84 (page 150)

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Avonex®	Avonex® (IFN β-1a)	19.46	[redacted]	5.09	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.56	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	19.47	[redacted]	5.15	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.07	[redacted]	0.51	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	19.43	[redacted]	4.92	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.10	[redacted]	0.74	[redacted]	[redacted]
Ocrelizumab	Ocrelizumab	19.55	[redacted]	5.72	-	-	-	-	-

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	Ofatumumab	19.54	[redacted]	5.66	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44 (IFN β-1a)**	19.46	[redacted]	5.05	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.61	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.89	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.11	[redacted]	0.77	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life-years gained; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 12: Base case results at ofatumumab PAS price, HA RRMS population (deterministic) – Document B, Section B.3.7, Table 85 (page 150)

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.46	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.05	[redacted]	-0.33	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	5.00	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.02	[redacted]	0.12	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.60	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.08	[redacted]	0.52	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	5.19	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.
Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

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Table 13: Base case results at ofatumumab PAS price, RES RRMS population (deterministic) – Document B, Section B.3.7, Table 86 (page 151)

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Alemtuzumab	Alemtuzumab	20.09	[redacted]	6.14	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.05	[redacted]	−0.37	[redacted]	[redacted]
Cladribine	Cladribine	20.02	[redacted]	5.66	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	Natalizumab	20.05	[redacted]	5.82	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.05	[redacted]	[redacted]
Ocrelizumab	Ocrelizumab	20.05	[redacted]	5.84	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; PAS: patient access scheme; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

A.14 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 Monte Carlo simulations, in order to incorporate the uncertainty in costs and outcomes. Results of the PSA for the comparison of ofatumumab (at PAS price) versus all comparators (at list price except for fingolimod, a Novartis product for which the PAS discount is known) in the RRMS, HA RRMS and RES RRMS populations are summarised in Table 14, Table 15 and Table 16, respectively. The cost-effectiveness acceptability curves for the base case RRMS population are presented in Figure 12. The cost-effectiveness acceptability curves for the HA RRMS and RES RRMS populations are presented in Document B, Section B.3.8.1 (pages 156–157).

Table 14: Probabilistic sensitivity results at ofatumumab PAS price (RRMS population) – Document B, Section B.3.8.1, Table 87 (page 152)

Treatment	Total costs (probabilistic)	Total QALYs (probabilistic)	Incremental costs (probabilistic)	Incremental QALY (probabilistic)	Fully incremental ICER (£/QALY)	Probability of being cost-effective at £30,000 WTP threshold
[redacted]	[redacted]	[redacted]	-	-	-	[redacted]

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

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; WTP: willingness-to-pay.

Table 15: Probabilistic sensitivity results at ofatumumab PAS price (HA RRMS population) – Document B, Section B.3.8.1, Table 88 (page 152)

Treatment	Total costs (probabilistic)	Total QALYs (probabilistic)	Incremental costs (probabilistic)	Incremental QALY (probabilistic)	Fully incremental ICER (£/QALY)	Probability of being cost-effective at £30,000 WTP threshold
[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]	[redacted]	[redacted]

[a] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.
Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 16: Probabilistic sensitivity results at ofatumumab PAS price (RES RRMS population) – Document B, Section B.3.8.1, Table 89 (page 153)

Treatment	Total costs (probabilistic)	Total QALYs (probabilistic)	Incremental costs (probabilistic)	Incremental QALY (probabilistic)	Fully incremental ICER (£/QALY)	Probability of being cost-effective at £30,000 WTP threshold
[redacted]	[redacted]	[redacted]	-	-	-	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Figure 12: Cost-effectiveness acceptability curves in the RRMS population – Document B, Section B.3.8.1, Figure 39 (page 155)

Abbreviations: RRMS: relapsing-remitting multiple sclerosis.

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A.15 Key sensitivity and scenario analyses

A.15.1 Deterministic sensitivity analyses

One-way deterministic sensitivity analyses (OWSA) were undertaken for ofatumumab versus ocrelizumab and dimethyl fumarate in the RRMS population and reported in Figure 13 and Figure 14, respectively; OWSAs versus all comparators in the RRMS and HA and RES RRMS populations are presented in Document B, Section B.3.8.2. Where possible, upper and lower bounds were based on CIs reported in the literature. In all other cases, bounds were assumed to be ±20% of the parameter value, in the absence of data. The tornado plots show the top ten drivers of cost-effectiveness in the comparison of ofatumumab with ocrelizumab and dimethyl fumarate. In both plots, it can be seen that the most influential parameters on the net monetary benefit (NMB) results at a £30,000 threshold were the estimates of effectiveness on disability worsening for each DMT. Other than disability worsening, results were largely robust to parameter uncertainty, demonstrating the stability of the model results to parameter uncertainty other than relative effectiveness.

Figure 13: Deterministic sensitivity results for ofatumumab versus ocrelizumab (NMB) – Document B, Section B.3.8.2, Figure 47 (page 160)

Abbreviations: NMB: net monetary benefit.

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Figure 14: Deterministic sensitivity results for ofatumumab versus dimethyl fumarate (NMB) – Document B, Section B.3.8.2, Figure 45 (page 159)

Abbreviations: NMB: net monetary benefit.

A.15.2 Scenario analyses

Deterministic scenario analyses were conducted to evaluate the robustness of the ICER estimates. The key scenario analyses and their impact on the base case NMB for the RRMS population are presented in Table 17. Further scenario analyses, including scenario analyses in the HA RRMS and RES RRMS populations, are presented in Document B, Sections B.3.8.

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Table 17: Key scenario analyses – Document B, Section B.3.8.3, Table 92 (page 167)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base case NMB versus comparator[a]
Efficacy estimate	Use of the pre-defined criteria NMA for a disability worsening event to inform the CDW-6 efficacy estimates	The base case used reanalysed ASCLEPIOS CDW-6 data ("aligned criteria") to reduce heterogeneity in the network and achieve greater concordance with a well-established cost-effectiveness model structure.[39, 43, 44] In this scenario, the impact of using the CDW definition from the ASCLEPIOS trials ("pre-defined criteria") was tested.	**Avonex®:** −76% **Dimethyl fumarate:** −18% **Glatiramer acetate:** −68% **Ocrelizumab:** −22% **Rebif® 44:** −54% **Teriflunomide:** −23%
Efficacy estimate	Use of the OPERA-aligned criteria NMA for a disability worsening event to inform the CDW-6 efficacy estimates	The base case used reanalysed ASCLEPIOS CDW-6 data ("aligned criteria") to reduce heterogeneity in the network and achieve greater concordance with a well-established cost-effectiveness model structure.[39, 43, 44] In this scenario, the impact of using a CDW definition fully aligned with the definition used in the OPERA trials ("OPERA-aligned criteria") was tested due to the importance of ocrelizumab as a key comparator (See Section B.2.9.2 of Document B for further details).	**Avonex®:** +96% **Dimethyl fumarate:** +23% **Glatiramer acetate:** +85% **Ocrelizumab:** +40% **Rebif® 44:** +62% **Teriflunomide:** +25%
All-cause discontinuation rate	Time-dependent all-cause discontinuation using the Weibull distribution	The base case assumes time-constant discontinuation from DMTs. This scenario explored the effect of assuming time-dependent all-cause discontinuation using the Weibull distribution as the best-fitting time-dependent discontinuation extrapolation curve.	**Avonex®:** +1% **Dimethyl fumarate:** 0% **Glatiramer acetate:** +3% **Ocrelizumab:** 0% **Rebif® 44:** −1% **Teriflunomide:** 0%
Source of health state utility values	Use of health state utility values from Orme et al., 2007	The base case considers utility values derived from the ASCLEPIOS trials as the most relevant and up to date data. This scenario explored the effect of use of utility values from another commonly used source.	**Avonex®:** −22% **Dimethyl fumarate:** −5% **Glatiramer acetate:** −25% **Ocrelizumab:** +1% **Rebif® 44:** −19% **Teriflunomide:** −8%

[a] NMB was valued at £30,000 per QALY.
Abbreviations: CDW-6: 6-month confirmed disability worsening; DMT: disease-modifying therapy; ITT: intent-to-treat; MS: multiple sclerosis; NMA: network meta-analysis; NMB: net monetary benefit; RRMS: relapsing-remitting multiple sclerosis.

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A.16 Innovation

Ofatumumab is a next generation B cell therapy for the treatment of RMS with a targeted mode of action. Ofatumumab, the only fully-human B cell depleting antibody for MS, selectively binds to CD20 on the cell surface of B lymphocytes, initiating their immune destruction to reduce the inflammatory processes underlying the symptoms of MS. Ofatumumab offers high efficacy, was well-tolerated in clinical trials and can be self-administered by patients at home, enabling its use first line in all RRMS patients unlike several other high-efficacy DMTs (alemtuzumab, cladribine, and natalizumab) which have been restricted by the EMA to patients with HA or RES disease due to their safety profiles.[57-59]

Ocrelizumab is the only B cell therapy currently recommended by NICE for use in patients with RRMS and the only high-efficacy DMT that can be used as a first-line treatment (non-RES RRMS). In contrast to ocrelizumab, which is administered in hospital via infusion lasting several hours, ofatumumab will be provided in pre-filled auto-injector pens for subcutaneous injection, intended for monthly self-administration at home by patients or their carers. It is considered that the introduction of a subcutaneous high-efficacy B cell therapy will significantly reduce the burden on the NHS associated with the IV administration of ocrelizumab, natalizumab or alemtuzumab. When accounting for the time needed for completion of pre-infusion requirements and post-infusion observation, patients typically spend [redacted] hours in the clinic for an MS DMT infusion appointment, with some patients also being treated as inpatients.[19] Already before the COVID-19 pandemic, patients often faced a considerable waiting time of several months for their first infusion appointment after the treatment decision for an IV DMT had been made.[19, 20] Given the continuing demands on the NHS under the current COVID-19 pandemic, capacity issues potentially affecting the timely and regular administration of MS infusion treatments are an area of concern. The availability of ofatumumab as the first high-efficacy DMT for subcutaneous at-home administration will therefore be beneficial for patients with MS and at the same time reduce the burden on the NHS by freeing up infusion treatment resources.

Self-administration would also address patient access issues associated with difficulties with travel to infusion clinics for high-efficacy DMTs, due to MS-associated disabilities or long distances to clinics. In addition, people with pre-existing medical conditions have a higher risk of becoming severely ill from COVID-19. Immunosuppressive therapies including MS DMTs may further predispose patients to contract coronavirus or increase the severity of infections.[60] Therefore, at a time when patients with MS may be shielding themselves but still need treatment to control their disease, self-administration of ofatumumab removes the need for infusion treatment in a hospital setting. Ofatumumab would provide an option to receive high-efficacy treatment in the safety of patients' homes and thus reduce the risk of potential exposure to infection.

As a monthly self-administered treatment, ofatumumab would be the first B cell therapy accessible for all patients with RRMS regardless of travel constraints, providing a high-efficacy and well-tolerated treatment option for all patients, including those for whom IV infusion therapies are unsuitable for the aforementioned reasons. Ofatumumab could therefore shift the treatment paradigm in the RRMS population towards early use of high-efficacy treatment which has been associated with improvements in clinical outcomes.[61, 62] At the same time, ofatumumab has the potential to reduce the burden on the NHS associated with the increasing use of infusion therapies, which is even more critical under the current capacity constraints imposed by the COVID-19 pandemic.

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A.17 Budget impact

The expected net budget impact of ofatumumab in the treatment of patients with RRMS is presented in Table 18.

Table 18: Net Budget impact – Company Budget Impact Analysis Document, Table 7 (page 14)

	Company estimate	Cross reference
Estimated annual budget impact on the NHS in England (with PAS)	Year 1: [redacted] Year 2: [redacted] Year 3: [redacted] Year 4: [redacted] Year 5: [redacted]	Company Budget Impact Analysis Document, page 14

Abbreviations: NHS: National Health Service; PAS: Patient Access Scheme.

A.18 Interpretation and conclusions of the evidence

The ASCLEPIOS trials met their primary endpoint and demonstrated that treatment with ofatumumab was associated with a significant reduction in ARR and a significantly reduced risk of CDW-3 and CDW-6 in patients with RRMS, compared to active treatment with teriflunomide.

A reduction in relapse rates has a meaningful impact on patients, both due to a reduction in the short-term negative effects of their occurrence and due to the significant and consistent correlation between clinical relapses and longer-term disability worsening.[6, 63, 64] In the ASCLEPIOS I and II trials, ofatumumab was associated with an adjusted ARR of 0.11 and 0.10, respectively, equivalent to one relapse in 10 years. Ofatumumab was further associated with reductions in risk of disability worsening, allowing patients to maintain their physical abilities for longer and extend the time before EDSS 7.0 is reached, at which point patients require the use of a wheelchair and all DMTs are discontinued. Additionally, the ASCLEPIOS trial results demonstrated ofatumumab to be generally well tolerated, with an acceptable and manageable AE profile and minimal monitoring required. This demonstrates ofatumumab offers patients a high-efficacy option which can be used first line. This could shift the treatment paradigm in RRMS towards early use of high-efficacy treatment which has been associated with improvements in clinical outcomes.[61, 62]

In the absence of head-to-head clinical trial evidence comparing ofatumumab versus all relevant comparators except for teriflunomide, NMAs were performed. Overall, ofatumumab displayed numerically favourable or numerically similar efficacy relative to all established high-efficacy DMTs for the analysed outcomes of ARR, CDW-3 and CDW-6; in addition, ofatumumab displayed meaningfully better efficacy across all outcomes relative to all moderate efficacy DMTs. Overall, the results of the NMA support that ofatumumab is a high-efficacy DMT for treating patients with RRMS.

In the cost-effectiveness analyses, the base case results show that ofatumumab at the confidential PAS price is cost-effective versus all comparators in the RRMS population and the probabilistic results align with the deterministic results. Sensitivity and scenario analyses found the results to be robust to parameter uncertainty and key assumptions tested. In the HA RRMS and RES RRMS subgroup analyses, ofatumumab is cost-effective versus all comparators except alemtuzumab (a safety-restricted treatment for which many people are contraindicated or otherwise unsuitable).

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Overall, ofatumumab offers people with RRMS a DMT which uniquely combines high efficacy, tolerability and ease of monthly administration at home while offering the NHS a cost-effective option for the treatment of RRMS.

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References

1. Peterson LK, Fujinami RS. Inflammation, demyelination, neurodegeneration and neuroprotection in the pathogenesis of multiple sclerosis. J Neuroimmunol 2007;184:37-44.
2. Multiple Sclerosis Trust. MS: The Facts. Available at: https://www.mstrust.org.uk/about-ms/what-ms/ms-facts [Last accessed: 25th February 2020].
3. NHS. Multiple Sclerosis: Symptoms. Available at: https://www.nhs.uk/conditions/multiple-sclerosis/symptoms [Last accessed: 25th February 2020].
4. National Multiple Sclerosis Society. Symptoms and Diagnosis: Vision Problems. Available at: https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Vision-Problems [Last accessed: 25th Febrary 2020].
5. NHS. Multiple Sclerosis: Overview. Available at: https://www.nhs.uk/conditions/multiple-sclerosis/ [Last accessed: 24th February 2020].
6. Hauser SL, Oksenberg JR. The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. Neuron 2006;52:61-76.
7. MS Society. MS in the UK. Available at: https://www.mssociety.org.uk/what-we-do/our-work/our-evidence/ms-in-the-uk. [Last accessed: 14th July 2020].
8. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278-286.
9. Lublin F, Reingold S. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-911.
10. Multiple Sclerosis Trust. Types of MS. Available at: https://www.mstrust.org.uk/about-ms/what-ms/types-ms [Last accessed: 25th February 2020].
11. MS Society. Types of MS: Relapsing Remitting MS. Available at: https://www.mssociety.org.uk/about-ms/types-of-ms/relapsing-remitting-ms [Last accessed: 25th February 2020].
12. Multiple Sclerosis Trust. Managing Relapses: What is a Relapse? Available at: https://www.mstrust.org.uk/about-ms/ms-symptoms/managing-relapses#what-is-a-relapse [Last accessed: 25th February 2020].
13. Inojosa H, Proschmann U, Akgün K, et al. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. Journal of Neurology 2019.
14. Kobelt G, Thompson A, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe. Multiple Sclerosis 2017;23:1123-1136.
15. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. Brain 2006;129:595-605.
16. Corry M, While A. The needs of carers of people with multiple sclerosis: a literature review. Scand J Caring Sci 2009;23:569-88.
17. NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf [Last accessed: 27th July 2020].
18. National Institute for Health and Care Excellence (NICE). Ofatumumab for Treating Relapsing Multiple Sclerosis [ID1677]: Final Scope. Available at: https://www.nice.org.uk/guidance/gid-ta10557/documents/final-scope [Last Accessed: 14th July 2020].
19. IQVIA. Ofatumumab HTA Submission Support Research. 2020.
20. Novartis (Data on File): Multiple Sclerosis Advisory Board. 2020.
21. Lehmann-Horn K, Kronsbein HC, Weber MS. Targeting B cells in the treatment of multiple sclerosis: recent advances and remaining challenges. Therapeutic advances in neurological disorders 2013;6:161-173.
22. Voge NV, Alvarez E. Monoclonal Antibodies in Multiple Sclerosis: Present and Future. Biomedicines 2019;7:20.
23. Pacheco-Fernandez T, Touil I, Perrot C, et al. Anti-CD20 Antibodies Ofatumumab and Ocrelizumab Have Distinct Effects on Human B-Cell Survival. Presented at AAN 2018.

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24. Ancau M, Berthele A, Hemmer B. CD20 monoclonal antibodies for the treatment of multiple sclerosis: up-to-date. Expert Opinion on Biological Therapy 2019;19:829-843.
25. Novartis (Data on File): Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials (22nd November 2019)
26. Hauser S. Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. Presented at ECTRIMS, 11-13 September 2019, Stockholm (Sweden). 2019.
27. Novartis (Data on File): ASCLEPIOS I Clinical Study Report (9th December 2019).
28. Novartis (Data on File): ASCLEPIOS II Clinical Study Report (9th December 2019).
29. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of neurology 2011;69:292-302.
30. Kuhle J, Kropshofer H, Haering DA, et al. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 2019;92:e1007-e1015.
31. Ruuls SR, Lammerts van Bueren JJ, van de Winkel JG, et al. Novel human antibody therapeutics: the age of the Umabs. Biotechnol J 2008;3:1157-71.
32. Davda J, Declerck P, Hu-Lieskovan S, et al. Immunogenicity of immunomodulatory, antibody-based, oncology therapeutics. Journal for ImmunoTherapy of Cancer 2019;7:105.
33. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. New England Journal of Medicine 2016;376:221-234.
34. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis. New England Journal of Medicine 2011;365:1293-1303.
35. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:247-56.
36. Novartis (Data on File): Additional ITT Analyses.
37. National Institute for Health and Care Excellence (NICE). Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA127]. Available at: https://www.nice.org.uk/guidance/ta127 [Last accessed: 28th February 2020].
38. National Institute for Health and Care Excellence (NICE). Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA254]. Available at: https://www.nice.org.uk/guidance/ta254 [Last accessed: 28th February 2020].
39. National Institute for Health and Care Excellence (NICE). Teriflunomide for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA303]. Available at: https://www.nice.org.uk/guidance/ta303 [Last accessed: 23rd March 2020].
40. National Institute for Health and Care Excellence (NICE). Alemtuzumab for treating relapsing-remitting multiple sclerosis: Technology appraisal guidance [TA312]. Available at: https://www.nice.org.uk/guidance/ta312 [Last accessed: 28th February 2020].
41. National Institute for Health and Care Excellence (NICE). Dimethyl fumarate for treating relapsing-remitting multiple sclerosis: Technology appraisal guidance [TA320]. Available at: https://www.nice.org.uk/guidance/ta320. [Last accessed: 31st March 2020].
42. National Institute for Health and Care Excellence (NICE). Cladribine for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA493]. Available at: https://www.nice.org.uk/guidance/ta493 [Last accessed: 31st March 2020].
43. National Institute for Health and Care Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis: Technology appraisal guidance [TA527]. Available at: https://www.nice.org.uk/guidance/ta527. [Last accessed: 23rd March 2020].
44. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA533]. Available at: https://www.nice.org.uk/guidance/ta533 [Last accessed: 17th March 2020].
45. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal: Process and methods [PMG9]. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword [Last accessed: 6th April 2020].

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46. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol 2015;15:273-9.
47. National Institute for Health and Care Excellence (NICE). Siponimod for treating secondary progressive multiple sclerosis: Appraisal consultation document. Available at: https://www.nice.org.uk/guidance/gid-ta10436/documents/129 [Last accessed: 20th July 2020].
48. Patzold U, Pocklington PR. Course of multiple sclerosis: First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurologica Scandinavica 1982;65:248-266.
49. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med 1997;29:101-6.
50. Orme M, Kerrigan J, Tyas D, et al. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.
51. Hawton AJ, Green C. Multiple sclerosis: relapses, resource use, and costs. The European Journal of Health Economics 2016;17:875-884.
52. National Institute for Health and Care Excellence (NICE). Siponimod for treating secondary progressive multiple sclerosis [ID1304]: In development [GID-TA10436]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10436 [Last accessed: 15th June 2020].
53. Office for National Statistics. National life tables: England and Wales (2019). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables. [Last accessed: 6th April 2020].
54. Giovannoni G, Comi G, Cook S, et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. New England Journal of Medicine 2010;362:416-426.
55. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case [Last accessed: 15th June 2020].
56. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012;15:708-15.
57. EMA. Tysabri (natalizumab): Assessment Report. Available at: https://www.ema.europa.eu/en/documents/scientific-discussion/tysabri-epar-scientific-discussion_en.pdf. [Last accessed: 27th April 2020].
58. EMA. Mavenclad (cladribine): Assessment Report. Available at: https://www.ema.europa.eu/en/documents/assessment-report/mavenclad-epar-public-assessment-report_en.pdf [Last accessed: 27th April 2020].
59. EMA. Lemtrada (alemtuzumab): Assessment Report. Available at: https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-procedure-prac-assessment-report_en.pdf. [Last accessed: 3rd August 2020].
60. Association of British Neurologists. ABN Guidance on COVID19 and MS Therapies Press Release (March 2020). Available at: https://www.theabn.org/news/492925/ABN-guidance-on-COVID19-and-MS-therapies.htm. [Last accessed: 30th July 2020].
61. Stankiewicz JM, Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. Neurology - Neuroimmunology Neuroinflammation 2020;7:e636.
62. Harding K, Williams O, Willis M, et al. Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. JAMA Neurology 2019;76:536-541.
63. Fahrbach K, Huelin R, Martin AL, et al. Relating relapse and T2 lesion changes to disability progression in multiple sclerosis: a systematic literature review and regression analysis. BMC Neurology 2013;13:180.
64. Goodin DS, Reder AT, Bermel RA, et al. Relapses in multiple sclerosis: Relationship to disability. Mult Scler Relat Disord 2016;6:10-20.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Clarification questions company response

September 2020

File name	Version	Contains confidential information	Date
ID1677 Ofatumumab ERG Clarification Questions Company Response [fully redacted]	1.0	No	11th September 2020

Section A: Clarification on effectiveness data

Literature Searching

A1. One reference marked data on file is missing from the reference pack. *Company submission Doc B bibliography number 45: Novartis (Data on File): Multiple Sclerosis Advisory Board. 2020.* Cited on page 19 of company submission document B. Can the company please supply this reference?

This reference has been provided in the 'ERG CQs Reference Pack' (Data on File Multiple Sclerosis Advisory Board 2020) and should be treated as Commercial in Confidence (CIC).

Trial design and methods

A2. PRIORITY QUESTION: The company indicates that '*Analyses of all efficacy outcomes and summary of demography and baseline characteristics were performed on the FAS*' (company submission document B, table 7, page 32-33), with the number of patients shown as n=927 for ASCLEPIOS I and n=955 for ASCLEPIOS II (i.e., total n=1882). However, fewer participants seem to have been included in the analyses of various outcomes compared with the Full Analysis Set (FAS), for example company submission document B:

a) Table 11, annualised relapse rate (ARR), page 38: n= 906 (n= 454 for Ofatumumab and n= 452 for Teriflunomide) for ASCLEPIOS I and n=938 (n= 469 in each arm) for ASCLEPIOS II (total n=1844)

b) Table 12 & 13, 3-month confirmed disability worsening (CDW-3) & 6-month confirmed disability worsening (CDW-6), page 39 & 40: n= 944 for ofatumumab and n=931 for teriflunomide (total n=1875); also note corresponding figures 2 & 3 show n=932 for teriflunomide

c) Table 14, page 41, 6-month confirmed disability improvement (CDI-6), n= 749 for ofatumumab and n=723 for teriflunomide (total n=1472).

Please clarify the reasons behind the discrepancies in the numbers between those stated in the FAS and the numbers included in the analyses for the primary outcome and other outcomes in the company submission.

All patients in the full analysis set (FAS) are considered in the analysis of efficacy outcomes. However, patients who had missing values for covariates or completely missing values for all post-baseline assessments were implicitly excluded from the statistical analysis by the statistical procedure. The number of evaluable patients in the statistical model for each endpoint is provided in the results tables in the company submission. This number may be equal to or smaller than the total number of patients in the FAS.

a) Annualised relapse rate (ARR)

Among the 927 patients included in the FAS of ASCLEPIOS I, 21 patients were excluded from the analysis of the primary endpoint, ARR, due to missing values on model covariates. In ASCLEPIOS II, among the 955 patients included in the FAS, 17 patients were excluded from the analysis of ARR due to missing values on model covariates. Exclusions by treatment arm are summarised in Table 1.

Table 1: Patients excluded from the FAS in the ARR analysis

	ASCLEPIOS I			ASCLEPIOS II		
	OMB	TER	Total	OMB	TER	Total
FAS	465	462	927	481	474	955
Included in ARR analysis	454	452	906	469	469	938
Excluded from ARR analysis	11	10	21	12	5	17
Due to missing baseline EDSS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Due to missing data on Gd-enhancing T1 lesions at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

Abbreviations: EDSS: Extended Disability Status Scale; FAS: full analysis set; Gd: gadolinium; OMB: ofatumumab; TER: teriflunomide.
Source: Table 1-10 of Novartis (Data on File): ASCLEPIOS I Clinical Study Report Appendix 16.1.9,[1] Table 1-10 of Novartis (Data on File): ASCLEPIOS II Clinical Study Report Appendix 16.1.9.[2]

b) 3- and 6- month confirmed disability worsening (CDW-3 and CDW-6)

The FAS for the pooled analysis of the ASCLEPIOS I and II trials, as pre-specified for the key secondary outcomes measuring changes in disability, included 1,882 patients. Seven patients were excluded from the CDW-3 and CDW-6 analyses as their baseline and/or all post-baseline Expanded Disability Status Scale (EDSS) values were missing. Exclusions by treatment arm are summarised in Table 2.

Table 2: Patients excluded from the FAS in the CDW-3 and CDW-6 analyses

	Pooled ASCLEPIOS I and ASCLEPIOS II trials		
	OMB	TER	Total
FAS	946	936	1,882
Included in CDW-3 and CDW-6 analyses	944	931	1,875
Excluded from CDW-3 and CDW-6 analyses	2	5	7
Due to missing EDSS (no assessment at all)	[redacted]	[redacted]	[redacted]
Due to missing baseline EDSS only	[redacted]	[redacted]	[redacted]
Due to all post-baseline EDSS missing	[redacted]	[redacted]	[redacted]

Abbreviations: CDW-3: 3-month confirmed disability worsening; CDW-6: 6-month confirmed disability worsening; EDSS: Extended Disability Status Scale; FAS: full analysis set; OMB: ofatumumab; TER: teriflunomide.
Source: Table 1-4 in Appendix 16.1.9 of Novartis (Data on File): Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials.[3]

The discrepancy in the patient number in the teriflunomide group between Tables 12 and 13, Pages 39 and 40 (N=931) and Figures 3 and 4, Pages 40 and 41 (N=932) of the company submission (CS) Document B arises from one patient being excluded from the CDW-3 and CDW-6 analyses shown in Tables 12 and 13 due to a missing baseline EDSS value despite having post-baseline values. The Kaplan–Meier plots in Figures 3 and 4 include all patients at risk for whom post-baseline EDSS values are available, irrespective of the availability of a baseline EDSS value. Therefore, this patient is included in the Kaplan–Meier plots.

c) 6-month confirmed disability improvement (CDI-6)

For patients with a baseline EDSS of 0–1.5, no disability improvement was possible based on the protocol definition of improvement as presented in CS Document B, Table 5, Page 30. Therefore, among the 1,882 patients in the FAS, [redacted] patients with a baseline EDSS of <2 were not included in the analysis of the CDI-6 endpoint. [redacted] patients were excluded due to missing the baseline and/or all post-baseline EDSS values. Exclusion by treatment arm are summarised in Table 3..

Table 3: Patients excluded from the FAS in the CDI-6 analysis

	Pooled ASCLEPIOS I and ASCLEPIOS II trials		
	OMB	TER	Total
FAS	946	936	1,882
Included in CDI-6 analysis	749	723	1,472
Excluded from CDI-6 analysis	197	213	410
Baseline EDSS <2	[redacted]	[redacted]	[redacted]
Due to missing EDSS (no assessment at all)	[redacted]	[redacted]	[redacted]
Due to missing baseline EDSS only	[redacted]	[redacted]	[redacted]
Due to all post-baseline EDSS missing	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: CDI-6: 6-month confirmed disability improvement; EDSS: Extended Disability Status Scale; FAS: full analysis set; OMB: ofatumumab; TER: teriflunomide.
Source: Table 1-4 in Appendix 16.1.9 of Novartis (Data on File): Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials;[3] Novartis (Data on File): CDI-6 exclusions due to baseline EDSS <2.[4]

A3. PRIORITY QUESTION: In addition to the discrepancies in patient numbers between the FAS and those reported in various analyses in the company submission document B as noted in Question A2 above, the ERG note that the numbers of patients included in the analyses reported in table 2 of the recently published trial paper (Hauser et al. NEJM 2020;383:546-57) also differ from those reported in company submission document B:

- **For CDW-3 and CDW-6, the number of patients analysed for ASCLEPIOS I and II were 924 and 951 respectively.**

- **For Disability Improvement at 6 months, the number of patients analysed for ASCLEPIOS I and II were 738 and 734 respectively.**

Can the company explain the apparent discrepancies in the numbers reported between company submission document B and the published NEJM paper, and whether one set of numbers should be used in preference over the other set?

The patient numbers included in the analysis of CDW-3, CDW-6, and CDI-6, as reported in the company submission, are consistent with those reported in the recent publication of the ASCLEPIOS trials by Hauser et al.[5] For CDW analyses, 924 and 951 patients were included from ASCLEPIOS I and II, respectively; as specified in the protocol, data from both trials were pooled for CDW analysis and included 944 ofatumumab-treated and 931 teriflunomide-treated patients. For the CDI-6 analysis, 738 and 734 patients were included from ASCLEPIOS I and II, respectively; after trials were pooled, the analysis included 749 ofatumumab-treated and 723 teriflunomide-treated patients. These patient numbers, which are summarised in Table 4, as well as the reported results are consistent across Table 2 of the Hauser et al. 2020 publication and the company submission (CS Document B: Tables 11–14, Pages 38–41). Novartis suspects the ERG's question may have arisen due to a confusion between patient numbers per study and patient numbers by treatment arm (pooled across both trials).

Table 4: Patient numbers analysed for the ARR, CDW and CDI outcomes of the ASCLEPIOS trials as reported in both the company submission and a recent publication (Hauser, 2020)[5]

	ASCLEPIOS I		ASCLEPIOS II		Pooled trials	
	OMB	TER	OMB	TER	OMB	TER
ARR analysis						
N	454	452	469	469	923	921
Total across treatment arms	906		938		1,844	
CDW-3 and CDW-6 analyses						
N	465	459	479	472	944	931
Total across treatment arms	924		951		1,875	
CDI-6 analysis						
N	375	363	374	360	749	723
Total across treatment arms	738		734		1,472	

Abbreviations: ARR: annualised relapse rate; CDI-6: 6-month confirmed disability improvement; CDW-3/6: 3-/6-month confirmed disability worsening; OMB: ofatumumab; TER: teriflunomide.

A4. PRIORITY QUESTION: The company present Kaplan-Meier (KM) curves for CDW-3, CDW-6 and CDI-6 (company submission document B, figures 3-5, pages 40-42): the definitions for these outcomes seem to suggest that an event could not be confirmed until at least 3 months after baseline for CDW-3

and until at least 6 months after baseline for CDW-6 and CDI-6. However, the Kaplan-Meier curves mentioned above show that some events occurred prior to 3 months for CDW-3 and prior to 6 months for CDW-6 and CDI-6. Can the company please explain the reason(s) behind these events?

As per the definition of these outcomes, disability worsening or improvement had to be sustained for a minimum duration of 3 (CDW-3) or 6 months (CDW-6, CDI-6) in order for the event to be *confirmed*. Therefore, the earliest time point at which disability worsening or improvement could be *confirmed* was Month 3 or Month 6. However, the event time used in the statistical analysis is the *onset* time of the confirmed disability event, i.e. the time when the patient first experienced a clinically relevant change in disability that was confirmed 3 or 6 months later.

As per the clinical study protocol, patients were instructed to immediately report new neurological symptoms, re-occurring or worsening of previous symptoms to the Investigator.[5] An unscheduled visit had to be scheduled as soon as possible, whenever possible within 7 days of onset of the symptoms. During such an unscheduled visit, a disability worsening may have remained unconfirmed or may have been confirmed as a clinical relapse. If the subsequent longitudinal EDSS data for the same patient confirmed that the change in EDSS was sustained for the required period of 3 or 6 months, and confirmed in a scheduled visit, the disability worsening may later have been confirmed as the onset of a disability event.

The Kaplan–Meier curves presented in the company submission are time-to-event plots where the time of the event is defined by the *onset* of the confirmed disability event. The onset of the disability event, as illustrated in the Kaplan-Meier curve, could occur at any time from Day 1 after baseline, provided that based on the patient's longitudinal data the clinically relevant change was sustained for the required minimum duration of 3 or 6 months and then confirmed in a next scheduled visit. Therefore, events on the Kaplan–Meier curve may appear before Month 3 or Month 6, and also between scheduled visits.

A5. PRIORITY QUESTION: Can the company please provide the following, <u>separately for each arm</u> of both ASCLEPIOS I and II trials:

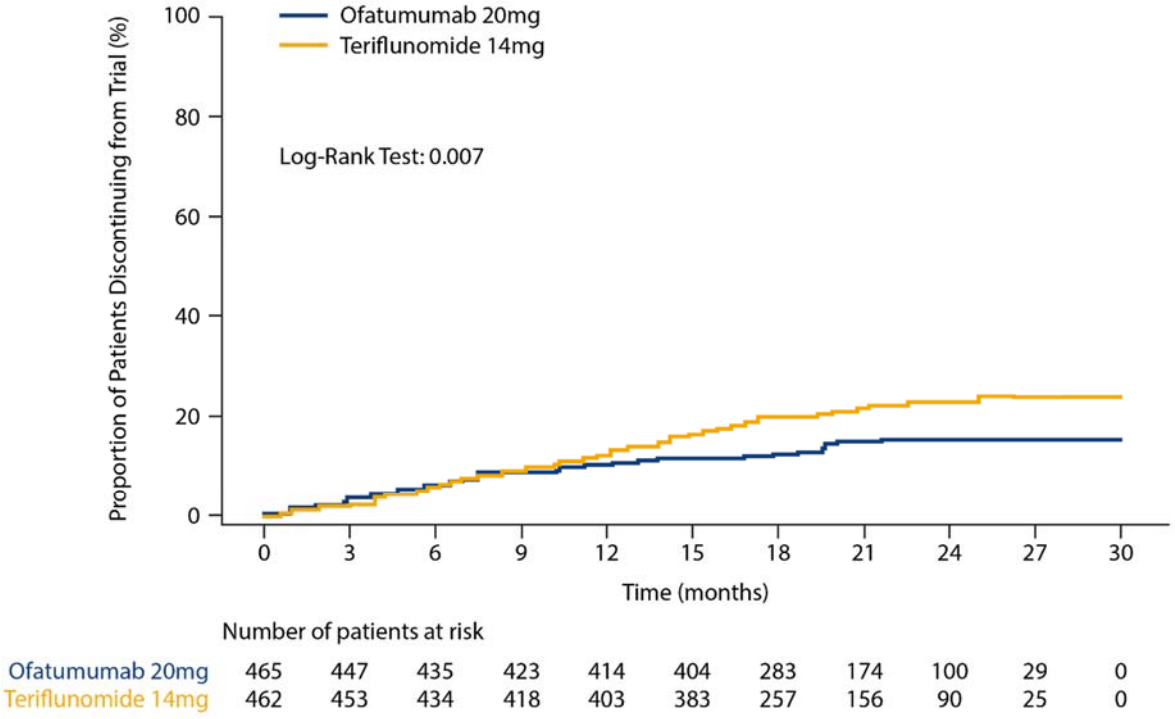
- **Time to discontinuation KM data**

Please provide these data disaggregated by events recorded (e.g. death, loss to follow-up), flagging which events are treated as events and which as censoring, in the format of the table below.

Event type flag		Event/Censor	Event/Censor	Event/Censor	
Timepoint	N at risk	Event 1	Event 2	Etc…	S(t)
T=0	N=?	0	0	0	100%
T=?	N=?	N=?	N=?	N=?	? %
T=?	N=?	N=?	N=?	N=?	? %
Etc…	Etc…	Etc…	Etc…	Etc…	Etc…

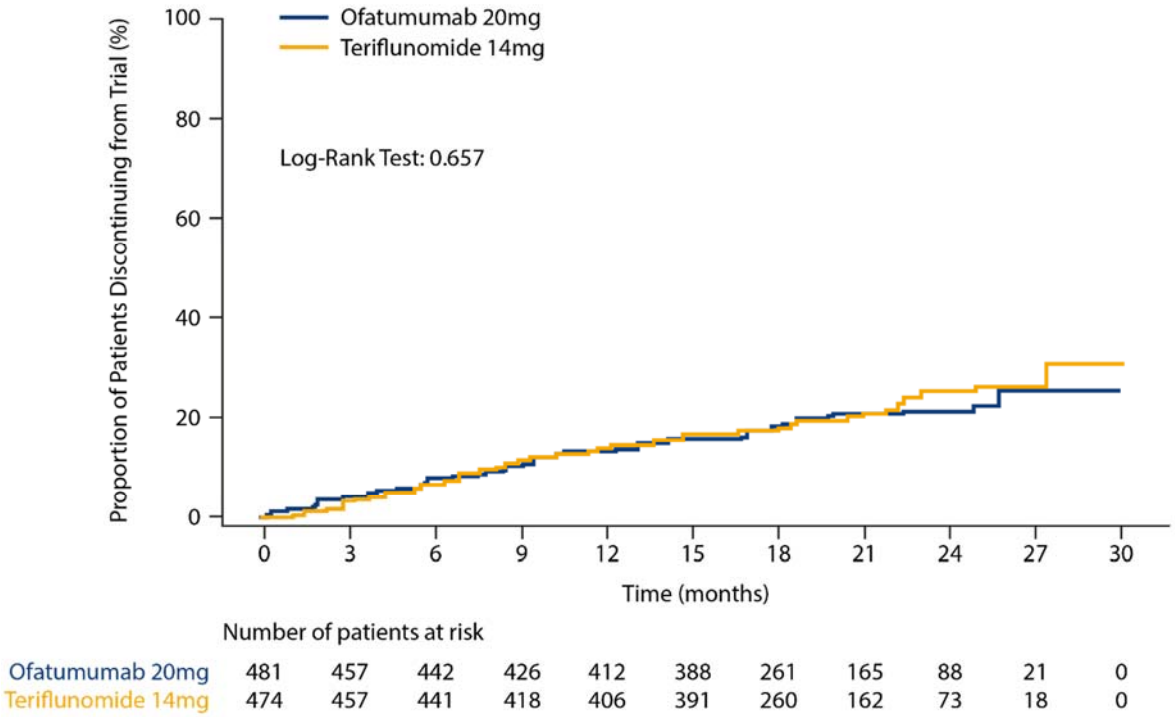
The Kaplan–Meier curves for time to study drug discontinuation in each treatment arm of the ASCLEPIOS I and II trials are presented in Figure 1 and Figure 2 respectively.

Figure 1: Time to study drug discontinuation in the ASCLEPIOS I trial



Source: Supplementary Figure S3 in Hauser et al., 2020.[5]

Figure 2: Time to study drug discontinuation in the ASCLEPIOS II trial



Source: Supplementary Figure S3 in Hauser et al., 2020.[5]

The full data by timepoint in table format is provided in the file '[A5] Novartis (Data on File) Time to Study Drug Discontinuation' in the ERG CQs Reference Pack: the data for the ofatumumab arm of ASCLEPIOS I can be found on Pages 1–40; the teriflunomide arm of ASCLEPIOS I on Pages 41–80; the ofatumumab arm of ASCLEPIOS II on Pages 81–120; and the teriflunomide arm of ASCLEPIOS II on Pages 121–161.

As described in the Statistical Analysis Plan of the ASCLEPIOS trials (published within the protocol alongside Hauser et al. 2020[5]), any reason for discontinuation was treated as an event in the analysis of time to study drug discontinuation. Only patients who completed study drug treatment were censored in the analysis.

The primary reason for study drug discontinuation is given alongside the number of events (number of patients with study drug discontinuation) for each individual time point in the file provided in the ERG CQs Reference Pack. For time points where more than two patients discontinued study drug treatment and where it is not clear to how many patients each of the given reasons applied, further details are given below in Table 5.

Table 5: Study drug discontinuations – Supplementary information

Study	Treatment group	Time point (months)	Events	Event type
ASCLEPIOS I	OMB	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
ASCLEPIOS II	OMB	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
ASCLEPIOS II	OMB	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]

ASCLEPIOS II	**OMB**	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]

Event: Study drug discontinuation. Event type: Reason for study drug discontinuation.
Abbreviations: OMB: ofatumumab.

A6. PRIORITY QUESTION: Please can the company provide justification for using the exponential distribution to model the time to discontinuation of ofatumumab (table 70, company submission document B). The exponential curve appears to have the worst fit in terms of both AIC and BIC.

The committee-preferred model in several previous appraisals in relapsing-remitting multiple sclerosis (RRMS) have used time-constant all-cause discontinuation.[6-8] In alignment with these prior appraisals, all-cause discontinuation from ofatumumab was modelled to be time-constant in the base case. Time-constant discontinuation models a fixed proportion of patients to discontinue with each cycle, which is mathematically equivalent to exponential decay.

In order to evaluate the impact of the assumption of time-constant discontinuation, a scenario was presented in the CS Document B in which time-dependent discontinuation was considered using the Weibull distribution, which was found to be the best-fitting discontinuation extrapolation curve (CS Document B, Figure 37 and Table 70, Page 135). As presented in the CS Document B (Tables 84, Page 150 and 92–94, Pages 167–179) and summarised below in Table 6, the use of this alternative, best-fitting model had minimal impact on the results and did not affect the conclusions of cost-effectiveness drawn.

Table 6: Results summary at ofatumumab PAS price for base case and Weibull scenario discontinuation modelling

Comparator	Pairwise ICER (£/QALY) Ofatumumab vs comparator	
	Time-constant discontinuation (i.e. exponential) [Base case]	Time-dependent discontinuation using a Weibull distribution [Scenario analysis]
RRMS population		
Avonex® (IFN β-1a)	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Rebif® 44 (IFN β-1a)	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
HA RRMS population		
Alemtuzumab	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]
Fingolimod[b]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
RES RRMS population		
Alemtuzumab	[redacted]	[redacted]

Cladribine	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses. All other comparators are included at their list prices.
Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; IFN: interferon; PAS: Patient Access Scheme; QALY: quality-adjusted life year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis.

A7. In company submission document B, B.2.3.1, page 25, the company state "*Following the treatment epoch, patients were eligible to enter an ongoing open-label an ofatumumab Extension study for up to five years. Patients who did not (or not directly) enter the Extension Study instead entered a Safety Follow-Up epoch of at least 9 months".*

a. Can the company please define the eligibility criteria to determine entry to the open-label follow up study, and provide the reasons why patients did not (or not directly) enter the extension study?

b. Can the company provide the number and patient characteristics of those entering the extension and safety follow up groups?

a) Eligibility criteria

The eligibility criteria for entry to the long-term ofatumumab extension study 'ALITHIOS' (NCT03650114) are described in Table 7.[9, 10] Patients can enter the long-term extension study if they have completed a previous Novartis study investigating an ofatumumab dose of 20 mg s.c. every 4 weeks in adult patients with relapsing multiple sclerosis (RMS). Therefore, in addition to patients from the ASCLEPIOS trials, the extension study also allows the enrolment of patients from other ofatumumab trials, including APLIOS (comparison of autoinjector pen with pre-filled syringes; NCT03560739) and APOLITOS (study conducted primarily in Japan; NCT03249714).

Table 7: Eligibility criteria for long-term study ALITHIOS

Trial name	**ALITHIOS (COMB157G2399)**
Trial design	An open-label, single arm, multi-centre extension study evaluating long-term safety, tolerability and effectiveness of ofatumumab in subjects with relapsing multiple sclerosis
Eligibility criteria for participants	A summary of the inclusion and exclusion criteria is provided below. For full details of the exclusion criteria please refer to the protocol included in the reference pack. Inclusion criteria: • Must have participated in a Novartis MS study: o which dosed ofatumumab 20 mg s.c. every 4 weeks, o was an adult (≥ 18 years of age) study in RMS, o must have completed the study on study treatment (subjects that are on temporary drug interruption at the time of EOS are considered completers) • Written informed consent must be obtained before any assessment is performed

	Exclusion criteria: • Premature discontinuation from previous ofatumumab study or from study treatment in previous ofatumumab study • Subjects that have had their previous ofatumumab study EOS > 6 months prior to screening and/or been given another MS DMT between EOS of previous study and screening of this study • Less than 3.5-month washout of teriflunomide for subjects that will not complete the Accelerated Elimination Procedure[a] prior to Day 1 • Subjects with a history of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the Investigator • Subjects that have any unresolved adverse event or condition from the previous study or prior to Day 1 that necessitates temporary interruption of the study treatment, until such time as the event or condition has resolved (the subject will be monitored within the safety follow-up of the previous study and not consented into study COMB157G2399 until the AE or condition has resolved) • Emergence of any clinically significant condition/disease during previous ofatumumab study or prior to Day 1 in which study participation might result in safety risk for subjects • Subjects with neurological findings consistent with PML or confirmed PML

[a] As described in the EU and US labels for teriflunomide, elimination can be accelerated by administration of cholestyramine and by administration of activated charcoal powder. Only applicable to subjects completing the ASCLEPIOS trials (COMB157G2301 and COMB157G2302).
Abbreviations: AE: adverse event; DMT: disease-modifying therapy; EOS: end of study; MS: multiple sclerosis; PML: progressive multifocal leukoencephalopathy; RMS: relapsing multiple sclerosis; s.c.: subcutaneous.

Reasons for not enrolling into the extension study were not formally collected. Some patients who would have been eligible for enrolment into the extension study chose not to enrol (patient's decision, e.g. due to a wish to get pregnant or a move to a different location) while some others could not be enrolled due to administrative issues, such as approval of the site or the ALITHIOS study protocol not being granted in time for the patient to still meet the eligibility criteria in terms of the maximum permitted time period between ASCLEPIOS EOS and screening for ALITHIOS (see exclusion criteria listed in Table 7).

b) Patient characteristics

Following the clarification call with the NICE Technical team and the ERG on 7th September 2020, Novartis understand this question to refer to patients entering the extension study and safety follow-up from the ASCLEPIOS trials, and these patients' baseline characteristics at time of enrolment into ASCLEPIOS.

The numbers and proportions of patients entering the extension study and safety follow-up from the ASCELPIOS trials are presented in Figure 3, based on the latest data cut-off (30 November 2019). The majority of patients, at this time point [redacted]% and [redacted]%, continued into the extension study following ASCLEPIOS I and II, respectively.

Figure 3: Distribution of patients following ASCLEPIOS studies for ofatumumab (data cut-off 30 November 2019)

Patient numbers are based on the data cut from 30th November 2019

Further enrolment for the long-term extension study 'ALITHIOS' is ongoing. As of 6 August 2020, a total of 1,701 patients were enrolled in the extension study.[11] This included patients from APLIOS and APOLITOS as well as an additional [redacted] patients from the ASCLEPIOS trials who had entered the extension study after the latest data cut-off available for formal analysis from 30 November 2019. Reasons for the delayed roll-over of ASCLEPIOS patients into the long-term extension study included the required washout for teriflunomide-treated patients, ongoing adverse events prohibiting earlier entry, or pending regulatory approval of the protocol or site for the extension study.

The baseline characteristics of patients from the ASCLEPIOS trials who had entered the extension study, safety follow-up or neither by the 30 November 2019 cut-off date (the latest data cut available for formal analysis) are presented in Table 8, Table 9 and Table 10, respectively.

Table 8: Summary of baseline characteristics of patients in the ASCLEPIOS trials who subsequently entered the extension study

Characteristic		ASCLEPIOS I		ASCLEPIOS II	
		20 mg OMB (N=[redacted])	14 mg TER (N=[redacted])	20 mg OMB (N=[redacted])	14 mg TER (N=[redacted])
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	n	[redacted]	[redacted]	[redacted]	[redacted]
	Years, mean (SD)	[redacted]	[redacted]	[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]
	n	[redacted]	[redacted]	[redacted]	[redacted]

Total volume of T2 lesions	cm^3, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients free of Gd-enhancing T1 lesions, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Gd-enhancing T1 lesions	n	[redacted]	[redacted]	[redacted]	[redacted]
	Number, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 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; OMB: ofatumumab; SD: standard deviation; TER: teriflunomide.
Sources: Novartis (Data on File) ASCLEPIOS Patient Baseline Characteristics by Trial Follow-Up.[12]

Table 9: Summary of baseline characteristics of patients in the ASCLEPIOS trials who subsequently entered the safety follow-up

Characteristic		ASCLEPIOS I		ASCLEPIOS II	
		20 mg OMB (N=[redacted])	14 mg TER (N=[redacted])	20 mg OMB (N=[redacted])	14 mg TER (N=[redacted])
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	n	[redacted]	[redacted]	[redacted]	[redacted]
	Years, mean (SD)	[redacted]	[redacted]	[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]
Gd-enhancing T1 lesions	n	[redacted]	[redacted]	[redacted]	[redacted]
	Number, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 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; OMB: ofatumumab; SD: standard deviation; TER: teriflunomide.
Sources: Novartis (Data on File) ASCLEPIOS Patient Baseline Characteristics by Trial Follow-Up.[12]

Table 10: Summary of baseline characteristics of patients in the ASCLEPIOS trials who subsequently neither entered the extension study nor the safety follow-up

Characteristic	ASCLEPIOS I		ASCLEPIOS II	
	20 mg OMB (N=[redacted])	14 mg TER (N=[redacted])	20 mg OMB (N=[redacted])	14 mg TER (N=[redacted])
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	n	[redacted]	[redacted]	[redacted]	[redacted]
	Years, mean (SD)	[redacted]	[redacted]	[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]
Gd-enhancing T1 lesions	n	[redacted]	[redacted]	[redacted]	[redacted]
	Number, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 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; OMB: ofatumumab; SD: standard deviation; TER: teriflunomide.
Sources: Novartis (Data on File) ASCLEPIOS Patient Baseline Characteristics by Trial Follow-Up.[12]

A8. In company submission document B, B.2.4.1, page 33, 'participant disposition,' can the company provide the patient characteristics of the 48 ofatumumab patients and 81 teriflunomide patients who discontinued ASCLEPIOS I, and the same for the 83 ofatumumab patients and 84 teriflunomide patients who discontinued ASCLEPIOS II?

The baseline characteristics of patients who discontinued from the ASCLEPIOS I and II trials are provided in Table 11.

Table 11: Baseline characteristics in patients who discontinued ASCLEPIOS I and ASCLEPIOS II

Characteristic		ASCLEPIOS I		ASCLEPIOS II	
		OMB (N=48)	TER (N=81)	OMB (N=83)	TER (N=84)
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	n	[redacted]	[redacted]	[redacted]	[redacted]
	Years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Previously treated patients, n (%)		[redacted]	[redacted]	[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]

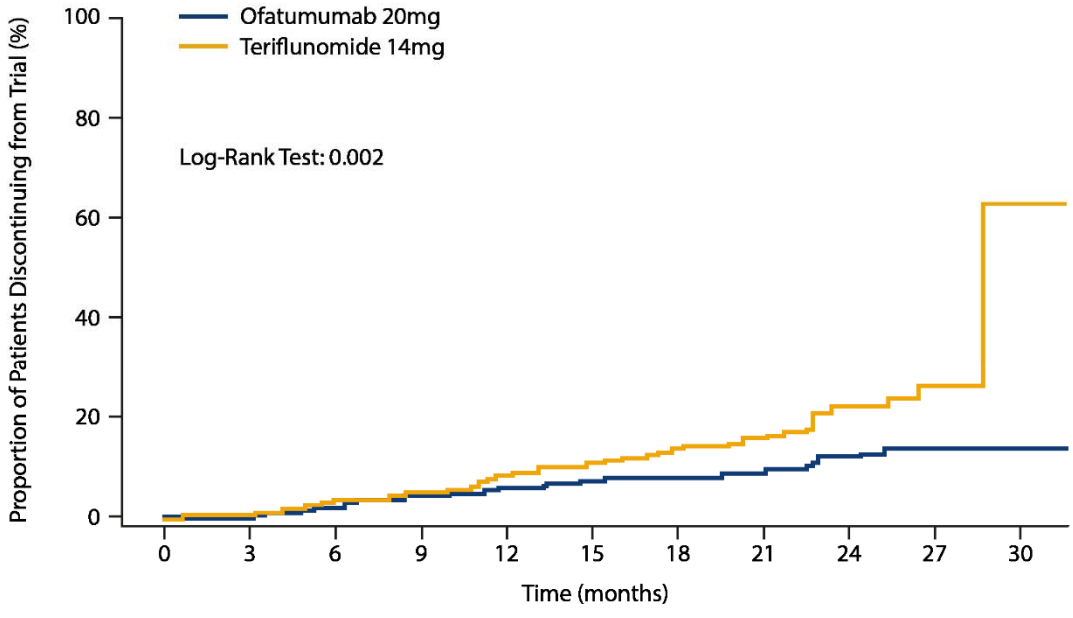
Number of patients free of Gd-enhancing T1 lesions, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Gd-enhancing T1 lesions	n	[redacted]	[redacted]	[redacted]	[redacted]
	Number, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 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; OMB: ofatumumab; SD: standard deviation; TER: teriflunomide.
Source: Novartis (Data on File): ASCLEPIOS Baseline Characteristics for Patients who Discontinued Study.[13]

A9. In company submission document B, table 8, page 33-34, can the company please provide information regarding when participants withdrew from the study (e.g., study week or month)?

The time to trial discontinuation in each treatment arm of the ASCLEPIOS I and II trials is presented in Figure 4 and Figure 5 and in Table 12 and Table 13. In the second year of treatment, the rate of discontinuation from the trial was found to be higher for the teriflunomide treatment arm of ASCLEPIOS I as compared with the ofatumumab treatment arm (Figure 4), whereas the discontinuation rates from ofatumumab and teriflunomide remained similar throughout the ASCLEPIOS II trial (Figure 5).

Figure 4: Time to trial discontinuation in the ASCLEPIOS I trial

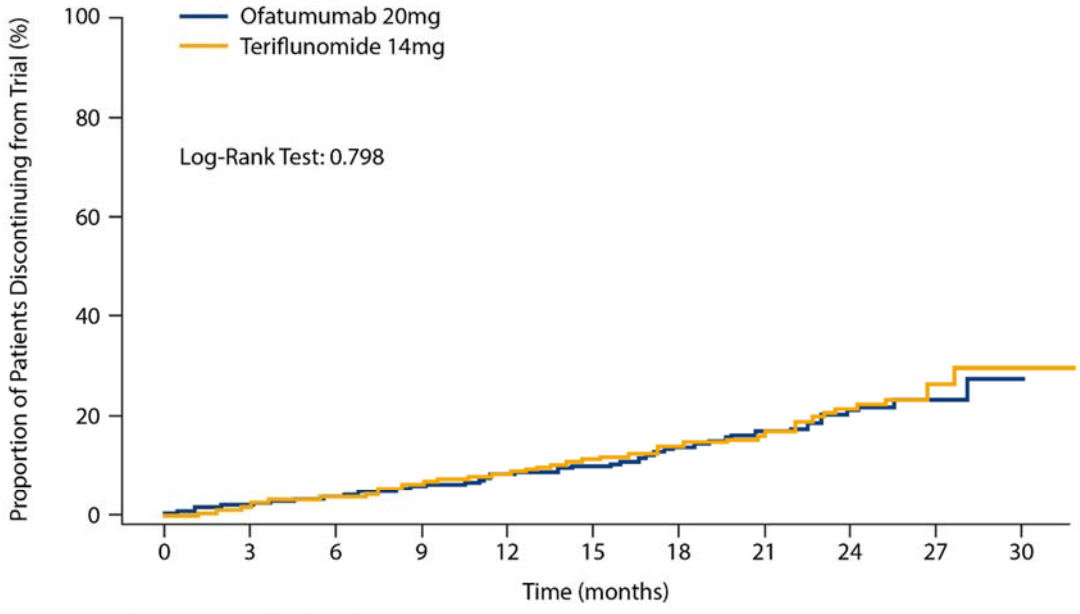


Number of patients at risk

Ofatumumab 20mg	465	463	456	444	437	429	311	192	108	36	1
Teriflunomide 14mg	462	459	445	439	424	412	282	177	96	30	1

The 'jump' in the teriflunomide Kaplan–Meier curve between Month 27 and Month 30 is caused by a single patient who discontinued from the teriflunomide group at a time point when less than 30 patients were at risk.
Source: Supplementary Figure S3 in Hauser et al., 2020.[5]

Figure 5: Time to trial discontinuation in the ASCLEPIOS II trial



Source: Supplementary Figure S3 in Hauser et al., 2020.[5]

Table 12: Time to discontinuation from ASCLEPIOS I – Kaplan–Meier estimates (FAS)

Time interval (months)	Patients at risk	Patients with event at visit-window (censored)		Cumulative information	
		n	%	n	KM % estimate with event, % (SE) (95% CI)
Ofatumumab (N=465)					
≥Day 1 to ≤M6	465	[redacted]	[redacted]	[redacted]	[redacted]
>M6 to ≤M12	456	[redacted]	[redacted]	[redacted]	[redacted]
>M12 to ≤M18	437	[redacted]	[redacted]	[redacted]	[redacted]
>M18 to ≤M24	311	[redacted]	[redacted]	[redacted]	[redacted]
>M24 to ≤EOS	108	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide (N=462)					
≥Day 1 to ≤M6	462	[redacted]	[redacted]	[redacted]	[redacted]
>M6 to ≤M12	445	[redacted]	[redacted]	[redacted]	[redacted]
>M12 to ≤M18	424	[redacted]	[redacted]	[redacted]	[redacted]
>M18 to ≤M24	282	[redacted]	[redacted]	[redacted]	[redacted]
>M24 to ≤EOS	96	[redacted]	[redacted]	[redacted]	[redacted]

Day 1 = Day of first dose; n = number of people with event.
Abbreviations: CI: confidence interval; EOS: end of study; FAS: full analysis set; M: month; SE: standard error.
Source: Table 14.1-1.1e of Novartis (Data on File): ASCLEPIOS I Clinical Study Report.[14]

Table 13: Time to discontinuation from ASCLEPIOS II – Kaplan–Meier estimates (FAS)

Time interval (months)	Patients at risk	Patients with event at visit-window (censored)	Cumulative information

		n	%	n	KM % estimate with event, % (SE) (95% CI)
Ofatumumab (N=481)					
≥Day 1 to ≤M6	481	[redacted]	[redacted]	[redacted]	[redacted]
>M6 to ≤M12	461	[redacted]	[redacted]	[redacted]	[redacted]
>M12 to ≤M18	441	[redacted]	[redacted]	[redacted]	[redacted]
>M18 to ≤M24	298	[redacted]	[redacted]	[redacted]	[redacted]
>M24 to ≤EOS	99	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide (N=474)					
≥Day 1 to ≤M6	474	[redacted]	[redacted]	[redacted]	[redacted]
>M6 to ≤M12	457	[redacted]	[redacted]	[redacted]	[redacted]
>M12 to ≤M18	434	[redacted]	[redacted]	[redacted]	[redacted]
>M18 to ≤M24	280	[redacted]	[redacted]	[redacted]	[redacted]
>M24 to ≤EOS	84	[redacted]	[redacted]	[redacted]	[redacted]

Day 1 = Day of first dose; n = number of people with event.
Abbreviations: CI: confidence interval; EOS: end of study; FAS: full analysis set; M: month; SE: standard error.
Source: Table 14.1-1.1e of Novartis (Data on File): ASCLEPIOS II Clinical Study Report.[15]

Network Meta-Analysis (NMA)

A10. In company submission document B, table 29, page 58-61, and B.2.9.3, page 78, please can the company provide a more detailed explanation of what 'being an outlier' entails for the exclusion of Pegylated IFN (ADVANCE trial) from the NMA?

The ADVANCE trial (pegylated interferon β-1a versus placebo) was excluded from the network meta-analysis (NMA) as an outlier. This is in alignment with the conclusion reached in the appraisal of ocrelizumab (TA533), where the NICE committee found clinically implausible results were caused by inclusion of the ADVANCE trial in an NMA of time to 6-month confirmed disability progression (CDP-6): pegylated interferon ß-1a "*appeared to be more effective than other beta interferons and high efficacy treatments such as natalizumab. The committee heard this was contrary to clinical experience, so it disregarded the comparison with pegylated interferon for this appraisal*".[16]

The results presented in the CS for time to CDW-6, the most relevant outcome from a clinical perspective and in economic modelling, aligned with this finding. As presented in CS Appendix D, Table 22, Page 85, the ADVANCE trial investigating pegylated interferon ß-1a versus placebo reports the same hazard ratio (HR; 0.46, 95% confidence interval [CI]: 0.26, 0.81) for time to CDW-6 as the AFFIRM trial investigating natalizumab versus placebo (HR: 0.46, 95% CI: 0.33, 0.64). Additionally, in a scenario NMA which included the ADVANCE trial (presented in Appendix D.1.6 of the CS Appendices), pegylated interferon β-1a (HR: [redacted], 95% credible interval [CrI]: [redacted]) was found to be the [redacted] most effective treatment in CDW-6 versus placebo with [redacted] (HR: [redacted], 95% CrI: [redacted]) after [redacted] (HR: [redacted], 95% CrI: [redacted]). As stated by the clinical expert opinion in the ocrelizumab appraisal, the finding that pegylated interferon β-1a shows similar efficacy with natalizumab lacks clinical face validity.[16]

Furthermore, the clinical evidence base for pegylated interferon β-1a is limited. In the TA527 appraisal, this was highlighted by the Assessment Group report, which noted that their

"*assessment of Plegridy, in particular, relied on one trial with one year of follow-up connected to evidence networks only via placebo*."[17]

Together, clinical expert opinion accepted by the committee in TA533, results presented by Novartis in the CS Appendices, and the limited clinical evidence base for pegylated interferon β-1a as noted by the TA527 Assessment Group support the exclusion of the ADVANCE trial from NMA analyses.

A11. In company submission Appendix D, table 22, page 85-89, please can the company provide data on the exposure (total person-years) for individual trial arms used in the NMA for ARR?

For the NMA of ARR, the exposure time (in total person–years) for each trial was estimated by multiplying the number of patients by the follow-up time. The follow-up time in years was estimated by dividing the follow-up time in weeks by 52. These exposure estimates for the individual trial arms used in the NMA for ARR are presented in Table 14.

Table 14: Exposure (total person–years) in individual trial arms in the ARR NMA

Trial Name	Treatment	Number of patients	Follow-Up Time (Weeks)	Estimated Exposure (Total Person–Years)[a]
ADVANCE[b]	Placebo	500	48	462
	PEG-IFNB-1a SC 125 ug Q2W	512	48	473
AFFIRM	Placebo	315	104	630
	Natalizumab IV 300 mg Q4W	627	104	1254
ASCLEPIOS I	Teriflunomide PO 14 mg QD	452	130	1130
	Ofatumumab SC 20 mg Q4W	454	130	1135
ASCLEPIOS II	Teriflunomide PO 14 mg QD	469	130	1173
	Ofatumumab SC 20 mg Q4W	469	130	1173
ASSESS	Glatiramer acetate SC 20 mg QD	324	52	324
	Fingolimod PO 0.5 mg QD	345	52	345
BEYOND	IFNB-1b SC 250 ug Q2D	888	182	3108
	Glatiramer acetate SC 20 mg QD	445	182	1558
Boiko et al. 2018a[b]	Placebo	28	48	26
	Glatiramer acetate SC 20 mg QD	122	48	113
Bornstein et al., 1987	Placebo	23	104	46
	Glatiramer acetate SC 20 mg QD	25	104	50
BRAVO	Placebo	450	104	900
	IFNB-1a IM 30 ug QW	447	104	894
Calabrese et al., 2012	IFNB-1a SC 44 ug TIW	46	104	92
	IFNB-1a IM 30 ug QW	47	104	94
	Glatiramer acetate SC 20 mg QD	48	104	96
CAMMS223	IFNB-1a SC 44 ug TIW	111	156	333
	Alemtuzumab IV 12 mg	112	156	336

Trial Name	Treatment	Number of patients	Follow-Up Time (Weeks)	Estimated Exposure (Total Person–Years)[a]
CARE-MS I	IFNB-1a SC 44 ug TIW	187	104	374
	Alemtuzumab IV 12 mg	376	104	752
CARE-MS II	IFNB-1a SC 44 ug TIW	202	104	404
	Alemtuzumab IV 12 mg	426	104	852
CLARITY	Placebo	437	96	807
	Cladribine PO 3.5 mg/kg	433	96	799
	Cladribine PO 5.25 mg/kg	456	96	842
CombiRx	IFNB-1a IM 30 ug QW	250	156	750
	Glatiramer acetate SC 20 mg QD	259	156	777
CONFIRM	Placebo	363	104	726
	Dimethyl fumarate PO 240 mg BID	359	104	718
	Glatiramer acetate SC 20 mg QD	350	104	700
Copolymer 1 MS trial	Placebo	126	104	252
	Glatiramer acetate SC 20 mg QD	125	104	250
DEFINE	Placebo	408	96	753
	Dimethyl fumarate PO 240 mg BID	410	96	757
EVIDENCE	IFNB-1a IM 30 ug QW	338	48	312
	IFNB-1a SC 44 ug TIW	339	48	313
FREEDOMS	Placebo	418	104	836
	Fingolimod PO 0.5 mg QD	425	104	850
FREEDOMS II	Placebo	355	104	710
	Fingolimod PO 0.5 mg QD	358	104	716
GALA	Placebo	461	52	461
	Glatiramer acetate SC 40 mg TIW	943	52	943
IFNB MS	Placebo	123	104	246
	IFNB-1b SC 250 ug Q2D	124	104	248
INCOMIN[b]	IFNB-1a IM 30 ug QW	92	104	184
	IFNB-1b SC 250 ug Q2D	96	104	192
MSCRG	Placebo	143	104	286
	IFNB-1a IM 30 ug QW	158	104	316
OPERA I	IFNB-1a SC 44 ug TIW	411	96	759
	Ocrelizumab IV 600 mg	410	96	757
OPERA II	IFNB-1a SC 44 ug TIW	418	96	772
	Ocrelizumab IV 600 mg	417	96	770
PRISMS	Placebo	187	104	374
	IFNB-1a SC 22 ug TIW	189	104	378
	IFNB-1a SC 44 ug TIW	184	104	368
REGARD	IFNB-1a SC 44 ug TIW	386	96	713
	Glatiramer acetate SC 20 mg QD	378	96	698

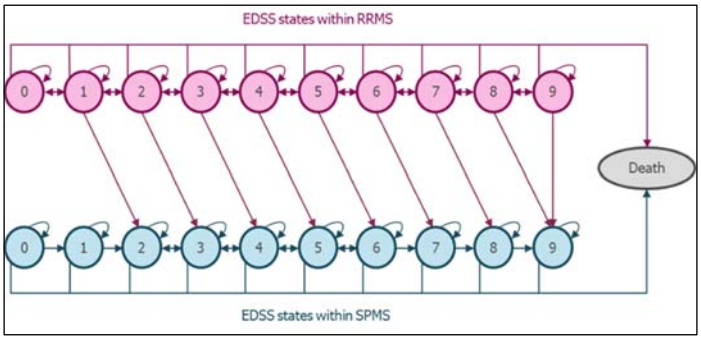
Trial Name	Treatment	Number of patients	Follow-Up Time (Weeks)	Estimated Exposure (Total Person–Years)[a]
Stepien et al., 2013	IFNB-1b SC 250 ug Q2D	18	156	54
	IFNB-1a IM 30 ug QW	20	156	60
TEMSO	Placebo	363	108	754
	Teriflunomide PO 7 mg QD	365	108	758
	Teriflunomide PO 14 mg QD	358	108	744
TENERE	IFNB-1a SC 44 ug TIW	104	115	230
	Teriflunomide PO 7 mg QD	109	115	241
	Teriflunomide PO 14 mg QD	111	115	245
TOWER	Placebo	388	152	1134
	Teriflunomide PO 7 mg QD	407	152	1190
	Teriflunomide PO 14 mg QD	370	152	1082
TRANSFORMS	IFNB-1a IM 30 ug QW	431	52	431
	Fingolimod PO 0.5 mg QD	429	52	429

[a] Exposure was estimated by multiplying the patient number by the follow-up time. The follow-up time in years was estimated by dividing the follow-up time in weeks by 52.
[b] These trials were not included in the base case ARR NMA network.
Abbreviations: ARR: annualised relapse rate; BID: twice a day; IFNB-1b: interferon β-1b; IM: intramuscular; IV: intravenous; NMA: network meta-analysis; PEG-IFNB-1a: pegylated IFN β-1a; PO: orally; Q2D: once every 2 days; Q2W: once every two weeks; Q4W: once every four weeks; QD: once a day; QW: once a week; SC: subcutaneous; TIW: three times a week.

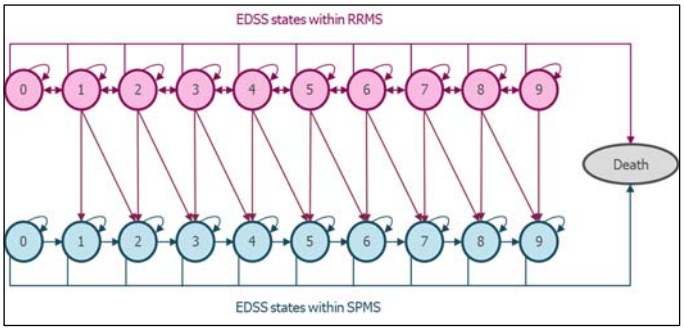
Section B: Clarification on cost-effectiveness data

Model structure and Excel

B1. PRIORITY QUESTION: Figure 11, company submission document A, page 32 and figure 36, in company submission document B, page 118 are identical. However, there are inconsistencies within the model between these figures and the model provided in the Excel file (Structure worksheet). Please clarify which figure accurately reflects the illustrative structure used in the economic analysis?



Illustrative structure presented in company submission documents A and B



Illustrative structure presented in Excel

Novartis apologise for the inconsistency in these illustrations and can confirm that the illustrative structure presented in the CS Documents A and B is accurate and reflects the structure implemented within the economic analysis. The figure in the structure worksheet in the Excel model, which was not previously reflective of the model submitted, has been corrected in the version of the model submitted as part of the response to these clarification questions.

B2. PRIORITY QUESTION: In both the Excel model (Structure worksheet), and on page 119 of company submission document B, the company states: "*Progress from RRMS to SPMS (always modelled to occur alongside an increase in EDSS, as progression is a necessary criterion for diagnosis of SPMS.*" If this statement is correct, then the model structure in the Excel file needs to be corrected. Please can the company clarify?

Novartis apologise for the inconsistency between this statement and the illustration presented in the model. Novartis can confirm that this statement is correct, and the figure in the structure worksheet in the Excel model has been corrected in the version of the model submitted as part of the response to these clarification questions.

B3. PRIORITY QUESTION: In the Excel model (Structure worksheet), the company states: "*Disability progression (move to higher EDSS state), improvement in the disability status (move to lower EDSS state) or remain at their current level of disability (same EDSS state) within SPMS.*" However, on page 119 of company submission document B, the company states: "*Disability worsening (move to higher EDSS state), improvement in the disability status (move to lower EDSS state; this only applies to EDSS states 3–6) or remain at their current level of disability (same EDSS state) within SPMS*." Please can the company clarify which of these statements is correct and amend the structure of the model accordingly.

Novartis apologise for the inconsistency in these statements and can confirm that the second, presented in the company submission, is correct. The statement on the structure worksheet in

the Excel model has been corrected in the version of the model submitted as part of the response to these clarification questions.

B4. PRIORITY QUESTION: The ERG would like the company to clarify/elaborate on the patient disposition in the model to better understand the sequence of events. What sequence do these events occur for people on treatment?

- **Transition probability matrix is applied**
- **People who have discontinued treatment are moved to off-treatment**
- **Relapses are calculated**
- **People who die move to a dead state**
- **People who discontinued due to progressing to EDSS ≥7 are moved to off-treatment**
- **People who discontinued due to progression to secondary progressive multiple sclerosis (SPMS) are moved to off-treatment**

For patients who are 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 discontinued due to progressing to EDSS ≥7 are moved to off-treatment. Simultaneously, people who discontinued due to progression to secondary progressive multiple sclerosis (SPMS) are moved to off-treatment
5. Relapses are calculated, based on the 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

B5. In the Excel model (Structure worksheet), adverse events (AEs) have been listed under SPMS states whereas on page 119 of company submission document B, AEs are not listed under SPMS states. Please can the company clarify the discrepancy?

Novartis apologise for the inconsistency between the company submission and the structure worksheet of the model. Novartis can confirm that the company submission is correct and the

structure worksheet in the Excel model has been corrected in the version of the model submitted as part of the response to these clarification questions.

B6. There appears to be an inconsistency in the total treatment monitoring costs for subsequent years reported in table 159 (document Appendices, page 572) and the Excel model (Costs worksheet). Please can the company clarify which values should be used in the model?

Table 1: Total treatment monitoring costs for subsequent years

Treatment	Appendix M	Economic model
Natalizumab	£744.33	£459.00

Novartis apologise for the discrepancy in these values and can confirm that the value presented in the CS Appendices is erroneous for two reasons. Firstly, the value of £744.33 presented in Table 159, Page 572, CS Appendix M.5.3 is a typographical error and does not apply to any of the years of natalizumab monitoring. Secondly, Table 159, Page 572, CS Appendix M.5.3 does not make clear that natalizumab monitoring costs are different for Year 2 and Years 3+. Different monitoring cost for natalizumab in Years 3+ compared to Year 2 is driven by the requirement given in the Summary of Product Characteristics (SmPC) for patients at high risk of progressive multifocal leukoencephalopathy (PML) to receive additional MRI scans in Year 3 onwards. Specifically, these high risk patients include those who are anti-JCV antibody positive and have received more than two years of natalizumab therapy, and have received prior immunosuppressant therapy, and those who have a high anti-JCV antibody index who have received more than 2 years of natalizumab therapy and without prior history of immunosuppressant therapy.[18]

The correct monitoring costs associated with natalizumab in Year 1, Year 2 and Years 3+ have been summarised in Table 15. These correct values were used in the model and should therefore be considered in place of the relevant section of Table 159, Page 572, CS Appendix M.5.3. Updates as compared with Table 159 of the CS Appendices have been italicised.

Table 15: Monitoring costs associated with natalizumab in Year 1, Year 2 and Year 3+

Natalizumab	Year 1			Year 2			Years 3+		
	ARU (units)	Unit cost	Annual cost	ARU (units)	Unit cost	Annual cost	ARU (units)	Unit cost	Annual cost
Neurology Visit (NHS Reference Costs 2018-2019; WF01B; Neurology)	1	£220.24		1	£168.84		1	£168.84	
MS Nurse visit (30 mins) PSSRU 2019 - 13. Hospital based nurses, Band 7 Cost per hour of patient contact*	2	£66.12		2	£66.12		2	£66.12	
MRI (NHS Reference Costs 2018-2019; Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over, RD01A)	2	£142.67		1	£142.67		1	£142.67	
MRI Year 3+ (NHS Reference Costs 2018-2019; Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over, RD01A); **4 MRI scans, assuming 50% of patients are JCV+ and require additional MRI scans**	0	£142.67	£653.07	*0*	£142.67	*£459.00*	*2*	£142.67	*£601.68*
Liver Function (NHS Reference Costs 2018-2019; Clinical Biochemistry, DAPS04)	2	£1.10		2	£1.10		2	£1.10	
JCV tests (NHS Reference Costs 2018-2019; Immunology, DAPS06)	2	£6.53		2	£6.53		2	£6.53	

Italics indicate updates as compared with Table 159, Page 572, CS Appendix M.5.3.
* Cost not directly available, so Band 6 ratio of Cost per working hour (£47) to Cost per hour of patient contact (£113) was calculated and conservatively applied to Band 7 Cost per working hour (£55), (i.e. ((£113/47)*£55)/2 = £66.12)
Abbreviations: ARU: annual resource use; JCV: John Cunningham virus; MRI: magnetic resonance imaging; MS: multiple sclerosis.

B7. In the 'Input store' worksheet, cell G373 shows the annual cost of £85,260 for glatiramer acetate, which was derived by multiplying the number of participants with highly active by those with rapidly-evolving severe multiple sclerosis (MS). Please can the company clarify if this figure is used in the economic model?

Novartis can clarify that this figure is not used in the economic model at any time. When the reset to default function is initiated, the formula (not the value) contained within the cell in question will be copied into cell G47 in the 'Costs' worksheet. On the 'Costs' worksheet the formula will draw from cells F47 and E47 and produce the correct value of £46 for the annual cost of administration of glatiramer acetate in the first year of treatment.

Utilities

B8. PRIORITY QUESTION: HRQoL information was collected using the EQ-5D-5L questionnaire collected across the ASCLEPIOS trials and used to estimate health state utilities for the economic analysis.

1. **Please can the company clarify how the EQ-5D information was pooled across ASCLEPIOS trials?**

For the analysis of EQ-5D by EDSS category, as required to derive utility values for use in the economic model, EQ-5D data were pooled across the ASCLEPIOS I and II studies in the same way as for the purpose of analysing the disability-related secondary outcomes, with patient data from both studies combined as though collected from a single study. Given the pre-planned pooling of the disability-related endpoints, the ASCLEPIOS trials had identical study design and simultaneous, global conduct. Beyond these *a priori* assumptions, the appropriateness of this pooling across studies was assessed by comparing the baseline characteristics in both studies and by testing for the similarity/dissimilarity of the between-treatment effect on disability outcomes between both studies (heterogeneity test in the meta-analysis).[3] For the analysis of EQ-5D by EDSS state, in addition to pooling across studies, pooling across treatment arms was also performed in the same manner.

2. **Please provide the EQ-5D results for all available time points in the trials including the mean EQ-5D values by trial and time point?**

The EQ-5D utility score summary statistics for the baseline, Week 48 and Week 96 visits in the ASCLEPIOS trials (by trial and pooled) are provided in Table 16.

Table 16: EQ-5D utility score summary statistics by trial and by visit

	ASCLEPIOS I (N=927)			ASCLEPIOS II (N=955)			Pooled trials (N=1,882)		
	Baseline	Value at timepoint	Change vs baseline	Baseline	Value at timepoint	Change vs baseline	Baseline	Value at timepoint	Change vs baseline
Baseline									
n	[redacted]	-	-	[redacted]	-	-	[redacted]	-	-
Mean (SD)	[redacted]	-	-	[redacted]	-	-	[redacted]	-	-
Range	[redacted]	-	-	[redacted]	-	-	[redacted]	-	-
Week 48									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96									
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

At each visit-window, only patients with a value at both baseline and that visit-window are included.
Baseline is the last assessment obtained prior to the first administration of study drug. The visit window for Week 48 ranged from Day 1 to Day 504 and the visit window for Week 96 from Day 505 to Day 839.
Abbreviations: EQ-5D: European Quality of Life-5 Dimensions; SD: standard deviation.
Source: Novartis (Data on File): EQ-5D Scores Summary Statistics.[19]

3. **Please also clarify whether there were any missing EQ-5D data and how these were addressed when estimating the health state utility values?**

As shown in Table 17, in the pooled ASCLEPIOS I and II trials EQ-5D data at baseline were missing for [redacted] patients ([redacted]% of FAS; N=1,882). For the Week 48 and Week 96 visit windows, EQ-5D data were not available from [redacted] and [redacted] patients, respectively ([redacted]% and [redacted]%, respectively, of the patients eligible for EQ-5D completion at the start of the pre-defined visit window).

Table 17: Number of patients completing EQ-5D assessments at each visit-window

Visit window	ASCLEPIOS I (N=927)		ASCLEPIOS II (N=955)		Pooled trials (N=1,882)	
	N	n	N	n	N	n
Baseline	927	[redacted]	955	[redacted]	1,882	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N=number of patients at the start of the visit window; n=number of patients completing an EQ-5D assessment at each visit-window.
Baseline is the last assessment obtained prior to the first administration of study drug. The visit window for Week 48 ranged from Day 1 to Day 504 and the visit window for Week 96 from Day 505 to Day 839.
Abbreviations: EQ-5D: European Quality of Life-5 Dimensions.
Source: Novartis (Data on File): EQ-5D Scores Summary Statistics.[19]

The analysis of health state utilities by EDSS category was based on all post-baseline EQ-5D assessments, with each patient's baseline EQ-5D being used as a predictor in the regression model (described in the CS Appendix M.4). No imputation of any missing values was performed. EQ-5D values from [redacted] patients were excluded from the analysis due to missing covariates required for the regression model.[19] The number of patients included in the analysis of EQ-5D by EDSS category was [redacted], and the total number of assessments included was [redacted].

B9. PRIORITY QUESTION: In table 74, company submission document B, page 139, a disability coefficient of [redacted] was applied to relapse severity states. Please can the company clarify if this disutility coefficient has been applied to people with SPMS who experienced relapses?

Novartis can confirm that this same disutility coefficient is also applied to people with SPMS who experience relapses. This approach to apply the same disutility to all patients who experience relapse, regardless of an RRMS or an SPMS phenotype, is considered appropriate given that the disutility associated with relapse is not expected to change dependent on the overall MS phenotype. It is understood by Novartis that this approach of applying the same disutility is consistent with TA533.[8]

B10. PRIORITY QUESTION: Table 73, company submission document B, page 139 reports the results of the utility modifiers derived from the ASCLEPIOS I and II trial data. The company further states that further information is

provided about how these coefficients were derived. Please can the company provide the regression model along with the p-values for these coefficients?

Error identified when preparing our response

In preparing to answer this clarification question, Novartis has discovered a programming error in the economic model that means all the economic results presented have **not** applied the two coefficients for male sex and time since diagnosis described in Table 73, Page 139 of CS Document B, as explained below. The exception is the scenario in which Orme et al. 2007 was used as the only source of the health state utility values (HSUVs) applied (Scenario 8); in this scenario, the two coefficients were applied correctly, but the values used for the coefficients have been found to be incorrect, as explained below. The effect on the incremental cost-effectiveness ratios (ICERs) is negligible.

Inclusion of the coefficients in the model

The rationale for inclusion of coefficients for sex and time since diagnosis in the model structure was that they were reported in the Orme et al. regression model and were compatible with the model structure.[20] Novartis have now identified that these coefficient values from Orme were inadvertently overwritten with values derived from the ASCLEPIOS trials during development of the model. Furthermore, contrary to the description provided in the CS, all analyses which sourced HSUVs from the ASCLEPIOS trials were run without these two coefficients being applied in the model. In the scenario in which Orme et al. was used as the only source of HSUVs (Scenario 8), these two coefficients were applied correctly however the values were incorrectly derived from the ASCLEPIOS trials.

Regression model for the ASCLEPIOS health state utility values

As requested, the coefficients and p-values for the health state utility regression model based on ASCLEPIOS data are presented in Table 18. The regression analysis to derive the utility decrement for relapses in the model is presented in Table 19. The difference between the two regression models is whether they consider *any* relapse or only *confirmed* relapses: the HSUVs were based on excluding *any* relapse whereas the utility decrement for relapses in the model was based on only *confirmed* relapses. This approach avoided both the HSUVs and the utility decrement for relapses being confounded by unconfirmed relapses. The HSUVs derived from the regression model in Table 18 are presented in Table 156, Page 563 of CS Appendix M.4.3 and repeated in Table 20 below. These values were used in the model base case except for EDSS 7 and 8 where insufficient data were available from ASCLEPIOS to provide usable estimates. For EDSS 7–9, the utility values from Orme et al. were used to supplement the ASCLEPIOS values, as explained in CS Document B, Section B.3.4.1, Page 138.

Table 18: Regression model used to derive health state utility values from the pooled ASCLEPIOS I & II trials (covariate for relapse includes any relapse, both confirmed and unconfirmed)

Predictor	Estimate (95% CI)	p-value
Baseline EQ-5D	[redacted]	[redacted]
EDSS 1–1.5 (reference: 0)	[redacted]	[redacted]
EDSS 2–2.5	[redacted]	
EDSS 3–3.5	[redacted]	
EDSS 4–4.5	[redacted]	

EDSS 5–5.5	[redacted]	
EDSS 6–6.5	[redacted]	
EDSS 7–7.5	[redacted]	
EDSS 8–8.5	[redacted]	
Relapse (reference: no)	[redacted]	[redacted]
Age	[redacted]	[redacted]
Sex (reference: male)	[redacted]	[redacted]
Time since diagnosis (years)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EDSS: Extended Disability Status Score; EQ-5D: European Quality of Life-5 Dimensions.

Table 19: Regression model used to derive utility decrement for relapses from the pooled ASCLEPIOS I & II trials (covariate for relapse includes only confirmed relapses)

Predictor	Estimate (95% CI)	p-value
Baseline EQ-5D	[redacted]	[redacted]
EDSS 1–1.5 (reference: 0)	[redacted]	[redacted]
EDSS 2–2.5	[redacted]	
EDSS 3–3.5	[redacted]	
EDSS 4–4.5	[redacted]	
EDSS 5–5.5	[redacted]	
EDSS 6–6.5	[redacted]	
EDSS 7–7.5	[redacted]	
EDSS 8–8.5	[redacted]	
Age	[redacted]	[redacted]
Relapse (reference: no)	[redacted]	[redacted]
Sex (reference: male)	[redacted]	[redacted]
Time since diagnosis (years)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EDSS: Extended Disability Status Score; EQ-5D: European Quality of Life-5 Dimensions.

Table 20: Health state utility values derived from the regression model presented in Table 18

EDSS	Number of subjects	Number of assessments	Adjusted Mean (95% CI)
0	[redacted]	[redacted]	[redacted]
1.0 to 1.5	[redacted]	[redacted]	[redacted]
2.0 to 2.5	[redacted]	[redacted]	[redacted]
3.0 to 3.5	[redacted]	[redacted]	[redacted]
4.0 to 4.5	[redacted]	[redacted]	[redacted]
5.0 to 5.5	[redacted]	[redacted]	[redacted]
6.0 to 6.5	[redacted]	[redacted]	[redacted]
7.0 to 7.5	[redacted]	[redacted]	[redacted]
8.0 to 8.5	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EDSS: Extended Disability Status Score.
Source: Novartis (Data on File): EQ-5D Scores by EDSS Status.[21]

No change to the Company base case results

Having reconsidered the regression models prompted by the ERG question, and noting the non-significance of the two coefficients for sex and time since diagnosis in Table 18, Novartis confirm that the ICER results provided in the CS where these two coefficients were not in fact applied continue to form their base case, and that the description of the two coefficients in the CS instead be applied to a new scenario analysis, presented below. For the scenario in the CS in which Orme et al. was used as the only source of HSUVs (Scenario 8), where the results in the CS contained an error, corrected results are supplied below.

Revised model

In order to correct the programming error in the model, a revised model has been supplied along with this response with the following changes:

- For the two coefficients for male sex and time since diagnosis, the 'Utilities' worksheet now provides a choice of coefficient values from ASCLEPIOS, Orme, or zero values. A new switch has been added in this worksheet to select from the above coefficients, allowing for a transparent application of the chosen values. The Company base case is to apply the zero values for the two coefficients for male sex and time since diagnosis, as per the results in the CS.

- Cells H443 and H444 in the worksheet 'Data store' have been reprogrammed to select from the coefficients entered in the 'Utilities' worksheet, depending on which coefficients are selected on that sheet.

Revised Orme et al. scenario results

Due to the programming error identified, coefficient values for male sex and time since diagnosis from the ASCLEPIOS utility regression model were in fact applied in the Orme et al. scenarios presented in the CS. Correcting these scenarios to use the coefficient values from Orme for male sex and time since diagnosis (presented in Table 21 below) gives the results for the RRMS, highly active (HA) RRMS and rapidly-evolving severe (RES) RRMS populations presented in Table 22, Table 23 and Table 24 below. The effect of this correction on the ICERs is negligible in all three populations.

Table 21: Utility coefficient values for years since diagnosis and male sex from the Orme et al. regression analysis

Additional utility modifier	Utility coefficient
Years since diagnosis	0.002
Male	0.017

Source: Orme et al., 2007.[20]

Table 22: Scenario using health state utility values from Orme et al.: results in the RRMS population (company submission and corrected scenario)

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Scenario presented in the CS [Document B, Table 92]: health state utility values from Orme et al. 2007									
Avonex®	**Avonex®**	19.46	[redacted]	3.50	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	4.00	0.08	[redacted]	0.50	[redacted]	[redacted]
Dimethyl fumarate	**Dimethyl fumarate**	19.47	[redacted]	3.55	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	4.00	0.07	[redacted]	0.44	[redacted]	[redacted]
Glatiramer acetate	**Glatiramer acetate**	19.43	[redacted]	3.34	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	4.00	0.10	[redacted]	0.65	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.55	[redacted]	4.05	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	4.00	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.46	[redacted]	3.47	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	4.00	0.08	[redacted]	0.53	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	3.32	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	4.00	0.11	[redacted]	0.68	[redacted]	[redacted]
Corrected scenario: health state utility values from Orme et al. 2007									
Avonex®	**Avonex®**	19.46	[redacted]	4.76	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.27	0.08	[redacted]	0.50	[redacted]	[redacted]
Dimethyl fumarate	**Dimethyl fumarate**	19.47	[redacted]	4.82	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.27	0.07	[redacted]	0.45	[redacted]	[redacted]
Glatiramer acetate	**Glatiramer acetate**	19.43	[redacted]	4.60	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.27	0.10	[redacted]	0.67	[redacted]	[redacted]

Ocrelizumab	**Ocrelizumab**	19.55	[redacted]	5.32	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.27	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.46	[redacted]	4.73	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.27	0.08	[redacted]	0.53	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.58	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.27	0.11	[redacted]	0.69	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 23: Scenario using health state utility values from Orme et al.: results in the HA RRMS population (company submission and corrected scenario)

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Scenario presented in the CS [Document B, Table 93]: health state utility values from Orme et al. 2007									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	3.76	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	3.48	−0.05	[redacted]	−0.28	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	3.37	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	3.48	0.02	[redacted]	0.11	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	3.02	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	3.48	0.08	[redacted]	0.46	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	3.53	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	3.48	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Corrected scenario: health state utility values from Orme et al. 2007									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.08	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.80	−0.05	[redacted]	−0.29	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	4.69	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.80	0.02	[redacted]	0.11	[redacted]	[redacted]

Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.33	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.80	0.08	[redacted]	0.47	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	4.85	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.80	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.
Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 24: Scenario using health state utility values from Orme et al.: results in the RES RRMS population (company submission and corrected scenario)

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Scenario presented in the CS [Document B, Table 94]: health state utility values from Orme et al. 2007									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	4.40	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	4.09	−0.05	[redacted]	−0.31	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	3.97	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	4.09	0.02	[redacted]	0.11	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	4.13	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	4.09	−0.01	[redacted]	−0.04	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	4.14	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	4.09	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Corrected scenario: health state utility values from Orme et al. 2007									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	5.69	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.37	−0.05	[redacted]	−0.32	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	5.26	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.37	0.02	[redacted]	0.11	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	5.42	-	-	-	-	-

	Ofatumumab	20.04	[redacted]	5.37	−0.01	[redacted]	−0.04	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	5.43	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.37	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

New scenario: applying the regression coefficients from ASLCEPIOS as described in the CS

For transparency, after correction of the above-described errors, the model has also been run applying the coefficients for sex and time since diagnosis from the ASCLEPIOS utility analysis as originally described in the CS. The results for the RRMS, HA RRMS and RES RRMS populations are presented alongside the base case results in Table 25, Table 26 and Table 27, respectively. The effect on ICERs is negligible in all three populations and the changes do not affect any of the conclusions of cost-effectiveness drawn. In the RRMS population, ofatumumab remains [redacted] versus dimethyl fumarate and teriflunomide, [redacted] versus Avonex®, glatiramer acetate and Rebif®, and [redacted] versus ocrelizumab [redacted] In the HA RRMS population, ofatumumab remains [redacted] versus cladribine and fingolimod and [redacted] versus ocrelizumab [redacted]. In the RES RRMS subgroup, ofatumumab remains [redacted] versus cladribine and [redacted] versus natalizumab and ocrelizumab [redacted]. Overall, ofatumumab remains cost-effective versus all comparators except alemtuzumab in HA and RES RRMS.

Table 25: Scenario applying utility coefficients derived from the ASCLEPIOS trials: results in the RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Avonex®	**Avonex®**	19.46	[redacted]	5.09	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.56	[redacted]	[redacted]
Dimethyl fumarate	**Dimethyl fumarate**	19.47	[redacted]	5.15	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.07	[redacted]	0.51	[redacted]	[redacted]
Glatiramer acetate	**Glatiramer acetate**	19.43	[redacted]	4.92	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.10	[redacted]	0.74	[redacted]	[redacted]

Ocrelizumab	**Ocrelizumab**	19.55	[redacted]	5.72	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.46	[redacted]	5.05	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.61	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.89	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.11	[redacted]	0.77	[redacted]	[redacted]
Scenario: ASCLEPIOS utility coefficients for sex and time since diagnosis applied									
Avonex®	**Avonex®**	19.46	[redacted]	4.67	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.23	0.08	[redacted]	0.56	[redacted]	[redacted]
Dimethyl fumarate	**Dimethyl fumarate**	19.47	[redacted]	4.73	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.23	0.07	[redacted]	0.50	[redacted]	[redacted]
Glatiramer acetate	**Glatiramer acetate**	19.43	[redacted]	4.49	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.23	0.10	[redacted]	0.74	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.55	[redacted]	5.29	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.23	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.46	[redacted]	4.62	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.23	0.08	[redacted]	0.61	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.46	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.23	0.11	[redacted]	0.77	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 26: Scenario applying utility coefficients derived from the ASCLEPIOS trials: results in the HA RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.46	-	-	-	-	-

	Ofatumumab	19.28	[redacted]	5.12	−0.05	[redacted]	−0.33	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	5.00	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.02	[redacted]	0.12	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.60	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.08	[redacted]	0.52	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	5.19	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: ASCLEPIOS utility coefficients for sex and time since diagnosis applied									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.01	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.68	−0.05	[redacted]	−0.33	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	4.56	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.68	0.02	[redacted]	0.12	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.16	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.68	0.08	[redacted]	0.52	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	4.74	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	4.68	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.

Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 27: Scenario applying utility coefficients derived from the ASCLEPIOS trials: results in the RES RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	6.14	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.05	[redacted]	−0.37	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	5.66	-	-	-	-	-

	Ofatumumab	20.04	[redacted]	5.78	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	5.82	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.05	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	5.84	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: ASCLEPIOS utility coefficients for sex and time since diagnosis applied									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	5.71	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.34	−0.05	[redacted]	−0.37	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	5.22	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.34	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	5.39	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.34	−0.01	[redacted]	−0.05	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	5.40	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.34	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

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B11. PRIORITY QUESTION: Can the company please clarify if utility decrements for caregivers of people with SPMS have been included in the economic model?

Novartis can confirm that the same caregiver disutilities have been included in the model for both RRMS and SPMS, as per Table 75, Page 140 of CS Document B which is reproduced below for reference (Table 28). These disutilities were obtained from TA127 and have been used and accepted in many subsequent NICE appraisals of RRMS disease-modifying therapies (DMTs).[6-8, 22]

Table 28: Caregiver disutility considered in the model derived from TA127

EDSS	Caregiver disutility	SE
0	0.000	0.000
1	0.001	0.000
2	0.003	0.001
3	0.009	0.002
4	0.009	0.002
5	0.020	0.004
6	0.027	0.005
7	0.053	0.011
8	0.107	0.021
9	0.140	0.028

Abbreviations: EDSS: Expanded Disability Status Scale; SE: standard error.
Source: Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis [TA127].[22]

B12. Please can the company clarify if age-related disutilities have been captured in the model?

Age-related utility adjustments, such as those published by Ara and Brazier,[23] are not applied in the model. Such adjustments may be pertinent in models structured around long-term response states where patients remain in one health state over a significant timeframe, for example in modelling interventions to reduce cardiovascular risk, or interventions providing long-term prevention of disease progression in rheumatoid arthritis. However, in MS, disease progression continues on all treatments and EDSS is therefore inherently correlated with age and time since diagnosis. As presented under the answer to clarification question B10 above, the regression model for utility included age as a covariate, although the resultant coefficient was not used in the model, and the effect of age on utility once EDSS was accounted for (as represented by the regression model coefficient for age) was found to be negligible. Consequently, no results explicitly incorporating age-adjusted utilities are presented. It may be noted that the inclusion of the time since diagnosis utility coefficient from ASCLEPIOS, which has the same value as the coefficient for age, in the scenario presented in clarification question B10 had a negligible effect on the ICERs. Further, it should be noted that Novartis are not aware that any previous NICE appraisal of DMTs in RRMS has used age-adjusted utilities.

B13. Based on the natural history of relapsing-remitting MS (RRMS), there might be differences in utilities for people by either gender or age range. Sub-group analyses

based on these characteristics could impact on the cost-effectiveness results regarding the incremental costs and quality adjusted life years. Please can the company clarify why these subgroups were not considered/included?

The regression model presented in the answer to clarification question B10 above suggests that EDSS is the primary determinant of utility, followed by relapse. Age and sex coefficients are provided and result in very negligible coefficient values. The new scenario presented in clarification question B10 including the two coefficients from the CS (sex and time since diagnosis) does in fact provide the same ICERs that would result from inclusion of age and sex in the model, as the age coefficient is equal to the time since diagnosis coefficient and the sex coefficient is included in that scenario. The negligible change in ICERs that results from their inclusion demonstrates that these subgroups are not pertinent to decision-making in the appraisal. It may also be noted that differential reimbursement recommendations on the basis of either sex or age are not likely to be compatible with the Equality Act.

Costs

B14. PRIORITY QUESTION: Please can the company clarify what management costs are being considered in the model for people with SPMS?

Novartis can confirm that the same disease management costs for the various EDSS health state, inflated from the UK MS Survey as presented in Table 80, Page 145 of CS Document B are used for both people with RRMS and SPMS in the economic model. This approach aligns with the final committee-preferred cost source and model used in NICE TA527 where health state costs did not differ by phenotype; the committee reported in TA533 that they preferred to use this source for decision making once again.[16, 24]

Adverse events

B15. The ERG notes some inconsistencies regarding the adverse events stated in the clinical effectiveness section tables 45, 46, 47 and 48, company submission document B, pages 102-107 and the cost-effectiveness section table 76, company submission document B, page 141.

Can the company clarify why adverse events (e.g. gastroenteritis, hypertension, pneumonia, neoplasms (breast/skin), liver disturbance (clinical or biochemical i.e. ALT or other liver function change), or pyrexia) have been excluded from the annual adverse event probabilities for each disease modifying therapy (DMT) included in the economic model?

Prior experience has suggested that adverse events (AEs) are not typically model drivers when comparing DMTs for RRMS. Therefore, Novartis aligned with the approach taken in the ocrelizumab appraisal (TA533), which is the most relevant recent appraisal of an RRMS DMT by NICE given the similarity in their mechanism of action.[8] In TA533, the approach taken was that AEs observed in ≥5% of patients in any treatment arm of the OPERA trials were considered in

the economic model. In the ofatumumab CS, all annual AE probabilities were initially sourced from TA533 to which the proportions of severe and non-severe AEs observed in the ASCLEPIOS trials ([redacted]% serious events, [redacted]% non-serious events) were applied. The exceptions were the annual probabilities of AEs associated with cladribine (a comparator not considered in TA533), which were derived from the CLARITY trial, and the annual probabilities of AEs associated with ofatumumab and teriflunomide, which were derived from the ASCLEPIOS trials. For simplicity, the AE data from CLARITY were taken for the list of AEs used in the TA533 appraisal; the approach taken for the AE data from the ASCLEPIOS trials is provided below. All AE disutilities, both for serious and non-serious AEs, were obtained from TA533.

Of the AEs reported in >3% of patients in any treatment arm during the ASCLEPIOS trials (presented in CS, Document B, Table 45, page 102), gastroenteritis, increased alanine aminotransferase (ALT) and pyrexia (all noted in the ERG question) were observed in less than 5% of patients in any treatment arm and therefore would not have been included in the model when applying the approach taken in TA533. Similarly, neoplasms (noted in the ERG question) were observed in ≤1% of patients in any treatment arm (CS, Document B, Table 47, page 105). The exclusion of hypertension (noted by the ERG question), pain in extremity and paraesthesia from the cost-effectiveness analysis was a conservative assumption, given that all were observed in >5% of the teriflunomide-treated patients of ASCLEPIOS I and/or II, whereas <5% of ofatumumab-treated patients reported these outcomes. The only TEAEs reported in >5% of patients in a treatment arm in which rates were higher among ofatumumab-treated patients than among teriflunomide-treated patients were decreased blood IgM levels, anxiety and nausea, none of which were expected to incur meaningful costs or disutilities. Alopecia and diarrhoea were both observed in >5% of patients in each treatment arm, but given their considerably greater occurrence in the teriflunomide treatment arm than in the ofatumumab treatment arm, their exclusion from the economic model was considered likely to be a conservative assumption, and again neither were deemed likely to incur meaningful costs. Therefore, overall, it is likely that the omission of these additional AEs from the economic model had no meaningful impact on the ICERs produced and, given the higher occurrence of many of these AEs in the teriflunomide population, their exclusion may be broadly conservative. In addition, their inclusion in the economic model would require incidence data on their occurrence in all other DMTs, which could in some cases be greater than that observed in ASCLEPIOS.

In order to explore the effect of AE incidence on the ICER, scenario analyses were run in which the AE incidence for ofatumumab was maintained as in the base case while the incidence of all AEs in all comparators was set to zero. The results for the RRMS, HA RRMS and RES RRMS populations are presented in Table 29, Table 30 and Table 31, respectively. The effect on ICERs is negligible and does not affect any of the conclusions of cost-effectiveness drawn. In the RRMS population, ofatumumab remains [redacted] versus dimethyl fumarate and teriflunomide, [redacted] versus Avonex®, glatiramer acetate and Rebif®, and [redacted] versus ocrelizumab [redacted] In the HA RRMS population, ofatumumab remains [redacted] versus cladribine and fingolimod and [redacted] versus ocrelizumab [redacted]. In the RES RRMS subgroup, ofatumumab remains [redacted] versus cladribine and [redacted] versus natalizumab and ocrelizumab [redacted]. Overall, ofatumumab remains cost-effective versus all comparators except alemtuzumab in HA and RES RRMS in this very conservative scenario, demonstrating the limited impact of AEs in the economic model.

Table 29: Scenario with no AEs in the comparator arms: results in the RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Avonex®	Avonex®	19.46	[redacted]	5.09	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.56	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	19.47	[redacted]	5.15	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.07	[redacted]	0.51	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	19.43	[redacted]	4.92	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.10	[redacted]	0.74	[redacted]	[redacted]
Ocrelizumab	Ocrelizumab	19.55	[redacted]	5.72	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	Rebif® 44	19.46	[redacted]	5.05	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.61	[redacted]	[redacted]
Teriflunomide	Teriflunomide	19.43	[redacted]	4.89	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.11	[redacted]	0.77	[redacted]	[redacted]
Scenario: No AE incidence in comparator arms									
Avonex®	Avonex®	19.46	[redacted]	5.12	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.54	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	19.47	[redacted]	5.17	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.07	[redacted]	0.49	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	19.43	[redacted]	4.94	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.10	[redacted]	0.72	[redacted]	[redacted]

Ocrelizumab	**Ocrelizumab**	19.55	[redacted]	5.77	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	−0.01	[redacted]	−0.11	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.46	[redacted]	5.07	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.59	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.91	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.11	[redacted]	0.75	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 30: Scenario with no AEs in the comparator arms: results in the HA RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.46	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.05	[redacted]	-0.33	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	5.00	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.02	[redacted]	0.12	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.60	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.08	[redacted]	0.52	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	5.19	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: No AE incidence in comparator arms									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.47	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.05	[redacted]	−0.34	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	5.02	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.02	[redacted]	0.11	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.63	-	-	-	-	-

	Ofatumumab	19.28	[redacted]	5.12	0.08	[redacted]	0.50	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	5.23	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.01	[redacted]	−0.11	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.

Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 31: Scenario with no AEs in the comparator arms: results in the RES RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	6.14	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.05	[redacted]	−0.37	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	5.66	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	5.82	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.05	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	5.84	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: No AE incidence in comparator arms									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	6.15	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.05	[redacted]	−0.38	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	5.67	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	0.02	[redacted]	0.10	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	5.89	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.11	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	5.89	-	-	-	-	-

	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.11	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

B16. In company submission document B, page 136, adverse event probabilities were assumed to remain constant across Year 1 and subsequent years of therapy. Please can the company justify their approach, as this might lead to either under or over estimation of AE probabilities?

As presented in the response to clarification question B15 above, AEs have been found not to be significant model drivers in this appraisal. Furthermore, as presented in CS Document B (Table 40, page 79), trials included in the NMAs varied in duration, from under one year to three years, and in trial design (event-driven vs fixed-duration designs). Therefore, equivalent data are not available for all comparators to inform discontinuation in subsequent years, particularly given that for trials longer than one year, many did not report annual discontinuation rates. For this reason, it was considered to be appropriate and justifiable to make the simplifying assumption that AEs remain constant across Year 1 and subsequent years of therapy in alignment with the most relevant recent NICE appraisal, ocrelizumab (TA533), and teriflunomide (TA303).[25, 26]

Discontinuation

B17. It is unclear to the ERG when people discontinue treatment if the full cost of the DMT is incurred or part thereof in the model cycle. Please can the company clarify?

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. As noted in the response to Question B4 above, these state occupancies are calculated, using the life table correction method, 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.

B18. In company submission document B, table 53, pages 120-21, the company stated that all-cause discontinuation is a suitable proxy for treatment effect waning. The ERG notes that patients are likely to discontinue treatment because the effectiveness reduces over time and as disease progresses, but there may be instances where people continue treatment even though the effectiveness reduces. In the absence of long-term information and in line with previous analyses in RRMS, please can the company provide a model with the functionality to explore waning of the treatment effect, by 50% after 5 years, or where it reduces by 25% after 2 years and 50% after 5 years?

To explore whether the currently available data from ASCLEPIOS provide any evidence indicative of the ofatumumab treatment effect waning over time, further analyses were conducted for the outcomes CDW-6 and ARR as the two main clinical effectiveness outcomes used in the economic model.

At end of study (EOS), patients included in ASCLEPIOS I had a median duration of exposure of [redacted] days in the ofatumumab group and [redacted] days in the teriflunomide group. In ASCLEPIOS II, the median duration of exposure was [redacted] days in the ofatumumab group and [redacted] days in the teriflunomide group. The proportion of patients with at least 48 weeks of treatment and with more than 96 weeks of treatment by EOS is given in Table 32.

Table 32: Duration of treatment exposure in the ofatumumab and teriflunomide treatment groups in the ASCLEPIOS trials

	ASCLEPIOS I[14]		ASCLEPIOS II[15]	
	20 mg OMB (N=465)	14 mg TER (N=462)	20 mg OMB (N=481)	14 mg TER (N=474)
Exposure (days), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Exposure (days), median	[redacted]	[redacted]	[redacted]	[redacted]
Duration of exposure, n (%)				
<48 weeks (1 year)	[redacted]	[redacted]	[redacted]	[redacted]
≥48 weeks (1 year)	[redacted]	[redacted]	[redacted]	[redacted]
48–96 weeks (1–2 years)	[redacted]	[redacted]	[redacted]	[redacted]
>96 weeks (2 years)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OMB: ofatumumab; SD: standard deviation; TER: teriflunomide.
Source: Table 12-1 of Novartis (Data on File): ASCLEPIOS I Clinical Study Report;[14] Table 12-1 of Novartis (Data on File): ASCLEPIOS II Clinical Study Report.[15]

In the protocol-defined main analysis of time to first CDW-6, ofatumumab demonstrated a statistically significant reduction in risk of 32.5% compared to teriflunomide (HR: 0.68 [95% CI: 0.50, 0.92], p=0.012).[5]

The Cox regression model assumes proportional hazards, i.e. it assumes that ofatumumab treatment compared with teriflunomide treatment lowers the hazard of a disability event by a constant factor. To assess whether there was any evidence for a reduction of efficacy over time, a treatment-by-time interaction variable was included in the Cox regression model to allow for a potential waning of effect in the model, and statistically tested. The statistical test for the treatment-by-time interaction was non-significant (p=[redacted] in treatment-by-time interaction test), suggesting that the assumption that the treatment effect does not wane over time is reasonable.[27]

To further investigate the possibility of a waning of effect, the effect size between ofatumumab and teriflunomide was quantified for different time intervals: ≤ Week 8, as the onset of action period for both treatments (consistent with a protocol-defined sensitivity analysis[14]), Week 8 to Week 48, as the year 1 effect at steady state, and > Week 48, as the year 2 effect at steady state. A piecewise Cox regression model containing a time-dependent indicator variable (≤ Week 8; Week 8 to Week 48; >Week 48) and a treatment-by-indicator interaction was used. After the onset-of-action period (8 weeks), ofatumumab demonstrated a [redacted] HR compared to teriflunomide in the Week 8 to Week 48 period (HR: [redacted] [95% CI: [redacted], [redacted]], p=[redacted]) with a [redacted] in the time interval beyond Week 48 (HR: [redacted] [95% CI: [redacted], [redacted]], p=[redacted]; it should be noted that fewer patients were at risk in this time interval).[28] These data support the conclusion that the CDW-6 treatment effect of ofatumumab as compared to teriflunomide does not appear to wane over time. Of particular note, the effect size at steady state (i.e. > Week 8) in year 1 and year 2 is [redacted] than the effect size estimated from the main analysis of CDW-6 (HR: 0.68 [95% CI: 0.50, 0.92], p=0.012), suggesting that the estimate from the main

analysis is a [redacted] estimate of the long-term efficacy that can be expected with ofatumumab.

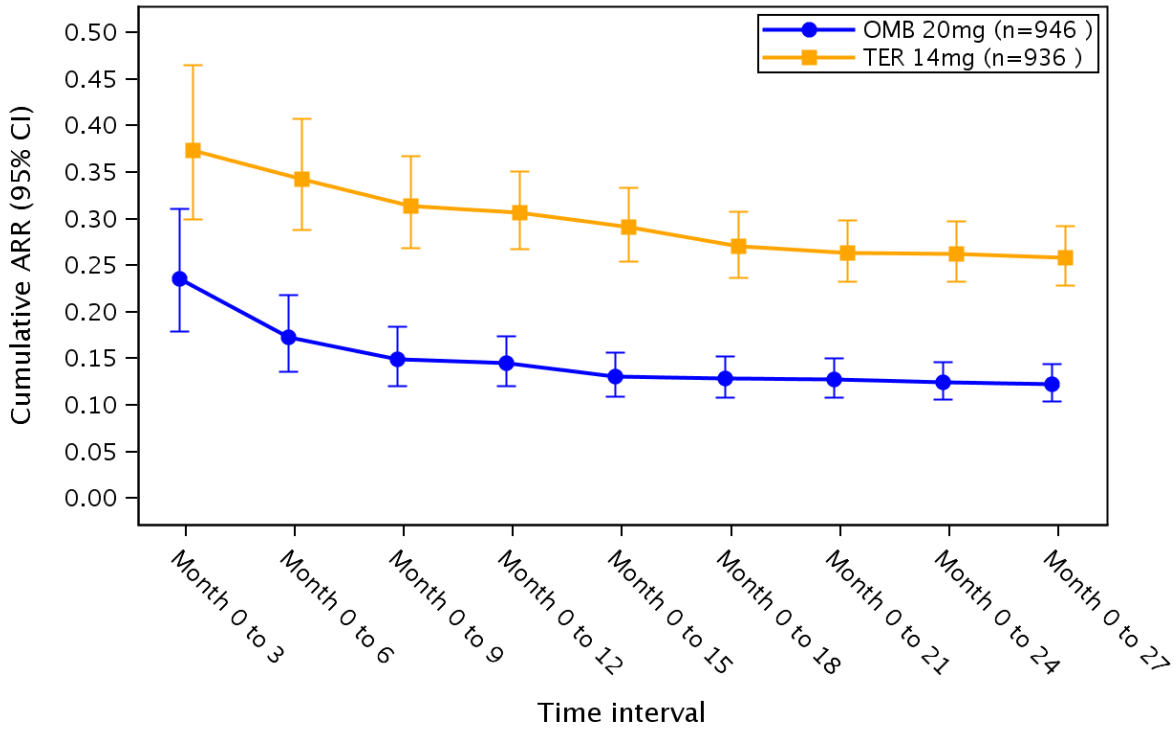
An analysis of cumulative ARR by time interval, ranging from Month 0–3 to Month 0–27, did not show evidence of waning of treatment effect with regard to the reduction of relapses with ofatumumab treatment as compared with teriflunomide treatment (pooled data from ASCLEPIOS I and II). Results are shown below in Table 33 and Figure 6. The ARR ratio for the comparison of ofatumumab with teriflunomide remained stable upon extension of the analysed time intervals, reaching statistical significance in each time interval. The 95% CI includes the ARR ratio estimates from the primary analysis (ASCLEPIOS I: HR: 0.495; ASCLEPIOS II: HR: 0.415)[29] in all time intervals from Month 0-6 onwards. Consistent with the analysis of disability worsening, the effect size in favour of ofatumumab was [redacted] in the first interval, before both medications reached steady state. Ofatumumab significantly reduced ARR compared with teriflunomide at all cumulative time intervals from Month 0 to 3 through Month 0 to 27, by a range of [redacted]% to [redacted]% from Month 0 to 6 onward (p<0.001) for all time intervals.[30, 31]

Table 33: Cumulative ARR (confirmed relapses) by time interval in the ASCLEPIOS trials (FAS)

	Adjusted ARR			Between-treatment comparison	
	OMB 20 mg (N=946)	TER 14 mg (N=936)	ARR reduction, %	ARR ratio (95% CI)	p value
Month 0 to 3	[redacted]	[redacted]	[redacted]	[redacted]	0.011
Month 0 to 6	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 9	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 12	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 15	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 18	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 21	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 24	[redacted]	[redacted]	[redacted]	[redacted]	<0.001
Month 0 to 27	[redacted]	[redacted]	[redacted]	[redacted]	<0.001

Relapses are obtained separately for each time interval by fitting a negative binomial regression model adjusted for treatment as factor.
The natural log of the time-in-study was used as offset to annualise the relapse rate.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; FAS: full analysis set; OMB: ofatumumab; TER: teriflunomide.
Source: Novartis (Data on File): Cumulative ARR by time interval.[30]

Figure 6: Cumulative ARR (confirmed relapses) by time interval in the ASCLEPIOS trials (FAS)



The ARR (95% CI) is estimated separately for each time interval by fitting a negative binomial regression model adjusted for treatment as factor.
The natural log of the time-in-study was used as offset to annualise the relapse rate.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; FAS: full analysis set; OMB: ofatumumab; TER: teriflunomide.
Source: Hauser et al. 2020.[31]

The presented analyses from the ASCLEPIOS trials do not show any indication that the treatment effect of ofatumumab wanes over time. While longer-term data are awaited for ofatumumab, ocrelizumab, which has a very similar mechanism of action (anti-CD20 monoclonal antibodies), provides a close analogue for predicting the likelihood of treatment effect waning with ofatumumab.

In the ocrelizumab for RRMS appraisal (TA533), "*the committee concluded that the rate of stopping treatments could have acted as a proxy to account for treatment waning in the absence of evidence for a waning effect for ocrelizumab.*" Three UK-based treating neurologists were consulted by Novartis in September 2020 in the context of the ERG clarification questions. Consistent with the feedback previously received from clinical experts, these neurologists agreed that should efficacy waning occur in an RRMS patient, that patient would no longer remain on this particular treatment and, as such, any observation of efficacy waning would be captured through discontinuation rates. One of the experts highlighted that with the wide range of different DMTs available in RRMS, there is "*zero chance*" of a patient remaining on a therapy that was no longer working. Another of the experts also noted that in their experience following reimbursement of ocrelizumab, they had observed only one or two failures amongst a large number of patients, further supporting the lack of treatment waning with B cell therapies.

As well as clinical experience with ocrelizumab demonstrating only very rare cases of reduced effect, long-term data from the open-label extension study of the OPERA trials of ocrelizumab also demonstrate a maintenance of treatment effect for up to five years.[32]

Furthermore, one of the treating neurologists consulted by Novartis also highlighted that, from a scientific perspective, ofatumumab should be less likely than other anti-CD20 monoclonal antibodies such as ocrelizumab to induce resistance over time due to the following additional features: ofatumumab is a fully human monoclonal antibody, it binds to both the small and the large extracellular loop of CD20, has a slower off-rate, and it depletes B-cells primarily via complement-dependent cytotoxicity.[33] Additionally, no patients developed neutralising antibodies in either of the ASCLEPIOS trials.[5]

Committee preferences regarding waning assumptions have varied considerably across previous MS technology appraisals and the scenarios requested by the ERG can be considered arbitrary.[6, 8, 22, 34] No evidence has been presented to support an assumption that the effectiveness of ofatumumab wanes in this way, and no evidence has been presented to support the assumption that a patient would continue to be prescribed a DMT where loss of efficacy had been observed. Therefore, Novartis does not support the validity of the ERG's request to see analyses assuming ofatumumab efficacy decreasing by 50% after 5 years or by 25% after 2 years and 50% after 5 years. As such, the Novartis base case remains as considering all-cause treatment discontinuation to act as a proxy for treatment effect waning, consistent with the recent most similar RRMS appraisal for ocrelizumab (TA533), another anti-CD20 monoclonal antibody, in which the Committee agreed with this approach in the absence of any clinical evidence to the contrary.

However, following the request from the ERG, the following scenarios have been provided to allow exploration of the impact of waning in the model on the ICERs:

- An extremely conservative scenario, as requested by the ERG, in which a precipitous 50% reduction in effectiveness is applied after 5 years: i.e. all patients who are still on treatment after 5 years experience a 50% reduction in the treatment effect, yet all patients would nevertheless stay on treatment, with the full treatment cost applying.
- A conservative scenario, in which effectiveness is modelled to wane in a tapered fashion with a 25% reduction after 5 years, then a 50% reduction after 8 years. Again, this reduction in the treatment effect would apply to all patients in the model who are still on treatment at that point in time, and again all patients would nevertheless stay on treatment. This tapering is in line with the tapered scenario requested by the ERG, but with the onset of waning aligned to the end of the published long-term data available for the DMT with the most similar mechanism of action, ocrelizumab. As the ocrelizumab data do not show any indication that a marked drop in efficacy should be expected after a treatment duration of 5 years,[32] even this scenario has to be considered as arbitrary and conservative.

Neither of these scenarios are plausible from a clinical point of view in RRMS due to the availability of other treatment options (as confirmed by the experts consulted by Novartis). In addition, applying waning in the model results in loss of efficacy being double-counted, as the all-cause discontinuation rates applied in the model base case already account for patients who discontinue treatment due to a perceived lack of efficacy.

For patients with RRMS, it is extremely unlikely and contrary to clinical practice that all patients would continue treatment with their current DMT despite such marked reductions in effectiveness. As loss of effectiveness can be considered an adverse event, continuing treatment would not be clinically appropriate under these circumstances, given the possibility to switch to another DMT which would offer the patient a more favourable benefit-risk ratio. Therefore, the

above scenarios where all patients continue DMT treatment despite a marked reduction in clinical effectiveness are not plausible for reimbursement decision making in RRMS.

Cost-effectiveness results for these two treatment waning scenarios are presented for the RRMS, HA RRMS and RES RRMS subgroups in Table 34, Table 35 and Table 36, respectively, to allow the exploration of the impact of waning on the ICER.

Table 34: Waning scenario results in the RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Avonex®	Avonex®	19.46	[redacted]	5.09	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.56	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	19.47	[redacted]	5.15	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.07	[redacted]	0.51	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	19.43	[redacted]	4.92	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.10	[redacted]	0.74	[redacted]	[redacted]
Ocrelizumab	Ocrelizumab	19.55	[redacted]	5.72	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	Rebif® 44	19.46	[redacted]	5.05	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.08	[redacted]	0.61	[redacted]	[redacted]
Teriflunomide	Teriflunomide	19.43	[redacted]	4.89	-	-	-	-	-
	Ofatumumab	19.54	[redacted]	5.66	0.11	[redacted]	0.77	[redacted]	[redacted]
Scenario: efficacy reduced by 50% after 5 years									
Avonex®	Avonex®	19.45	[redacted]	5.04	-	-	-	-	-
	Ofatumumab	19.51	[redacted]	5.49	0.06	[redacted]	0.45	[redacted]	[redacted]
Dimethyl fumarate	Dimethyl fumarate	19.45	[redacted]	5.09	-	-	-	-	-
	Ofatumumab	19.51	[redacted]	5.49	0.05	[redacted]	0.41	[redacted]	[redacted]
Glatiramer acetate	Glatiramer acetate	19.43	[redacted]	4.88	-	-	-	-	-
	Ofatumumab	19.51	[redacted]	5.49	0.08	[redacted]	0.61	[redacted]	[redacted]

Ocrelizumab	**Ocrelizumab**	19.52	[redacted]	5.55	-	-	-	-	-
	Ofatumumab	19.51	[redacted]	5.49	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.45	[redacted]	5.02	-	-	-	-	-
	Ofatumumab	19.51	[redacted]	5.49	0.06	[redacted]	0.47	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.85	-	-	-	-	-
	Ofatumumab	19.51	[redacted]	5.49	0.08	[redacted]	0.64	[redacted]	[redacted]
Scenario: efficacy reduced by 25% after 5 years, and further reduced by 50% after 8 years									
Avonex®	**Avonex®**	19.46	[redacted]	5.06	-	-	-	-	-
	Ofatumumab	19.52	[redacted]	5.54	0.06	[redacted]	0.48	[redacted]	[redacted]
Dimethyl fumarate	**Dimethyl fumarate**	19.46	[redacted]	5.11	-	-	-	-	-
	Ofatumumab	19.52	[redacted]	5.54	0.06	[redacted]	0.43	[redacted]	[redacted]
Glatiramer acetate	**Glatiramer acetate**	19.43	[redacted]	4.89	-	-	-	-	-
	Ofatumumab	19.52	[redacted]	5.54	0.09	[redacted]	0.65	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.53	[redacted]	5.60	-	-	-	-	-
	Ofatumumab	19.52	[redacted]	5.54	−0.01	[redacted]	-0.06	[redacted]	[redacted]
Rebif® 44	**Rebif® 44**	19.45	[redacted]	5.03	-	-	-	-	-
	Ofatumumab	19.52	[redacted]	5.54	0.06	[redacted]	0.51	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	19.43	[redacted]	4.87	-	-	-	-	-
	Ofatumumab	19.52	[redacted]	5.54	0.09	[redacted]	0.67	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 35: Waning scenario results in the HA RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Alemtuzumab	**Alemtuzumab**	19.33	[redacted]	5.46	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.05	[redacted]	-0.33	[redacted]	[redacted]
Cladribine	**Cladribine**	19.26	[redacted]	5.00	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.02	[redacted]	0.12	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.20	[redacted]	4.60	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	0.08	[redacted]	0.52	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.29	[redacted]	5.19	-	-	-	-	-
	Ofatumumab	19.28	[redacted]	5.12	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: efficacy reduced by 50% after 5 years									
Alemtuzumab	**Alemtuzumab**	19.27	[redacted]	5.17	-	-	-	-	-
	Ofatumumab	19.25	[redacted]	4.97	−0.02	[redacted]	−0.19	[redacted]	[redacted]
Cladribine	**Cladribine**	19.23	[redacted]	4.85	-	-	-	-	-
	Ofatumumab	19.25	[redacted]	4.97	0.02	[redacted]	0.12	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	19.19	[redacted]	4.53	-	-	-	-	-
	Ofatumumab	19.25	[redacted]	4.97	0.06	[redacted]	0.45	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.27	[redacted]	5.04	-	-	-	-	-
	Ofatumumab	19.25	[redacted]	4.97	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: efficacy reduced by 25% after 5 years, and further reduced by 50% after 8 years									
Alemtuzumab	**Alemtuzumab**	19.29	[redacted]	5.25	-	-	-	-	-
	Ofatumumab	19.26	[redacted]	5.02	−0.03	[redacted]	−0.23	[redacted]	[redacted]
Cladribine	**Cladribine**	19.24	[redacted]	4.90	-	-	-	-	-
	Ofatumumab	19.26	[redacted]	5.02	0.02	[redacted]	0.12	[redacted]	[redacted]

Fingolimod[b]	**Fingolimod**	19.19	[redacted]	4.55	-	-	-	-	-
	Ofatumumab	19.26	[redacted]	5.02	0.07	[redacted]	0.47	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	19.27	[redacted]	5.08	-	-	-	-	-
	Ofatumumab	19.26	[redacted]	5.02	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Table 36: Waning scenario results in the RES RRMS population

Comparator	Technologies	Total LYG	Total costs	Total QALYs	Incremental LYG	Incremental costs	Incremental QALYs	ICER (£/QALY)	NMB at £30,000 WTP
Base case									
Alemtuzumab	**Alemtuzumab**	20.09	[redacted]	6.14	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.05	[redacted]	−0.37	[redacted]	[redacted]
Cladribine	**Cladribine**	20.02	[redacted]	5.66	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.05	[redacted]	5.82	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.05	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.05	[redacted]	5.84	-	-	-	-	-
	Ofatumumab	20.04	[redacted]	5.78	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: efficacy reduced by 50% after 5 years									
Alemtuzumab	**Alemtuzumab**	20.03	[redacted]	5.80	-	-	-	-	-
	Ofatumumab	20.01	[redacted]	5.60	−0.02	[redacted]	−0.20	[redacted]	[redacted]
Cladribine	**Cladribine**	19.99	[redacted]	5.48	-	-	-	-	-
	Ofatumumab	20.01	[redacted]	5.60	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.02	[redacted]	5.64	-	-	-	-	-
	Ofatumumab	20.01	[redacted]	5.60	−0.01	[redacted]	−0.04	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.02	[redacted]	5.66	-	-	-	-	-

	Ofatumumab	20.01	[redacted]	5.60	−0.01	[redacted]	−0.06	[redacted]	[redacted]
Scenario: efficacy reduced by 25% after 5 years, and further reduced by 50% after 8 years									
Alemtuzumab	**Alemtuzumab**	20.04	[redacted]	5.89	-	-	-	-	-
	Ofatumumab	20.02	[redacted]	5.65	−0.03	[redacted]	−0.24	[redacted]	[redacted]
Cladribine	**Cladribine**	20.00	[redacted]	5.53	-	-	-	-	-
	Ofatumumab	20.02	[redacted]	5.65	0.02	[redacted]	0.12	[redacted]	[redacted]
Natalizumab	**Natalizumab**	20.03	[redacted]	5.70	-	-	-	-	-
	Ofatumumab	20.02	[redacted]	5.65	−0.01	[redacted]	−0.05	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	20.03	[redacted]	5.71	-	-	-	-	-
	Ofatumumab	20.02	[redacted]	5.65	−0.01	[redacted]	−0.06	[redacted]	[redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; NMB: net monetary benefit; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; WTP: willingness-to-pay.

Section C: Textual clarification and additional points

Systematic literature review (SLR) included studies

C1. The company submission states that 84 studies were included in the SLR. However, in company submission document B section B.2.9 on Indirect and mixed treatment comparisons and the summary at the start of section B.2 Clinical effectiveness, the company reports 92 studies. Can the company please confirm if this is a typographical error?

Novartis apologise for the inconsistency in these figures and can confirm that this should read 84 included studies in alignment with the PRISMA diagram presented in Figure 2, Page 42 of CS Appendix D.1.3.

C2. Similarly, in the cost-effectiveness search, (company submission document B, page 140) the company state 73 studies (from 74 publications). These numbers are one more than in table 80 and 81 (company submission appendix H, pages 333-337). Can the company please confirm if this is a typographical error?

Novartis apologise for the inconsistency in these figures and can confirm that this should read 73 studies from 74 publications. Novartis have identified Table 80, Page 333 and Table 81, Page 336 of the CS Appendix H.2 to have erroneously excluded one reference:

- Jones KH, Ford DV, Jones PA, et al. The physical and psychological impact of multiple sclerosis using the MSIS-29 via the web portal of the UK MS Register. PLoS ONE 2013; 8(1): e55422.

The addition of this reference resolves the inconsistency between CS documents.

References

1. Novartis (Data on File): ASCLEPIOS I Clinical Study Report Appendix 16.1.9.
2. Novartis (Data on File): ASCLEPIOS II Clinical Study Report Appendix 16.1.9.
3. Novartis (Data on File): Meta-Analysis Clinical Study Report of ASCLEPIOS I and ASCLEPIOS II trials (22nd November 2019)
4. Novartis (Data on File): CDI-6 exclusions due to baseline EDSS <2.
5. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. New England Journal of Medicine 2020;383:546-557.
6. National Institute for Health and Care Excellence (NICE). Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA254]. Available at: https://www.nice.org.uk/guidance/ta254 [Last accessed: 28th February 2020].
7. National Institute for Health and Care Excellence (NICE). Dimethyl fumarate for treating relapsing-remitting multiple sclerosis: Technology appraisal guidance [TA320]. Available at: https://www.nice.org.uk/guidance/ta320. [Last accessed: 31st March 2020].
8. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA533]. Available at: https://www.nice.org.uk/guidance/ta533 [Last accessed: 17th March 2020].
9. Novartis (Data on File): ALITHIOS Clinical Trial Protocol (1st July 2019).
10. Clinicaltrials.gov. ALITHIOS Clinical Study Record. Available at: https://clinicaltrials.gov/ct2/show/NCT03650114. [Last accessed: 2nd September 2020].
11. Fox EJ, Mayer L, Aungst A, et al. Long-term safety, compliance, and effectiveness of ofatumumab in patients with relapsing multiple sclerosis: The ALITHIOS Phase 3b study. Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, MSVirtual 2020.
12. Novartis (Data on File): ASCLEPIOS Patient Baseline Characteristics by Trial Follow-Up.
13. Novartis (Data on File): ASCLEPIOS Baseline Characteristics for Patients who Discontinued Study.
14. Novartis (Data on File): ASCLEPIOS I Clinical Study Report (9th December 2019).
15. Novartis (Data on File): ASCLEPIOS II Clinical Study Report (9th December 2019).
16. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing–remitting multiple sclerosis: Final Appraisal Document. Available at: https://www.nice.org.uk/guidance/ta533/documents/final-appraisal-determination-document [Last accessed: 1st September 2020].
17. National Institute for Health and Care Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]: Assessment Report. Available at: https://www.nice.org.uk/guidance/ta527/documents/assessment-report [Last accessed: 1st September 2020].
18. EMA. Tysabri (natalizumab): Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf. [Last accessed: 8th September 2020].
19. Novartis (Data on File): EQ-5D Scores Summary Statistics.
20. Orme M, Kerrigan J, Tyas D, et al. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.
21. Novartis (Data on File): EQ-5D Scores by EDSS Status.
22. National Institute for Health and Care Excellence (NICE). Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA127]. Available at: https://www.nice.org.uk/guidance/ta127 [Last accessed: 28th February 2020].
23. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health 2011;14:539-45.
24. National Institute for Health and Care Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis: Final Appraisal Document. Available at: https://www.nice.org.uk/guidance/ta527/documents/final-appraisal-determination-document-2. [Last accessed: 7th September 2020].
25. NICE. TA533 Ocrelizumab for treating relapsing–remitting multiple sclerosis. 2018.
26. National Institute for Health and Care Excellence (NICE). Teriflunomide for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA303]. Available at: https://www.nice.org.uk/guidance/ta303 [Last accessed: 23rd March 2020].

27. Novartis (Data on File): CDW-6 with time by treatment interaction.
28. Novartis (Data on File): CDW-6 piecewise Cox regression.
29. Hauser S. Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. Presented at ECTRIMS, 11-13 September 2019, Stockholm (Sweden). 2019.
30. Novartis (Data on File): Cumulative ARR by time interval.
31. Hauser, S. L., Bar-Or, A., Cohen, J. A. et al. Ofatumumab vs Teriflunomide in Relapsing Multiple Sclerosis: Analysis of No Evidence of Disease Activity (NEDA-3) from ASCLEPIOS I and II Trials. Presented at: 6th Congress of the European Academy of Neurology, May 23–26, 2020.
32. Hauser SL, Kappos L, Arnold DL, et al. Five-years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. Neurology 2020.
33. van Meerten T, Hagenbeek A. CD20-targeted therapy: the next generation of antibodies. Semin Hematol 2010;47:199-210.
34. National Institute for Health and Care Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis: Technology appraisal guidance [TA527]. Available at: https://www.nice.org.uk/guidance/ta527. [Last accessed: 23rd March 2020].

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Society is the UK's biggest MS charity. We have over 5,500 volunteers and 270 local groups supporting people with MS locally. Together we're researching, fundraising, campaigning and fighting to stop MS. We want a world free from the effects of MS. Our ultimate goal is to find a cure. Until then, we're working to make sure no one has to face MS alone. The vast majority of our income comes from voluntary donations and legacies.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have expertise from years of working alongside people with MS and their carers and gathering evidence about their experiences. We drew on the stories people with relapsing remitting MS have told us about treatments in general, as well as data from both our My MS My Needs survey 2019 (of people with MS in the UK) and Friends and Family survey 2019 (of people supporting those with MS in the UK).
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is one of the most common disabling neurological conditions affecting working age adults. We estimate that there are over 130,000 people with MS in the UK, and that each year nearly 7,000 people are newly diagnosed. This means around 1 in every 500 people in the UK lives with MS, and each week over 130 people are diagnosed with MS.[1] MS can be relentless, painful and exhausting. It's a condition which damages nerves in your body, making it harder to do everyday things like walk, talk, eat and think. Symptoms can fluctuate, making life unpredictable. They can include loss of balance, stiffness, spasms, speech problems, fatigue, pain, bladder and bowel, and vision problems. In the UK, people are most likely to find out they have MS in their thirties, forties and fifties. But the first signs of MS often start years earlier. Many people notice their first symptoms years before they get their diagnosis.

[1] Public Health England, Multiple sclerosis: prevalence, incidence and smoking status, February 2020

	Living with a chronic, disabling and degenerative condition such as MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week.[2] Around 85% of people with MS are first diagnosed with relapsing MS. A relapse is defined as an episode of neurological symptoms, which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. In relapses, symptoms usually come on over a short period of time but often remain for a number of weeks – usually three to four – and can sometimes last for months. People with MS can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a GP, MS specialist nurse and other healthcare professionals. Around half of all relapses can leave a range of residual problems. Evidence has highlighted that disability also progresses regardless of whether a person experiences relapses regularly.[3] These are further important reasons to reduce the frequency and severity of relapses through ensuring that those who are eligible find the best treatment for them as soon as possible. Relapses can have a resonating emotional impact on a person. The loss of independence that can often come with a relapse mean that people can often feel a burden on their family. Relapses are often unpredictable and distressing, leaving people feeling frustrated, anxious and causing disruption to everyday life. The majority of people with MS experience a progression of disability over the course of the condition. It is estimated that approximately 65% of people with relapsing MS will eventually go on to develop secondary progressive MS 15 years after being diagnosed. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses.

[2] Extra Costs Commission, Driving down the costs disabled people face : Final report, June 2015, pp. 13
[3] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015

	People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely normal life. As each person's response to DMTs is different the more effective options available on the NHS will result in more people finding a treatment which best suits them. **Impact on Carers** The progressive, fluctuating nature of MS presents particular challenges to families and carers. It can make balancing work, education and taking care of one's own health and wellbeing difficult. Our 2019 My MS My Needs survey found 1 in 3 people living with MS hadn't received the care and support they needed to assist with daily living in the past 12 months. Of those, 4 in 10 relied on unpaid care from family members and friends to some extent. The care and support people required ranged from help to complete essential day to day tasks – such as washing and dressing, preparing meals, and administering medications – often alongside support to leave the house, socialise and 'mop and shop' tasks. The survey found that the complexity of these needs increases with age, as the disease progresses. Treatments that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too.[4] Our 2019 Friends and family survey found 41% of respondents spent the equivalent of a full-time job or more each week supporting someone with MS. An overwhelming 90% of respondents reported negative impacts on their health and wellbeing, which is even more concerning considering that 40% of respondents were living with a long-term condition themselves. The fluctuating and progressive nature of MS adds a degree of complexity to their lives, as they may not know from one week to the next what support that person with MS will need. That can make juggling paid work and caring very difficult, which 3 in 5 working-age respondents are doing.[5]

[4] MS Society, My MS My Needs 2019 UK report, May 2020, available: https://www.mssociety.org.uk/what-we-do/our-work/our-evidence/ms-in-the-uk
[5] MS Society, MS Friends and Family survey 2019, February 2020, available: https://www.mssociety.org.uk/what-we-do/news/family-and-friends-arent-getting-enough-support

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	
8. Is there an unmet need for patients with this condition?	Our My MS My Needs survey 2019, found 2 in 5 people who could benefit from taking a DMT aren't currently taking one.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	People with MS want safe and highly effective treatments that slow the progressive of disease and reduce relapses, which they can take in a way that suits their lifestyle. People with MS often tell us about the convenience of DMTs that can be self-administered, as opposed to requiring visits to the hospital. For the many people with MS of working age, taking time out of work to attend hospital appointments can be challenging. Ofatumumab has been shown to be a highly effective treatment. The more such treatments that are available, increases patient choice and the likelihood that individual's will find a DMT that works for them. Two phase 3 trials (ASCLEPIOS I and II) found ofatumumab reduced relapses by 50.5% & 58.5% respectively, compared to teriflunomide, which is significant. As described above, replaces can have a very sever effect on all aspects of life for people with relapsing remitting MS (RRMS). The trials also found MRI lesions were reduced significantly. The trials found risk of disability progression on ofatumumab relative to teriflunomide was reduced by 34.4% (at three months) and 32.5% (at 6

	months – not significant). [6]
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

[6] Hauser S., Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials, 09/13/19, available: https://onlinelibrary.ectrims-congress.eu/ectrims/2019/stockholm/279581/stephen.hauser.efficacy.and.safety.of.ofatumumab.versus.teriflunomide.in.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dlate+breaking

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
14. This technology is self-administered by injection every 4 weeks. What impact would this have on carer and patient quality of life?	As above, people with MS often tell us about the convenience of DMTs that can be self-administered, as opposed to requiring visits to the hospital. For the many people with MS of working age, taking time out of work to attend hospital appointments can be challenging.

15. There are numerous treatment options for relapsing – remitting MS. What factors would influence a patient's choice of therapy?	Decisions on which DMT to take are determined by a variety of factors including the eligibility, efficacy, related side effects, the method and frequency of administration, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. Choosing which option to take requires access to evidence-based information, and support and advice from specialist health professionals.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission:

- Ofatumumab has been shown in trials to be a highly effective treatment for relapsing remitting MS. The more such treatments that are available, increases patient choice and the likelihood that individuals will find a DMT that works for them.
- The ability to self-administer Ofatumumab by injection will be advantageous and preferable for many patients, and a number of the existing highly effective that are available are infusions requiring hospital visits.

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Patient organisation submission

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding. We are not a membership organisation. We rely on donations, fundraising and gifts in wills to fund our services.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of	**Novartis** – £1, 600 – HP annual conference attendance **Bayer** – no funding **Biogen** – £74,955 – funding for specialist nurse programme; funding of HP bursaries; miscellaneous; honorarium **Celgene** – £900 – HP annual conference attendance; advisory board **Merck** – £80,000 – funding for specialist nurse programme; miscellaneous **Mylan** – no funding **Roche** – £11,413 – conference attendance; funding of HP bursaries; miscellaneous **Sanofi** – £28,500 – exhibitor at MS Trust annual conference for health professionals

manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to relapsing remitting MS: coping with the impact of diagnosis, choosing which treatment to take, understanding and balancing risk/benefit profiles, concern about switching to a new disease modifying drug (DMD), dealing with difficulties of self-injection or side effects, and coping with physical and financial consequences of relapses. To gain further insight into the experience of people taking ofatumumab, we interviewed an individual who has been taking ofatumumab in clinical trials.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well and not taken account of in cost effectiveness calculations. MS is sometimes mild, frequently relapsing remitting, but often progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on

	people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity. Good management of MS can be a huge challenge to health professionals because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers. Approximately 80% of people with MS will have relapsing remitting MS (RRMS). MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more obvious symptoms. Many of these invisible symptoms are sensitive areas and can be difficult to recognise or talk about, putting an extra burden on a person with MS to deal with on their own. Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect financial burden, both for the individual, their family and the state. They can have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends. In a cash-strapped NHS, the reality is that services to support people coping with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. For example, a caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems,

	introducing further distress to the individual and cost to the NHS. Research evidence supports the treatment of people with relapsing remitting MS with disease modifying drugs (DMDs) early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that if people with MS continue to have relapses while on therapy, this should prompt a discussion about switching treatments. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; signs of MS activity trigger a treatment review and escalation to an alternative disease modifying drug is considered. A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing forms of MS.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	MS care involves a mix of clinical management of symptoms, responsive services to manage relapses and other acute deteriorations, therapies including physiotherapy and occupational therapy, tailored, evidence based information, support for effective self-management and, for those with RRMS, access to the range of DMDs and support to make the choice that is right for their condition, their lifestyle and their treatment goals. The majority of people with RRMS are eager to start treatment with one of the DMDs and aware of the importance of starting treatment soon after diagnosis. A number of DMDs are available for RRMS: • beta interferons • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • cladribine

	• ocrelizumab • natalizumab • alemtuzumab The impact of relapses has been outlined in the previous section of this submission. All of these treatments are effective at reducing the frequency of relapses and the severity of relapses that do occur. It is not possible to say which of these treatments are preferred; the widening range of DMDs gives greater scope for personalised treatments. If MS remains active despite taking one of the DMDs there is more potential to switch to a treatment with a different mechanism of action. Different responses to DMDs from one person to another are not easily captured in clinical trial data but are important to address in clinical practice. Through different aspects of our work with people affected by MS, we are aware that a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, as is evidence of their effect on the underlying course of the condition and their impact on disease progression. Other issues will also be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD. During the coronavirus pandemic, patients needing to attend a hospital outpatient clinic for infusions or for monitoring have faced cancellation or postponement of planned treatments. This has been a cause of concern for those affected; treatments which are taken at home and require minimal testing for potential side effects will avoid treatment interruption as well as minimize demands on services People with MS rely heavily on their MS specialist team to provide information and guidance to help with treatment choices. MS teams are skilled and experienced in helping an individual make the choice that is the best match for their level of disease activity, their personal circumstances, their attitude to risk and their treatment goals.

8. Is there an unmet need for patients with this condition?	Clearly, the most significant unmet need for people with MS is a cure. In the absence of a cure, people with MS want to live a life free from the impact of their disease. For many people, the ultimate goal of taking one of the DMDs is to reduce their risk of disease progression and future disability. Inevitably, the frequency and severity of relapses rank highly for those with RRMS, not just for the disruption and distress that relapses cause, but also because of the risk of residual disability and increased chances of conversion to secondary progressive MS. Ranking the impact of individual symptoms is difficult and ultimately inadequate as the condition varies so widely between individuals. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to DMDs. For those people with very active relapsing MS - either rapidly evolving severe or highly active despite treatment - the side effects associated with the more effective DMDs are a cause for concern, for example the risk of PML with natalizumab and secondary autoimmune conditions with alemtuzumab. For people with very active relapsing MS, the option to switch to a more effective DMD with minimal or reversible side effects would be a major benefit. Remaining in employment is of critical importance to people with MS. Within 10 years of diagnosis, around 50% of people with MS will have left employment, with all the associated financial, social and psychological consequences. Cost effectiveness calculations do not take account of the burden of loss of work on the individual, their family and society.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The clinical trial data have demonstrated the effectiveness of ofatumumab compared to teriflunomide: • More effective at reducing the risk of relapses • More effective at reducing invisible MS activity (lesions on MRI scans) • More effective at reducing the risk of disability progression (three or six month confirmed disability progression) • Low level of side effects – resulting in minimal requirements for routine blood and urine tests • Convenient dosing schedule – subcutaneous self-injection once a month has minimal impact on

	lifestyle, resulting in high level of adherence Ofatumumab has a similar mechanism of action (B-cell depletion) to ocrelizumab, which is now established as a very effective treatment for RRMS. Unlike ocrelizumab, home-based self-injection means patients will not need to visit hospital for infusions. This results in less disruption for other activities, for example the need to take time off work, and reduces the burden on the NHS. It also reduces potential exposure to infection, a major cause for concern during the coronavirus pandemic which has resulted in cancellation or postponement of routine infusions for people taking ocrelizumab and natalizumab. Preliminary data have indicated that there is more rapid restoration of B-cell counts following ofatumumab treatment compared to ocrelizumab (median recovery time 38 weeks compared to 72 weeks)[1]. This may be beneficial in the management of side effects, for vaccine-readiness[2], and for those planning to start a family. The experience of one particular person who took part in ofatumumab clinical trials gives a more personal perspective. Following her diagnosis in 2016, she took up the invitation to participate in the ASCLEPIOS trial and elected to continue taking ofatumumab during the open-label extension. On completion, she learnt that she had been taking ofatumumab throughout the course of the study and has participated in subsequent studies. The shallow, subcutaneous injection has been easy to do and she has not experienced any side effects. She did not experience injection site reactions apart from on one occasion, when the injection caused a small bruise which did not trouble her.

[1] Savelieva M, et al. Comparison of the B-cell recovery time following discontinuation of anti-CD20 therapies. ePoster presented at ECTRIMS; October 25-28, 2017; Paris, France, EP1624. Available at https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/199644/david.leppert.comparison.of.the.b-cell.recovery.time.following.discontinuation.html

[2] Baker D, et al. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin Exp Immunol, 2020; 10.1111/cei.13495.

	She uses a calendar to remind her to do the 4-weekly injections; in between injections she has been able to ignore her MS and get on with life – this has helped her come to terms with her diagnosis. Being able to do her injections a few days early or later means she has been able to plan her injections around other activities such as weekends away. The 4-weekly injection intervals have also proved very practical for taking on holiday. In summary, the convenience of ofatumumab treatment has been a major factor in her acceptance of her diagnosis, has been free of relapses, and has meant that MS has not taken over her life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There will always be individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines. Overall, the potential risk of side effects from individual drugs tends to be the biggest barrier to starting a treatment. In clinical trials, side effects caused by ofatumumab were mild to moderate. Those which occurred more frequently in people taking ofatumumab were injection site reactions. The rate of serious infections (2.5% vs 1.85%) and malignancies (0.5% vs 0.3%) were higher for ofatumumab compared to teriflunomide. Some people may not wish to self-inject. However, as injections are done just once every four weeks using a patient-friendly autoinjector, this is unlikely to be a major cause for concern.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that we are aware of.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The subcutaneous route of administration means that ofatumumab can be taken at home, eliminating potential delays in starting treatment which has occurred with DMDs which require access to outpatient infusion clinics. Overall, this route of administration minimises demands on NHS services. As noted above, at-home treatment also avoids the risk of exposure to infections, which has emerged as a significant concern for patients during the coronavirus pandemic. Given the heterogeneous nature of MS, both in disease course and in response to treatments, a broadening range of drugs which work in different ways increases the potential for personalisation of treatment.
14. This technology is self-administered by injection every 4 weeks. What impact would this have on carer and patient quality of life?	Ofatumumab is injected subcutaneously once a month at home. This has benefits over other self-injected DMDs which require more frequent injections. Once monthly treatment will mean daily routines are not impacted and will also mean that injection related side effects are reduced. This more convenient treatment schedule will improve adherence and consequently effectiveness of the drug. Being able to inject at home results in less disruption to other activities, for example the need for time off work, compared to treatments which require regular hospital visits for infusions and also avoids the risk of exposure to infections, which has emerged as a significant concern for patients and carers during the coronavirus pandemic. The personal experience of one individual described in section 9 above illustrates the convenience of the treatment schedule and route of administration. This has had a positive impact on quality of life and lead to better acceptance of MS diagnosis.
15. There are numerous treatment options for relapsing – remitting MS. What factors would influence a patient's	As noted above, a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, as is evidence of their effect on the underlying course of the condition and their impact on disease progression. Other issues will also be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice

choice of therapy?	will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD. As already noted, new unanticipated factors can emerge, such as recent concerns about exposure to infections in hospital clinics or effectiveness of vaccinations. A wide range of DMDs gives greater scope for accommodating new factors which might influence a patient's choice of treatment.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission:

- MS is a complex and unpredictable condition which has an impact on all aspects of life, early proactive treatment is essential to prevent future disability
- As with other DMDs, an individual and their MS team will need to consider the risks and benefits of ofatumumab
- Ofatumumab shows efficacy comparable to ocrelizumab, a treatment with a similar mechanism of action, but avoids the need for regular hospital visits
- Once monthly subcutaneous route of administration minimises treatment burden and service usage
- Improved quality of life, reduced steroid administration and fewer hospital admissions (resulting from lower relapse rate)

Thank you for your time.

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Professional organisation submission

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**

3. Job title or position	**Consultant Neurologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Association of British Neurologists is the professional society for neurologists and clinical neurology researchers in the United Kingdom. The aim of the Association of British Neurologists is to promote excellent standards of care and champion high-quality education and world-class research in neurology. It is funded by member subscription.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of	**No**

manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment with ofatumumab is to reduce the relapse rate in relapsing forms of multiple sclerosis (MS). The primary end point in the two phase 3 randomised controlled trials of ofatumumab versus teriflunomide (ASCLEPIOS I and ASCLEPIOS II) was the annualised relapse rate. Note that the trials have not as yet been published in peer-reviewed journals. Secondary endpoints included time to disability progression confirmed at three and six months respectively, confirmed disability improvement at 6 months, gadolinium enhancing T1 lesions, number of new or enlarging T2 lesions, serum levels of neurofilament light chain (NfL), and rate of brain volume loss By reducing the number of relapses the treatment aims to reduce the accumulation of disability due to MS. This is referred to as disability progression in the clinical trials.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A clinically significant reduction in relapse rate for a treatment in MS would be a minimum reduction in relapses by a third compared to placebo. This is the efficacy of the least effective currently licensed treatments for relapsing MS. A higher reduction in relapse rate with an active comparator, e.g. licensed first line treatments such as

x cm, or a reduction in disease activity by a certain amount.)	teriflunomide, would be expected in new treatments for MS. In the ofatumumab trials there was a greater than 50% reduction in relapse rate when compared to an active comparator.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need for people with relapsing MS to have access to effective treatments with a better safety profile than some of the currently approved treatments. There is also a need for treatments which have less impact on people living with MS in terms of frequency of treatment, intensity of monitoring and hospital attendances.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Relapsing forms of MS are treated with licensed disease modifying treatments (DMTs) approved for use in the NHS using the NHSE Algorithm (Date published: 04 September 2018; Updated 8 March 2019).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHSE Algorithm NICE TAs for natalizumab TA127, fingolimod TA254, teriflunomide TA 303, alemtuzumab TA312, dimethyl fumarate TA320, beta interferons and glatiramer acetate TA527, ocrelizumab TA533, cladribine TA 616, peginterferon beta-1a TA624

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	A NHSE algorithm has been developed for prescribing DMTs in relapsing MS (RMS). The NHSE algorithm allows for different DMT choices for different disease definitions and at different time points in the evolution of RMS. The choice of DMT is a shared decision making process between the professionals and the person with MS and takes into account the individual's life situation and priorities eg reproductive issues. The use of high efficacy DMTs has to be approved by the multidisciplinary team. There is variation in prescribing across the UK as evidenced by the prescribing data in the Bluteq system.
• What impact would the technology have on the current pathway of care?	Ofatumumab is a fully humanised antiCD20 drug given by subcutaneous injection on a monthly basis at home. This avoids the need for attendance at an infusion centre / day-case unit in a hospital setting. This may be of particular relevance in the context of the Covid-19 pandemic and any subsequent local lockdowns or further waves of Covid-19. It will require MS Specialist nurse support for training on self-injection. This training is delivered for other MS DMTs for example interferons and glatiramer acetate.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in MS treatment centres with MS specialist neurologists and MS specialist nurses. Injectable treatments for MS are already used in clinical practice. MS nurses are skilled in training people with MS to safely self-inject DMTs.
• How does healthcare resource use differ between the technology and current care?	There will be no requirement for day-case/infusion unit admissions compared to ocrelizumab 6 monthly admissions, natalizumab.4-6 weekly admissions, alemtuzumab 5 days Year 1 and 3 days Year 2 admissions. MS Specialist Nurse time will be required for training patients in self-injection. This training is already

	delivered for interferons and glatiramer acetate.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment will be prescribed by MS specialist neurologists and will be delivered by subcutaneous self-injection at home.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The technology could be introduced in to existing MS specialist services. These services require adequate staffing with MS specialist neurologists, MS specialist nurses and neuro-pharmacists
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Although there are other DMTs with similar efficacy available, this is the only high efficacy monoclonal antibody DMT which does not require hospital admission for administration.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current	There may be an increase in quality of life compared to other less effective DMTs.eg the comparator drug teriflunomide was less effective in the RCTs. Monthly subcutaneous injections are less burdensome than some of the other DMTs for example daily injections or tablets or monthly infusions in a hospital setting. This may have less adverse impact on

care?	employment and time away from work for people with MS and less impact on home life and any caring responsibilities.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be more appropriate for confirmed relapsing remitting MS and so-called active MS or rapidly evolving severe MS.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional	Ofatumumab is delivered by monthly subcutaneous injection. This will be easier to deliver than the infusion treatments for MS as it can be given at home by self-injection. This avoids the need for attendance at hospitals or day case infusion units. This may be particularly relevant in the context of Covid-19. In some NHS hospitals infusions for people with MS were significantly delayed and infusion units were closed or re-purposed. This had unintended adverse consequences for PwMS Some PwMS may prefer a monthly treatment rather than more frequent injectable treatments on alternate days or 3 times weekly or daily oral treatments.

tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are defined starting, stopping or switching criteria for all DMTs in MS. These would apply to this technology which would be included in the NHSE Treatment Algorithm for MS DMTs.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The impact of reduced relapse rate on continued employment for people with MS should be considered. The short-term impact in terms of convenience and reduced time off work to attend hospital for either treatment or monitoring should also be considered.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The technology is innovative in its mode of delivery as a subcutaneous injection. Ocrelizumab which is a licensed anti-CD20 monoclonal antibody is delivered by 6 monthly infusions. B cell repopulation after treatment with ofatumumab is more rapid than following treatment with ocrelizumab. This may be a significant advantage if there are further waves of Covid 19 or localised Covid

improve the way that current need is met?	outbreaks and for the efficacy of future vaccines.
• Is the technology a 'step-change' in the management of the condition?	The technology has similar efficacy to other approved treatments
• Does the use of the technology address any particular unmet need of the patient population?	More flexible high efficacy treatment delivered in the home setting. There is an unmet need for people with MS to have access to a new effective treatment without a significant risk of PML or life-long autoimmune conditions.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The ASCLEPIOS I and II studies (NCT02792218 and NCT02792231) were identical design, flexible duration (up to 30 months), double-blind, randomized, multi-centre Phase III studies evaluating the safety and efficacy of ofatumumab 20mg monthly subcutaneous injections versus teriflunomide (Aubagio®) 14mg

	oral tablets taken once daily in adults with a confirmed diagnosis of RMS. The studies enrolled 1,882 patients with MS, between the ages of 18 and 55 years, with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5 The trial population is similar to that of other licensed DMTs in MS. In clinical practice patients with EDSS up to 6.5 are eligible to start treatment. The population in these trials was limited to those up to EDSS 5.5. The age range is restricted to adults under 55 years. **Note that the trials have not been published. The ABN has not been provided with the manufacturer's dossier. Our analysis has been limited to information currently in the public domain. Ofatumumab does not have FDA or EMA approval.**
• If not, how could the results be extrapolated to the UK setting?	In the UK setting PwMS up to EDSS 6.5 are currently treated with other licensed DMTs, and there is no restriction on upper age limit.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Annualised relapse rate was the primary end point which is the most important clinical outcome in relapsing MS. Reduction in sustained disability progression is less meaningful at 3 months. In these trials it was measured at 3 and 6 months.

	Confirmed disability improvement was also measured at 6 months which is a useful additional clinical outcome.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MRI surrogate outcome measures were appropriate including gadolinium enhancing T1 lesions, number of new or enlarging T2 lesions, and rate of brain volume loss. These measures are representative of the surrogate outcomes used in other trials of MS DMTs. Serum levels of neurofilament light chain (NfL) were also measured. The implications for long-term clinical outcomes are less well-established.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that we are aware of but as the trials have not yet been published, ofatumumab does not have either FDA or EMA approval and we have not had access to the manufacturer's dossier, we cannot comment further on this.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	Cladribine for treating relapsing-remitting MS (2019) TA 616

treatment(s) since the publication of NICE technology appraisal guidance TA533?	Peginterferon beta-1a for treating relapsing-remitting MS (2020) TA624
21. How do data on real-world experience compare with the trial data?	There is no real-world experience available yet.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Equitable access to MS Specialist Neurologists, MS Specialist Nurses, Neuropharmacists across different regions of England to deliver this treatment
22b. Consider whether these issues are different from issues with current care and why.	Applicable to delivery of all DMTs
Topic-specific questions	
23. What definition would be used in NHS clinical practice	The definitions used would be those used in the NHSE Treatment Algorithm

for relapsing-remitting MS in terms of: a. Progression on disease modifying therapy (including timeframe for assessment) b. Highly active relapsing-remitting MS c. Rapidly evolving severe relapsing-remitting MS	
24. What comparators are relevant for the expected positioning of ofatumumab in the relapsing-remitting MS pathway?	RRMS: Beta interferon, glatiramer acetate, teriflunomide, dimethyl fumarate, peginterferon, ocrelizumab Highly active despite previous treatment: alemtuzumab, cladribine, fingolimod, ocrelizumab Rapidly evolving severe RRMS: alemtuzumab, cladribine, natalizumab, ocrelizumab
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your submission.

- Ofatumumab is an effective new treatment for relapsing MS
- Two large phase III trials have shown a significant reduction in annualised relapse rate compared to an active comparator.
- The treatment is given by monthly subcutaneous injection at home which may be more convenient for some people with MS than other approved DMTs

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Malcolm Qualie**
2. Name of organisation	**NHS England & Improvement**

3. Job title or position	**Pharmacy Lead, Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	A NICE Clinical Guideline on MS, several TA's on the use of medicines in MS and a NHS England policy on the use of several medicines in MS including beta interferon and glatiramer acetate. The policy can be found at https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/ NHSE/I have also produced a treatment algorithm for MS disease modifying treatments (DMTs) for RRMS which can be found here: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf
6. Is the pathway of care well defined? Does it vary or are there differences of opinion	There is current variation in the approach to the treatment of multiple sclerosis with some clinicians taking an incremental approach, starting with drugs of lower toxicity and efficacy and escalating to more potent/toxic therapies if disease breaks through. Alternatively, advocates of "induction therapy" suggest early treatment with more potent/toxic treatments is favourable such as alemtuzumab. NHS England has

between professionals across the NHS? (Please state if your experience is from outside England.)	recently introduced a prior approval system for MS drugs which requires Trusts to register patients on treatment which overtime should identify the level of variation in practice. The key aim will be to agree a national algorithm based on NICE guidance and this clinical practice. The algorithm is due to be published shortly.
7. What impact would the technology have on the current pathway of care?	Relatively small as there are several treatments available for RRMS including oral options
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	It is not currently funded although some patients may be gaining access via eg clinical trials.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be delivered in the same way as other existing drugs such as beta interferon and glatiramer acetate which are also delivered as subcut preparations.
• How does healthcare resource use differ	No different to other treatments cited above.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should only be prescribed in settings where there is an appropriately constructed MS MDT.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities are already available. The main investment will be for the drug itself if it is more expensive than current treatments.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Unknown. Current treatments should be considered for stopping when patients record an EDSS of 7 or above.
10. What is the outcome of any evaluations or audits of the use of the technology?	There have been no audits on the use of this technology
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any
11b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
Is ofatumumab considered an appropriate treatment in the NHS for people with active secondary progressive multiple sclerosis (SPMS) as well as for people with relapsing remitting multiple sclerosis (RRMS)? Are people with highly active (HA) RRMS and people with rapidly evolving severe (RES) RRMS considered appropriate	Only if the evidence of benefit and cost effectiveness levels are appropriate

subgroups in which to classify people receiving treatment with ofatumumab or is ofatumumab considered to be suitable for people with both active symptoms of multiple sclerosis as well as those who are in a remitting state?	
Issues arising from technical engagement We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.	
Key Issue 1: Generalisability of ASCLEPIOS trials (the focus for company discussion)	
Key Issue 2: Trials included in the company network meta-analysis (NMA)	
Key Issue 3:	

Lack of transparency in the process of selecting studies from systematic literature review (SLR) into the NMA	
Key Issue 4: Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS	
Key Issue 5: Inclusion of disease management costs associated with treating people with SPMS	
Key Issue 6: Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to	

Secondary Progressive Multiple Sclerosis (SPMS):	
Key Issue 7: Source of annualised relapse rates (ARR)	
Key Issue 8: Source of health state utility values	
Key Issue 9: Inclusion of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years	
Are there any important issues that have been missed in ERG report?	

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

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Date completed	*12/10/2020*

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/19/76.

Declared competing interests of the authors
Prof. Olga Ciccarelli received consultancy fees from Novartis, Biogen-Idec and General-Electric, Genzyme, All payments were made to her employer, UCL Institute of Neurology. She also received reimbursement for attending a symposium from Novartis and ECTRIMS, and funds for research from the UK MS Society, EPSRC, UCLH and BRC. Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse.

Acknowledgements
The authors would like to acknowledge Professor Aileen Clarke and Dr Dan Todkill who independently quality assessed this report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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This report should be referenced as follows:
Auguste P, Zanganeh M, Chen Y-F, Patel M, Knerr W, Ogunlayi F, Moiz H, Park J-E, Court R, Brown A, Ciccarelli O, Counsell C, Arun T, Armoiry X, Grove A. Ofatumumab for treating

relapsing multiple sclerosis [ID1677]: A Single Technology Appraisal. Warwick Evidence, 2020.

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 0 provides an overview of the key issues. Section 1.1 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.2 to 1.5 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 1.3 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 1.5 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 1.3 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 1.5 of this summary and Section 3.2.8, and **Error! Reference source not found.** 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 1.5 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 1.5 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 1.5 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 1.5 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 1.4 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 **Error! Reference source not found.**
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 **Error! Reference source not found.** 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 3.3.3.3 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**Error! Reference source not found.**Table 5 (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 8.

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 8. 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 7). 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

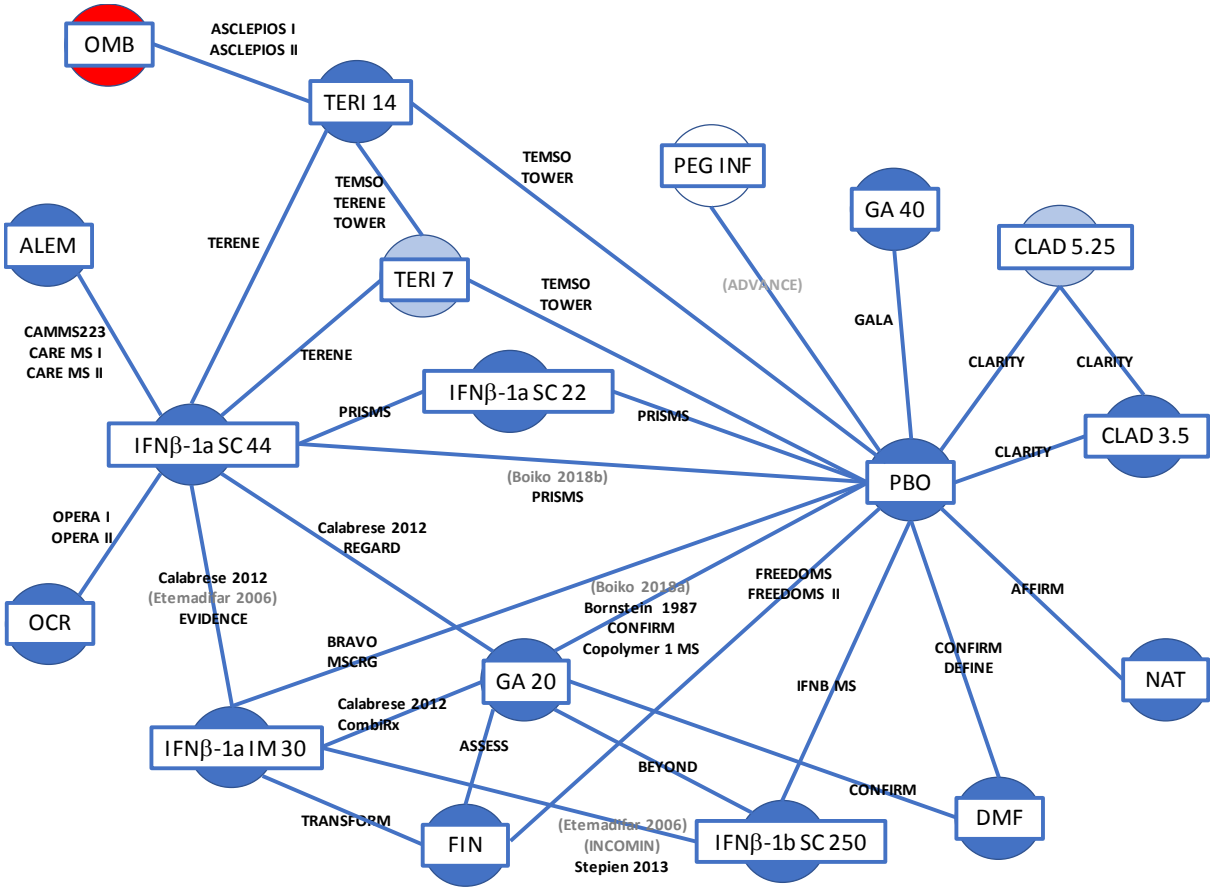

Figure 1. ERG mapped evidence network showing all trials included in the company's feasibility assessment for the NMAs

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 3.4.1 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 14). 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 3.3.2.2). 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], [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], [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 [redacted]2 and [redacted]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 19), 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).

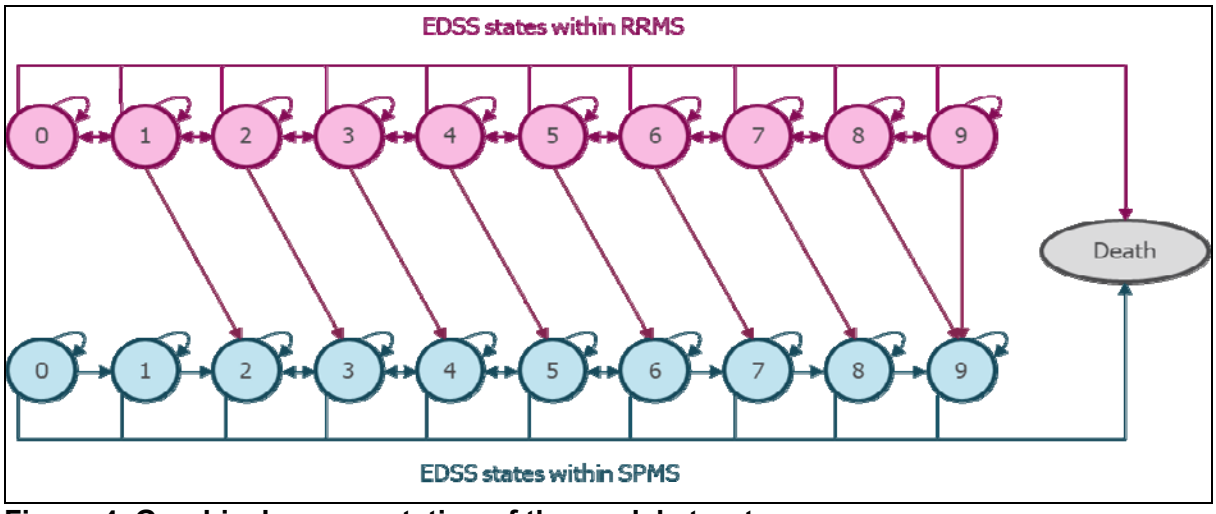

Figure 4. Graphical representation of the model structure

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:* o *Interferon β-1a (Avonex®)* o *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 25 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	
Ocrelizumab		
Alemtuzumab		
Cladribine		
Natalizumab		
Fingolimod		
Teriflunomide		
Dimethyl fumarate		
Glatiramer acetate		
IFN β-1a (Avonex®)		
IFN β-1a (Rebif® 44)		

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. ***[redacted] 5 and [redacted] 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**Error! Reference source not found.**) 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)
[redacted]					

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)
[redacted]					

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)
[redacted]					

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 4.3.6.10
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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a (Avonex®)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a (Rebif® 44)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[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; 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]	[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]	[redacted]	[redacted]	[redacted]	[redacted]	[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

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]						
Alemtuzumab							
Cladribine							
Natalizumab							
Ocrelizumab							
[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]					

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 [redacted] 9 and [redacted] 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 [redacted] and [redacted], 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 ***[redacted]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].

[redacted]

[redacted]11

[redacted]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.

[redacted]

[redacted]12

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

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.

8 REFERENCES

1. Boiko A, Lashch NY, Sharanova S, Zakharova M, Trifonova O, Simaniv T*, et al.* A comparative placebo-controlled clinical trial of the efficacy and safety of glatiramer acetate 20 mg in patients with remitting multiple sclerosis: first-year study results. *Neuroscience and Behavioral Physiology* 2018;**48**(3):351-7.
2. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. *Acta Neurol Scand* 2006;**113**(5):283-7. http://dx.doi.org/10.1111/j.1600-0404.2006.00585.x
3. Comi G, Patti F, Rocca MA, Mattioli FC, Amato MP, Gallo P*, et al.* Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study). *J Neurol* 2017;**264**(12):2436-49. http://dx.doi.org/10.1007/s00415-017-8642-5
4. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K*, et al.* Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology* 2009;**72**(23):1976-83. http://dx.doi.org/10.1212/01.wnl.0000345970.73354.17
5. National Institute for Health and Care Excellence. *Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA624]*. 2020. URL: https://www.nice.org.uk/guidance/ta624 (Accessed 10 September 2020).
6. National Institute for Health and Care Excellence. *Beta interferons and glatiramer acetate for treating multiple sclerosis: Technology appraisal guidance [TA527]*. 2018. URL: https://www.nice.org.uk/guidance/ta527 (Accessed 10 September 2020).
7. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health* 2007;**10**(1):54-60. http://dx.doi.org/10.1111/j.1524-4733.2006.00144.x
8. National Institute for Health and Care Excellence. *Ofatumumab for Treating Relapsing Multiple Sclerosis [ID1677]: Final Scope*. 2020. URL: https://www.nice.org.uk/guidance/gid-ta10557/documents/final-scope (Accessed 10 September 2020).
9. National Institute for Health and Care Excellence. *Siponimod for treating secondary progressive multiple sclerosis [ID1304]: In development [GID-TA10436]*. 2020. URL: https://www.nice.org.uk/guidance/indevelopment/gid-ta10436 (Accessed 10 September 2020).
10. U.S. Food and Drug Administration. *Label for KESIMPTA [version SUPPL-70]*. 2020. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125326s070lbl.pdf (Accessed 8 September 2020).
11. NHS. *Multiple Sclerosis: Overview*. 2018. URL: https://www.nhs.uk/conditions/multiple-sclerosis/ (Accessed 15 September 2020).
12. MS Society. *Causes of MS*. URL: https://www.mssociety.org.uk/about-ms/what-is-ms/causes-of-ms (Accessed 10 September 2020).

13. Hauser SL, Oksenberg JR. The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. *Neuron* 2006;**52**(1):61-76. http://dx.doi.org/10.1016/j.neuron.2006.09.011
14. Riñon A, Buch M, Holley D, Verdun E. The MS Choices Survey: findings of a study assessing physician and patient perspectives on living with and managing multiple sclerosis. *Patient preference and adherence* 2011;**5**:629-43. http://dx.doi.org/10.2147/PPA.S26479
15. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. *Multiple Sclerosis* 2017;**23**(8):1123-36.
16. NHS England. *Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies*. 2019. URL: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf (Accessed 10 September 2020).
17. National Institute for Health and Care Excellence. *Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA254]*. 2012. URL: https://www.nice.org.uk/guidance/ta254 (Accessed 10 September 2020).
18. National Institute for Health and Care Excellence. *Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA127]*. 2007. URL: https://www.nice.org.uk/guidance/ta127 (Accessed 10 September 2020).
19. National Institute for Health and Care Excellence. *Ocrelizumab for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA533]*. 2018. URL: https://www.nice.org.uk/guidance/ta533 (Accessed 10 September 2020).
20. National Institute for Health and Care Excellence. *Alemtuzumab for treating relapsing-remitting multiple sclerosis: Technology appraisal guidance [TA312]*. 2014. URL: https://www.nice.org.uk/guidance/ta312 (Accessed 10 September 2020).
21. Hutchinson M. Predicting and preventing the future: actively managing multiple sclerosis. *Pract Neurol* 2009;**9**(3):133-43, discussion 44. http://dx.doi.org/10.1136/jnnp.2009.177212
22. Stankiewicz JM, Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. *Neurology - Neuroimmunology Neuroinflammation* 2020;**7**(1):e636. http://dx.doi.org/10.1212/nxi.0000000000000636
23. Harding K, Williams O, Willis M, Hrastelj J, Rimmer A, Joseph F*, et al.* Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. *JAMA Neurology* 2019;**76**(5):536-41. http://dx.doi.org/10.1001/jamaneurol.2018.4905
24. Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK*, et al.* Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med* 2020;**383**(6):546-57. http://dx.doi.org/10.1056/NEJMoa1917246
25. ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS II)*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT02792231 (Accessed 10 September 2020).
26. ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS I)*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT02792218 (Accessed 10 September 2020).
27. Melendez-Torres GJ, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J*, et al.* Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation. *Health Technol Assess* 2017;**21**(52):1-352. http://dx.doi.org/10.3310/hta21520
28. Sorensen PS, Lisby S, Grove R, Derosier F, Shackelford S, Havrdova E*, et al.* Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. *Neurology* 2014;**82**(7):573-81. http://dx.doi.org/10.1212/wnl.0000000000000125
29. Bar-Or A, Grove RA, Austin DJ, Tolson JM, VanMeter SA, Lewis EW*, et al.* Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: The MIRROR study. *Neurology* 2018;**90**(20):e1805-e14. http://dx.doi.org/10.1212/wnl.0000000000005516

30. ClinicalTrials.gov. *Long-term Safety, Tolerability and Effectiveness Study of Ofatumumab in Patients With Relapsing MS*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT03650114 (Accessed 10 September 2020).
31. ClinicalTrials.gov. *Efficacy and Safety of Ofatumumab Compared to Placebo in Patients With Relapsing Multiple Sclerosis Followed by Extended Treatment With Open-label Ofatumumab*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT03249714 (Accessed 10 September 2020).
32. ClinicalTrials.gov. *An Open-label Study Evaluating Ofatumumab Treatment Effectiveness and PROs in Subjects With RMS Transitioning From Dimethyl Fumarate or Fingolimod to Ofatumumab (ARTIOS)*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT04353492 (Accessed 10 September 2020).
33. ClinicalTrials.gov. *A Single Arm Study Evaluating the Efficacy, Safety and Tolerability of Ofatumumab in Patients With Relapsing Multiple Sclerosis (OLIKOS)*. 2020. URL: https://clinicaltrials.gov/ct2/show/NCT04486716 (Accessed 10 September 2020).
34. McCool R, Wilson K, Arber M, Fleetwood K, Toupin S, Thom H*, et al.* Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2019;**29**:55-61. http://dx.doi.org/10.1016/j.msard.2018.12.040
35. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology* 2001;**56**(11):1496-504. http://dx.doi.org/10.1212/wnl.56.11.1496
36. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet* 1998;**352**(9139):1491-7.
37. Boiko A, Bosenko L, Vasilovskii V, Volkova L, Zakharova M, Kotov S*, et al.* A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Interferon β-1a Formulations for SC Administration in Patients with Remitting Multiple Sclerosis: First-Year Results. *Neuroscience and Behavioral Physiology* 2018;**48**(7):883-9.
38. Pakdaman H, Abbasi M, Gharagozli K, Ashrafi F, Delavar Kasmaei H, Amini Harandi A. A randomized double-blind trial of comparative efficacy and safety of Avonex and CinnoVex for treatment of relapsing-remitting multiple sclerosis. *Neurol Sci* 2018;**39**(12):2107-13. http://dx.doi.org/10.1007/s10072-018-3550-8
39. *Protocol for: Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221-34.* URL: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1601277/suppl_file/nejmoa1601277_protocol.pdf (Accessed 8 October 2020).
40. Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. *Clin Ther* 2003;**25**(1):105-18. http://dx.doi.org/10.1016/s0149-2918(03)90013-0
41. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J*, et al.* Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014;**13**(7):657-65. http://dx.doi.org/10.1016/s1474-4422(14)70068-7
42. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A*, et al.* Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet* 2002;**359**(9316):1453-60. http://dx.doi.org/10.1016/s0140-6736(02)08430-1
43. Tolley K, Hutchinson M, You X, Wang P, Sperling B, Taneja A*, et al.* A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis. *PLoS One* 2015;**10**(6):e0127960. http://dx.doi.org/10.1371/journal.pone.0127960
44. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sørensen PS*, et al.* A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. *New England Journal of Medicine* 2010;**362**(5):416-26. http://dx.doi.org/10.1056/NEJMoa0902533
45. Oliveira ML, Lucchetta RC, Bonetti AF, Fernandez-Llimos F, Becker J, Goncalves MVM*, et al.* Efficacy outcomes reported in trials of multiple sclerosis: A systematic scoping

review. *Multiple Sclerosis and Related Disorders* 2020;**45**:102435. http://dx.doi.org/10.1016/j.msard.2020.102435
46. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2015; 10.1002/14651858.CD011381.pub2(9). http://dx.doi.org/10.1002/14651858.CD011381.pub2
47. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP*, et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;**365**(14):1293-303. http://dx.doi.org/10.1056/NEJMoa1014656
48. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP*, et al.* Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;**13**(3):247-56. http://dx.doi.org/10.1016/s1474-4422(13)70308-9
49. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L*, et al.* Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler* 2014;**20**(6):705-16. http://dx.doi.org/10.1177/1352458513507821
50. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B*, et al.* Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *New England Journal of Medicine* 2017;**376**(3):221-34. http://dx.doi.org/10.1056/NEJMoa1601277
51. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013: The reference case*. 2013. URL: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case (Accessed 10 September 2020).
52. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M*, et al.* UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. *BMJ Open* 2014;**4**(1):e004073. http://dx.doi.org/10.1136/bmjopen-2013-004073
53. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R*, et al.* Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018;**391**(10127):1263-73. http://dx.doi.org/10.1016/s0140-6736(18)30475-6
54. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur Med* 1997;**29**(2):101-6.
55. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I*, et al.* Technical Supplement to Chapter 4: Searching for and selecting studies: 2.2.2 Searching MEDLINE and Embase: specific issues. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ*, et al.*, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.1*: Cochrane; 2020. URL: https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies (Accessed 10 September 2020).
56. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *Bmj* 1996;**313**(7052):275-83. http://dx.doi.org/10.1136/bmj.313.7052.275
57. Hawton AJ, Green C. Multiple sclerosis: relapses, resource use, and costs. *The European Journal of Health Economics* 2016;**17**(7):875-84. http://dx.doi.org/10.1007/s10198-015-0728-3
58. National Institute for Health and Care Excellence. *Teriflunomide for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA303]*. 2014. URL: https://www.nice.org.uk/guidance/ta303 (Accessed 10 September 2020).
59. National Institute for Health and Care Excellence. *Dimethyl fumarate for treating relapsing-remitting multiple sclerosis: Technology appraisal guidance [TA320]*. 2014. URL: https://www.nice.org.uk/guidance/ta320 (Accessed 10 September 2020).
60. National Institute for Health and Care Excellence. *Cladribine for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA493]*. 2017. URL: https://www.nice.org.uk/guidance/ta493 (Accessed 10 September 2020).

61. European Medicines Agency. *EPAR : Rebif - Product Information*. 2020. URL: https://www.ema.europa.eu/en/documents/product-information/rebif-epar-product-information_en.pdf (Accessed 10 September 2020).
62. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J*, et al.* The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain* 1989;**112 (Pt 6)**:1419-28. http://dx.doi.org/10.1093/brain/112.6.1419
63. Institute for Clinical and Economic Review (ICER). *Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value*. 2019. URL: https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Evidence_Report_050219.pdf (Accessed 11 September 2020).
64. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. *Journal of neurology* 2014;**261**(8):1508-17. http://dx.doi.org/10.1007/s00415-014-7370-3
65. Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J*, et al.* Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry* 2012;**83**(1):61-6. http://dx.doi.org/10.1136/jnnp-2011-300616
66. Patzold U, Pocklington PR. Course of multiple sclerosis: First results of a prospective study carried out of 102 MS patients from 1976-1980. *Acta Neurologica Scandinavica* 1982;**65**(4):248-66. http://dx.doi.org/10.1111/j.1600-0404.1982.tb03084.x
67. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics* 2008;**26**(7):617-27. http://dx.doi.org/10.2165/00019053-200826070-00008
68. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res* 2013;**13**:346. http://dx.doi.org/10.1186/1472-6963-13-346
69. National Institute for Health and Care Excellence. *BNF*. 2020. URL: https://bnf.nice.org.uk/ (Accessed 20 September 2020).
70. European Medicines Agency. *EPAR : Mavenclad - Product Information*. 2020. URL: https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf (Accessed 20 September 2020).
71. European Medicines Agency. *Extavia (interferon beta-1b): Product information*. 2019. URL: https://www.ema.europa.eu/en/documents/product-information/extavia-epar-product-information_en.pdf (Accessed 31 July 2020).
72. NHS Improvement. *Archived Reference Costs: 2017/18 Reference Costs*. 2018. URL: https://improvement.nhs.uk/resources/reference-costs/ (Accessed 12 September 2020).
73. Curtis L, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury: Personal Social Services Research Unit, University of Kent; 2019. http://dx.doi.org/10.22024/UniKent/01.02.79286
74. Walter E, Berger T, Bajer-Kornek B, Deisenhammer F. Cost-utility analysis of alemtuzumab in comparison with interferon beta, fingolimod, and natalizumab treatment for relapsing-remitting multiple sclerosis in Austria. *J Med Econ* 2019;**22**(3):226-37. http://dx.doi.org/10.1080/13696998.2018.1556668
75. National Institute for Health and Care Excellence. *Beta interferons and glatiramer acetate for treating multiple sclerosis [TA527]: Final Appraisal Document*. 2018. URL: https://www.nice.org.uk/guidance/ta527/documents/final-appraisal-determination-document-2 (Accessed 18 September 2020).
76. National Institute for Health and Care Excellence. *Ocrelizumab for treating relapsing–remitting multiple sclerosis [TA533]: Final Appraisal Document*. 2018. URL: https://www.nice.org.uk/guidance/ta533/documents/final-appraisal-determination-document (Accessed 1 September 2020).

77. Tyas D, Kerrigan J, Russell N, et al. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? Value Health 2007;10:386-9.

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

Appendix C: OPERA-aligned criteria for CDW

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

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

Appendix F: ERG scenario analyses

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

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]					
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]					
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]					
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]					
[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 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]					
[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 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]					
[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 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	

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **21 October** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1 Factually Inaccurate Statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 of the ERG report states that one way in which ofatumumab increases QALYs in the RRMS population is by: "*Reduction in caregivers' disutilities in all comparators except ocrelizumab*" The reduction in caregivers' disutility associated with the use of ofatumumab is greater than the reduction observed in all other comparators except for ocrelizumab. This statement is inaccurate as it suggests that ofatumumab reduces caregiver disutilities in its comparators, and that ocrelizumab does not reduce caregiver disutility.	Please amend this wording to the following: "*Reduction in caregivers' disutilities* ***against*** ~~*in*~~ *all comparators except ocrelizumab*"	This statement is factually inaccurate.	We do not consider this to be factually inaccurate. However, we have used the company's wording for clarity.
Page 15 of the ERG report states: *"The CS does not provide sufficient subgroup data to perform indirect comparisons or cost-effectiveness analyses in the active SPMS population."* As stated in the CS, due to the small sample size of patients with active SPMS, insufficient subgroup data were available from the ASCLEPIOS trials to conduct analyses in the active SPMS population. The limitation of availability of subgroup data lies with the trials, rather than with the CS.	Please amend this wording to the following: *"The ASCLEPIOS trials do not provide sufficient subgroup data to perform indirect comparisons or cost-effectiveness analyses in the active SPMS population."*	The current statement is misleading and as such, factually inaccurate.	We do not consider this to be factually inaccurate. However, we have used the company's wording for clarity.

The Issue 5 table on Pages 19 – 20 is captioned "*Inclusion of disease management costs associated with treating people with SPMS*" and describes the issue identified by the ERG as: "*Disease management costs associated with treating people with SPMS not included in the company submission*." Table 55 on Page 149 of the ERG report states: "*For consistency with other recent technology appraisals, the ERG suggest that disease management costs associated with treating people with SPMS should have been included in the economic analysis*." These statements are inaccurate as they suggest that no costs associated with the management of SPMS were included in the model, rather than that the ERG would prefer different costs to be used for RRMS and SPMS.	Issue 5 caption on Page 19: "*Inclusion of **SPMS-specific** disease management costs*" Issue 5 description of issue identified on Page 19: "***SPMS-specific** disease management costs **which differ from those associated with treating people with RRMS were** not included in the company submission*." *"For consistency with other recent technology appraisals, the ERG suggest that **SPMS-specific** disease management costs **which differ from those** associated with treating people with **RRMS** ~~SPMS~~ should have been included in the economic analysis*."	The current statements are factually inaccurate.	We have made the necessary changes in the report.
Page 21 of the ERG report states: *"In the CS, the company derived and used health state values from participants with SPMS in the ASCLEPIOS trials."* This statement is incorrect. The statement currently implies health state utility were derived solely from patients with SPMS whereas they were derived from the ITT population, which includes patients with	Please amend this wording to the following: *"In the CS, the company derived and used health state values from all participants in the ASCLEPIOS trials, including those with active SPMS."*	The current statement is misleading and as such, factually inaccurate.	In context, we are referring to the health state utility values used for when people progressed to SPMS. However, for clarity we have used the suggested text.

RRMS and active SPMS.			
Page 24 of the ERG report states: *"The company's PSA results for RRMS showed that ofatumumab compared to best supportive care had a [redacted] probability of being cost-effective at a WTP threshold of £30,000 per QALY."* Page 93 of the ERG report states: *"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 when compared to ocrelizumab."* Page 144 of the ERG report states: *"Table 52 reports the probability of each DMT being cost-effective against best supportive care at a willingness-to-pay threshold of £30,000 per QALY. These results show that ofatumumab compared to best supportive care has a [redacted] probability of being cost-effective."* The caption of Table 52 on Page 144 of the ERG report is: "*Probability of each DMT being cost-effective against best supportive care, RRMS population*." Page 166 of the ERG report states: *"The company's PSA results for RRMS showed that ofatumumab compared to best supportive care had a [redacted] probability of being*	Please amend this wording to the following: Page 24: *"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."* Page 93: *"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."* Page 144: *"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 caption on Page 144: "*Probability of each DMT being cost-effective, RRMS population*." Page 166: "*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 current statements are factually inaccurate.	We have removed 'best supportive care' from the following statements.

cost-effective at a WTP threshold of £30,000 per QALY." These statements are incorrect. The results discussed are from a fully incremental PSA including all relevant comparators in the same analysis which calculates the probability of being cost-effective compared with other DMTs rather than best supportive care.			
Page 26 of the ERG report states: "*The anticipated full EU MA wording for ofatumumab is "*for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS), including patients both with RRMS or active SPMS)*" (CS Document B, pg.20).*" This statement is inaccurate as it does not align with the anticipated license wording which reads "*for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS)*". The inclusion of a closed parenthesis after "*SPMS*" is also a typographical error.	Please amend this wording to the following: "*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)."*	This statement is factually inaccurate and contains a typographical error.	We have made the suggested change.
Page 28 of the ERG report states: "*Regarding the definition of HA RRMS (CS Document B, pg.19) it should be noted that HA RRMS can additionally be defined by either:* • *An unchanged or increased relapse rate (i.e. not just ongoing severe*	Please remove this text from the report.	The "alternative" definitions are in fact older, outdated and superseded definitions.	We have removed the requested text.

relapses) in comparison to the previous year (despite treatment with beta-interferon) *or* • *One relapse in the previous year and magnetic resonance imaging (MRI) evidence of disease activity*." The "additional" definitions given by the ERG are in fact derived from much earlier iterations of the Summary of Product Characteristics of natalizumab and fingolimod, respectively, which have since been updated; the definition presented in the CS aligns to the current SmPCs for fingolimod and natalizumab and the "additional" definitions proposed by the ERG should be considered outdated as they have now been superseded. Relatedly, the definition of HA RRMS presented in the NHS England treatment algorithm (2019) is derived from NICE TA254, published in 2012, which was based on the SmPC wording current at that time. Notably the NHS England treatment algorithm has subsequently been updated to include prior glatiramer acetate, teriflunomide or DMF treatment, as well as the original prior beta-interferon treatment as a qualifying criterion for an HA diagnosis. Given these changes since the early 2010s, the definition provided in the CS represents the current definition of HA RRMS.			

Page 29 of the ERG report states: • *"Ocrelizumab: recommended for RRMS where Alemtuzumab is contraindicated (and the company provides it according to the commercial arrangement).[19]* • *Alemtuzumab*: recommended in patients who have HA RRMS despite adequate treatment with at least one DMT (in addition to its authorised use for RES RRMS).[20]* o ** 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. The recommendations in NICE TA312 will be updated to reflect this in due course.[8]"* These statements are incorrect for the following reasons: Firstly, the restriction applied to ocrelizumab is incomplete; the NICE guidance is for	Please amend this wording to the following: • *"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]* o ** 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. ~~The recommendations in~~*	The current statements are factually inaccurate.	We have made the suggested change.

patients where "alemtuzumab is contraindicated or otherwise unsuitable." Secondly, the restriction to alemtuzumab is also incomplete; the NICE guidance is for patients with HA RRMS despite "a full and adequate course of treatment with at least one DMT". Finally, the recommendations in NICE TA312 have already been updated in line with the changes to the EMA marketing authorisation. The recommendation for alemtuzumab as described in the ERG report also incorporates these changes, and so the final sentence is no longer accurate.	~~*NICE TA312 will be updated to reflect this in due course*~~*.[8]"*		
Page 29 of the ERG report states: "*Stopping criteria common to all DMTs includes: ineffectiveness, intolerable effects, development of secondary progressive disease or inability to walk*." This statement is incorrect. The wording from the NHS England Treatment Algorithm cited states confirmation of SPMS as a stopping criterion.	Please amend this wording as follows: "*Stopping criteria common to all DMTs includes: ineffectiveness, intolerable effects,* ***confirmed*** *development of secondary progressive disease or inability to walk*."	The current statement contains missing details of relevance.	We have made the suggested change.
Page 30 of the ERG report states: *"It suggests that IV ocrelizumab administration is subject to infusion capacity constraints and limitations in patient travel, although supporting data for this is not provided in the CS."* This statement is incorrect. Supporting data	Please update the text to remove the final clause as follows: *"It suggests that IV ocrelizumab administration is subject to infusion capacity constraints and limitations in patient travel*~~*, although supporting data for this is not provided in the CS*~~*."*	The current statement is factually inaccurate.	We do not consider this to be factually inaccurate. However, we have amended the text to improve clarity. *"It suggests that IV ocrelizumab administration is subject to infusion*

for these statements were provided as part of the IQVIA market research and the advisory board report, both shared in the reference pack to the CS, and cited in the CS Document B: Page 19 of CS Document B: "*UK clinical experts at a recent Novartis advisory board agreed that these can render ocrelizumab treatment inaccessible for some patients, including due to disability or the distance required to travel for treatment."* [citation provided: Novartis (Data on File): Multiple Sclerosis Advisory Board. 2020.] Page 108 of CS Document B: *"Clinical experts at an advisory board run by Novartis in January 2020 highlighted that the number of infusions has dramatically increased since the introduction of ocrelizumab, resulting in increased pressure on resources and longer waiting times for patients."* [citation provided: Novartis (Data on File): Multiple Sclerosis Advisory Board. 2020.] *"In market research interviews commissioned by Novartis and conducted by an independent agency, business managers of infusion clinics across the UK (N=12) described the extension of working hours into evenings and weekends and the re-allocation of MS patients to other wards or clinics as their (pre-COVID-19) strategies to overcome capacity constraints for MS infusion therapies, but also the extension of dosing intervals (e.g. 6-weekly instead of 4-weekly administration) or the increase of 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****."*

speed." [citation provided: IQVIA. Ofatumumab HTA Submission Support Research. 2020.]			
Page 30 of the ERG report states: *"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."* This statement is misleading. As per slide 4 of the IQVIA market research shared as part of the reference pack, all survey respondents were based in the UK. "Unknown" refers to which devolved UK country the respondent is based in (i.e. England, Wales, Scotland or Northern Ireland).	Please amend this wording to the following: *"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****."*	The current statement is misleading and as such, factually inaccurate.	We have amended the text as requested.
Page 38 of the ERG report states: *"However, the main Medline database has not been searched for the update, which ERG testing suggests may have missed a few records"* This statement is incorrect. As per Page 12 of the CS Appendices, the MEDLINE database was searched as part of the clinical SLR update conducted on 27th February 2020.	Please remove this text from the report.	The current statement is factually inaccurate.	The title of table 2 on page 18 of the CS Appendices only mentions MEDLINE Daily, MEDLINE In-Process, Epub Ahead of Print and Embase. As these tables are usually saved at the time of searching, they are more likely to reflect which databases were actually searched. However, the ERG accepts that there could be a typo in the table title and as such

			will amend the text in the ERG report to say: *"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"*
Pages 38–39 of the ERG report state: *"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).* *However, in CS Document B (Section B.2.9, pg.56) it was stated that "an SLR identified 731 publications on 92 unique studies of DMTs in RMS". Reasons behind the discrepancy between the reported numbers of unique studies are not clear."* Page 64 of the ERG report states: *"Nevertheless, the ERG is concerned that the process of selecting the 37 RCTs for NMA feasibility assessment from the 92 studies (or 84 studies based on CS Appendix D, Section D.1.3) lacked transparency as reasons for exclusion were not provided for individual studies…"* The discrepancy between 92 and 84 studies was identified as a typographical error in the	Pages 38–39: Please update the wording to remove the second sentence and add an explanatory sentence regarding this resolved discrepancy as follows: *"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).* ~~*However, in CS Document B (Section B.2.9, pg.56) it was stated that "an SLR identified 731 publications on 92 unique studies of DMTs in RMS". Reasons behind the discrepancy between the reported numbers of unique studies are not clear."*~~	The current statements are factually incorrect as this discrepancy has already been resolved.	Proposed amendment accepted. We have removed the text as suggested.

company submission (CS) and clarified in response to clarification question C1, where Novartis confirmed that this should read 84 included studies in alignment with the PRISMA diagram presented in Figure 2, Page 42 of CS Appendix D.1.3.	Page 64: Please update this text to the following: *"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."*		
Page 39 of the ERG report states: "*Based on data presented in the CS and its appendices, the ERG's understanding is that data extraction was conducted only for studies and outcomes subsequently included in the NMAs (i.e. not for other studies meeting the SLR inclusion criteria, nor for outcomes not used in the NMAs).*" This statement is incorrect. As per Section D.1.2 of the CS appendices document which outlines the approach taken in the clinical SLR, full texts which were deemed ultimately eligible for inclusion in the review were extracted by one reviewer and checked by a second reviewer.	Please amend this wording to the following: "*Based on the methodology described in the CS and its appendices, the ERG's understanding is that data extraction was conducted for all studies meeting the SLR inclusion criteria and for outcomes not ultimately used in the NMAs, but that data were presented only for studies and outcomes subsequently included in the NMAs.*"	The current statement is factually inaccurate based on the information provided in the CS.	Not factual error. ERG cannot verify the claimed data extraction where no data were presented in the CS and its appendices. The ERG proposes the following alternative text: "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."
Page 42 of the ERG report states: *"ASCLEPIOS I and II were designed to investigate the use of ofatumumab versus teriflunomide in people with RRMS or*	Please amend this wording to the following: *"ASCLEPIOS I and II were designed to investigate the safety and efficacy of*	The current statement is factually inaccurate.	We have amended the text as requested.

SPMS." This statement is incorrect. As per the inclusion and exclusion criteria of the ASCLEPIOS trials presented in Table 4, Page 27 of the CS Document B, the ASCLEPIOS trials enrolled patients with RMS (RRMS or active SPMS) and did not enroll patients with SPMS without disease activity. Further, as per Section B.2.3 of the CS Document B, the ASCLEPIOS trials aimed to investigate the safety and efficacy of ofatumumab versus teriflunomide.	*ofatumumab versus teriflunomide in adults with RMS (RRMS or active SPMS)."*		
Pages 42–43 of the ERG report state: *"In summary, patients were included if they were aged 18-55 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, and at least one relapse during previous year or two relapses during previous two years 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, had been treated with specified medications or within specified timeframes."*	Please amend this wording to the following: *"In summary, patients were included if they were aged 18-55 years* ***(inclusive)*** *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*	The current statement contains missing details of relevance.	We have amended the text as requested.

There are a number of small errors in this text that do not align with the inclusion and exclusion criteria of the ASCLEPIOS trials presented in Table 4, Page 27 of the CS Document B.	*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."*		
Page 44 of the ERG report states: *"However, the CSRs and study protocol indicate that patients who discontinued the study drug (ofatumumab) were encouraged [redacted]."* This statement is incorrect. In this context, the phrase "study drug" in the CSRs refers to both ofatumumab or teriflunomide, depending on which is being received. Reference to ofatumumab alone could be misleading and inaccurately suggest possible bias.	Please amend this wording to the following: *"However, the CSRs and study protocol indicate that patients who discontinued the study drug (ofatumumab **or teriflunomide**) were encouraged [redacted]."*	The current statement is misleading and as such, factually inaccurate.	We have amended the text as requested.
Page 47 of the ERG report states: *"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; rate of brain volume loss; 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-*	Please amend this wording: *"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; 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*	The current statement is factually inaccurate.	We have amended the text as requested.

5D-5L), Multiple Sclerosis Impact Scale (MSIS-29), and Impact of MS Disease on Work Productivity and Activity (WPAI:MS).” This statement is incorrect. As per Table 3, Page 23 of the CS Document B, only CDW-3, CDW-6, CDI-6, the number of T1 Gd-enhancing lesions, the number of new or enlarging T2 lesions per year (annualised T2 lesion rate), the rate of brain volume loss and serum NfL concentrations were pre-specified as key secondary outcomes of the ASCLEPIOS trials. The other outcomes listed are all examples of the trials' non-key secondary outcomes.	*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).”*		
Page 61 of the ERG report states: “*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).*” This statement does not mention that no	Please amend this wording to the following: *“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).* ***No patients in either trial developed neutralising antibodies.*** *From the above results, the company concludes that “*long-term treatment effect waning due to	The current statement contains missing details of relevance.	We do not consider this to be factually inaccurate. No amendment made to the text.

patients in the ASCLEPIOS trials developed neutralising antibodies as reported in Section B.2.10.7 of the CS. Given the significance of neutralising antibodies in the waning of treatment efficacy, this statement is ambiguous by omission. Furthermore, the observation that no patients developed neutralising antibodies during the trials was a key consideration in the Company's conclusion that long-term treatment effect waning due to formation of neutralising antibodies is considered unlikely.	formation of neutralising antibodies is considered unlikely with ofatumumab*" (CS Document B, pg. 107)."*		
Page 61 of the ERG report states: *"Therefore, the ERG cannot conclude that treatment waning does not occur as waning could be related to other aspects of disease progression (e.g., adherence, AE, loss of effectiveness) and not just the development of antibodies. Therefore, treatment waning in included in the ERG base case in the cost-effectiveness analysis (see Section 4.3.6.12)."* This statement is incorrect. Treatment waning relates only to a loss of effectiveness for ARR or CDW.	Please amend this wording to the following: *"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."* *Please also correct the typographical error in the second sentence: "Therefore, treatment waning* ***is*** ~~*in*~~ *included in the ERG base case in the cost-effectiveness analysis (see Section 4.3.6.12)."*	The current statement is factually inaccurate.	We have amended the text as requested.
Page 62 of the ERG report states: "*The CS references data, but does not present data from two other dose-finding RCTs of ofatumumab: Sorensen 2014 (N=38) and the MIRROR study (N=232). The ERG agrees that these smaller, shorter-term trials provide less robust information*	Please amend this wording to the following: "*The CS references data, but does not present data from two other dose-finding RCTs of ofatumumab: Sorensen 2014 (N=38) and the MIRROR study (N=232). The ERG agrees that these smaller,*	The current statement contains missing details of relevance.	We do not consider this to be factually inaccurate. No amendment made to the text.

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. These potential adverse effects should be considered in assessing the safety profile of ofatumumab for RRMS*." Given the relevance of administration method on observed AEs, it should be acknowledged that a distinct route of ofatumumab administration (IV infusion) is used in the Sorensen 2014 trial and is used in the treatment of other diseases, like leukemia, with ofatumumab. Therefore, findings on the safety profile of ofatumumab from the Sorensen or from other disease areas are not directly relevant or applicable to this appraisal given the difference in administration method.	*shorter-term trials provide less robust information about safety, when compared to the main RCTs,* ***particularly as the Sorensen 2014 trial investigated IV infusion of ofatumumab, an administration method which is likely to affect the AE profile observed as compared with s.c. administration****. 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* ***and with a different route of administration (IV versus s.c.)****, but for which there are some indications of potential adverse effects. These potential adverse effects should be considered in assessing the safety profile of ofatumumab for RRMS*"		
Pages 62–63 of the ERG report state: *"The CS (Document B, pg.108) refers to an*	Please amend this wording to the following:	The current statement is factually inaccurate.	We have amended the text as requested.

open-label extension study of the ASCLEPIOS trials (ALITHIOS), for which initial data are expected in [redacted]*, and another open-label trial of ofatumumab in Japan (APOLITOS trial of ofatumumab vs. placebo, N=64), which is expected to be completed in 2020."* This statement is incorrect. As per the trial description on clinicaltrials.gov, the APOLITOS study (NCT03249714) is a *"24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study […] followed by an extended treatment of at least 24 weeks with open-label ofatumumab."* As such, its description as a solely open-label study is factually inaccurate.	*"The CS (Document B, pg.108) refers to an open-label extension study of the ASCLEPIOS trials (ALITHIOS), for which initial data are expected in* [redacted]*, and* ***a*** *trial of ofatumumab in Japan (APOLITOS trial of ofatumumab vs. placebo, N=64),* ***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."*		

Table 11 on Pages 66–69 of the ERG report includes the following statements that are incorrect: *"**Key eligibility criteria:*** • *ASSESS: Aged 18–55 (inclusive)* • *ASSESS: Diagnosis of RMS* • *Boiko et al, 2018a: Documented history of relapses of at least 2 in past 2 years* • *Boiko et al, 2018a: [no history of relapse criteria provided]* • *Boiko et al, 2018a: [no disease duration criteria provided]* • *CLARITY: [no age criteria provided]* • *Copolymer I MS trial: Aged 18–55 (inclusive)* • *FREEDOMS: Diagnosis of RMS* • *IFNB MS: [no age criteria provided]* • *MSCRG: EDSS 0–5.5 (inclusive) at screening* • *PRISMS: EDSS 0–5.5 (inclusive)* • *PRISMS: [no disease duration criteria provided]* • *PRISMS: [no history of relapse criteria provided]* • *REGARD: [no age criteria provided]*	Please update these statements as follows: *"**Key eligibility criteria:*** • *ASSESS: Aged 18–**6**~~5~~5 (inclusive)* • *ASSESS: Diagnosis of **R**RMS* • *Boiko et al, 2018a: Documented history of relapses of at least **1 in the past 12 months**~~2 in past 2 years~~* • *Boiko et al, 2018a: **No relapse in previous 4 weeks*** • *Boiko et al, 2018a: **Disease duration of one year or more*** • *CLARITY: **Aged 18–65 (inclusive)*** • *Copolymer I MS trial: Aged 18–**4**~~5~~5 (inclusive)* • *FREEDOMS: Diagnosis of **R**RMS* • *IFNB MS: Aged **18–50 (inclusive)*** • *MSCRG: EDSS **1.**0–**3**~~5~~.5 (inclusive) at screening* • *PRISMS: EDSS 0–5.**0**~~5~~ (inclusive)* • *PRISMS: **Disease duration of one year or more***	The current statements are factually inaccurate.	Proposed amendments accepted. The ERG have amended the text accordingly.

• *TEMSO: Diagnosis of MS* • *TRANSFORMS: [no age criteria provided]* • *TRANSFORMS: [no EDSS range criteria provided]* ***Blinding:*** *CONFIRM: Double blinding"* The correct data were provided in the appendices document of the CS (Table 14, Page 66).	• *PRISMS:* ***History of relapses of at least 2 in the past 2 years*** • *REGARD:* ***Aged 18–60 (inclusive)*** • *TEMSO: Diagnosis of* ***R****MS* • *TRANSFORMS:* ***Aged 18–55 (inclusive)*** • *TRANSFORMS:* ***EDSS 0–5.5 (inclusive)*** ***Blinding:*** *CONFIRM: ~~Double~~* ***Mixed*** *blinding"*		
Page 72 of the ERG report states: "*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, although the exact differences between the pre-defined criteria and the OPERA-aligned criteria used in the re-analyses were not clearly listed in the CS*." Pages 72–73 of the ERG report state: "*However, we suggest great caution in the interpretation of findings based on these analyses given the lack of clear explanation of the differences between the "*pre-defined*" and "*OPERA-aligned*" criteria, the* post hoc *nature of the analyses, and other differences in the design and conduct of the trials and in*	Please amend this wording to the following: Page 72: "*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 exact differences between the pre-defined criteria and the OPERA-aligned criteria used in the re-analyses* ***described in the appendices of*** *the CS* ***(section D.1.5)***." Pages 72 – 73: "*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*	The current statements are factually inaccurate.	We acknowledge that further details were provided in CS appendices p.81, Table 18 and has revised the text on page 72 to read: "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, p.81)."

patient populations that could not be addressed by the use of the criteria." These statements are inaccurate. A full description of the differences between the "pre-defined" and "OPERA-aligned" criteria used in the re-analyses was provided by the company in the appendices document of the CS, Section D.1.5 (pages 80–81).	*criteria*."		Suggested amendment for the text on Pages 72-73 was accepted.
Page 82 of the ERG report states: "*In this scenario NMA,* [redacted]." This statement is inaccurate. Ocrelizumab was [redacted] in the base case and scenario analysis using the pre-defined CDW outcome, as shown in Tables 16 and 17 of the ERG report. Alemtuzumab was [redacted].	Please amend this wording: "*In this scenario NMA,* [redacted]."	The current statement is factually inaccurate.	We have amended the text as requested.
Page 92 of the ERG report states: "*Additionally, in each cycle, people may have experienced relapses (mild, moderate, or severe), treatment-related AE or discontinued treatment, all of which are captured in separate health states*." This statement is incorrect. As described in the CS, there are 21 health states in the model (10 states each [EDSS 0–9] for RRMS	Please update the text to remove the final clause as follows: "*Additionally, in each cycle, people may have experienced relapses (mild, moderate, or severe), treatment-related AE or discontinued treatment*."	The current statement is factually inaccurate.	We do not consider this statement as factually inaccurate, but we have updated the text for clarity.

and SPMS, and a 'Death' state). Relapses, treatment-related AEs and discontinuation do not represent separate health states.			
Page 118 of the ERG report states: "*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 Orme et al. (2007) study of natural history for people with SPMS*." This statement is inaccurate. As per Table 58 in Section B.3.3.2 of the CS, the natural history transition probability matrix for people in SPMS health states was derived from the people randomised to placebo in the EXPAND trial, supplemented with information from the London Ontario Dataset. Orme et al. (2007) was used as a source of utility data, as described in Table 72 in Section B.3.4.1 of the CS.	Please amend this wording to the following: "*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***." 	The current statement is factually inaccurate.	We have updated this text.

Page 120 of the ERG report states: *"In Table 19, the ERG has provided ARRs and have noted the clear differences between the ARRs provided by the company and those obtained from TA527 assessment, which were derived from the Risk Sharing Scheme (RSS) data."* This statement is inaccurate as relapse data were not collected in TA527 for use in the RSS model. As per the Assessment Group report on TA527, "a weighted average of the frequency of relapse for people with RRMS and SPMS, irrespective of EDDS [sic] level was derived based on information from the 2002 survey by the MS Trust." The reference to Table 19 is also inaccurate.	Please update the text to remove the final clause and to amend the table reference, as follows: "*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, ~~which were derived from the Risk Sharing Scheme (RSS) data~~*."	The current statement is factually inaccurate.	We have updated this cross-reference and text.
Page 120 of the ERG report states: *"In scenario analysis, the company provided treatment specific rate ratios, which were applied to the natural history ARR to derive the relapse rates by EDSS for people on DMTs."* This statement is incorrect. The scenario analysis referred to considered an EDSS-independent approach.	Please amend this wording to the following, to align with the text provided further down Page 121 (under the 'ERG summary'): *"In a scenario analysis, the company provided an alternative method that applied treatment specific rate ratios to declining relapse rates irrespective/independent of EDSS"*	The current statement is factually inaccurate.	This text has been updated.
Page 121 of the ERG report states: *"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*	Please amend this wording to the following: *"In the company's base-case results it was assumed that the treatment effect with ofatumumab and all comparators was*	The current statement is factually inaccurate as it omits relevant additional detail and misreports Novartis' conclusions in the clarification	We have amended our current statement to include the additional detail provided by the company.

time. In response to the ERG's clarification question to consider including scenarios with waning of the treatment effect, the company stated that no waning of the treatment effect existed." This statement is misleading as it does not fully capture the approach taken by Novartis; it was assumed that treatment effect was not expected to wane over time, but also that all-cause discontinuation accounts for patients experiencing any perceived loss of effect. Additionally, the summary of Novartis' response in the clarification questions is misleading and does not accurately reflect the conclusions made by Novartis.	*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."*	question responses.	
Pages 122–123 of the ERG report states: "*Utility modifiers were applied in the model. A utility coefficient of [redacted] was applied per year since diagnosis, derived from a regression model applied to the ASCLEPIOS trial data, and a utility coefficient of [redacted] per year was applied to males. Both decrements were applied to people with RRMS and SPMS*." As clarified by the company in response to clarification question B10, the coefficients reported here were derived from a regression analysis applied to the ASCLEPIOS data, but they were *not* applied in the cost-effectiveness model (CEM) base case presented in the CS. Their application in the CEM was instead presented as a scenario	Please amend this wording to the following: "*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****."*	The current statement is factually inaccurate.	We have amended our current statement to that suggested by the company.

analysis at the clarification questions stage.			
Page 123 of the ERG report states: "*However, in scenario analysis that used the utility values form Orme et al. (2007) these coefficients had been correctly applied. At clarification, the company stated that the regression coefficients were incorrectly derived from the ASCLEPIOS trials*." This statement is inaccurate. The coefficients were correctly derived from the ASCLEPIOS trial data, but were subsequently incorrectly applied in the Orme scenario.	Please amend this wording to the following: "*However, in **a** scenario analysis that used the utility values from Orme et al. (2007) 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 current statement is factually inaccurate.	We have amended the wording.
Page 123 of the ERG report states: *"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)."* This statement is incorrect. The ERG's suggestion of using Orme et al. health state utility values only applies to the SPMS population; the ERG's base case model applies Orme et al. utilities to SPMS health states and maintains the ASCLEPIOS utilities, supplemented with Orme et al. for RRMS health states. The current statement reads as if to suggest utilising Orme et al. values for all patients. Further, Table 58 on Page 151 presents the	Please amend this wording to the following: Page 123: *"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) **for SPMS**."* Table 58: Please update the utility values reported for the ERG's preferred values in RRMS to ASCLEPIOS and Orme, as has been used in the ERG's model.	The current statement is misleading and as such, factually inaccurate.	We have amended the wording on page 123 and the column heading in Table 53 to accurately reflect the ERG's preferred assumptions.

ERG's preferred values as if Orme et al. utilities are applied in RRMS also, which contradicts the ERG's base case.			
Page 124 of the ERG report states: "*AEs included in the model were based on the average proportion of severe adverse events that occurred in the treatment arms of the ASCLEPIOS trials (see Table 38).*" This statement is incorrect. As stated in Section B.3.4.4 of the CS, the proportion of severe adverse events that occurred in the treatment arms of the ASCLEPIOS trials defined the proportion of AEs assumed to be serious or non-serious in the economic model. It did not define which AEs were included in the model.	Please amend this wording to the following: "*The severity of AEs in the model was based on the average proportion of severe adverse events that occurred in the treatment arms of the ASCLEPIOS trials*"	The current statement is factually inaccurate.	We have amended the wording.
Table 40 on Page 131 of the ERG report attaches the following footnote to teriflunomide: "*In the base case, administration costs do not apply after Year 2.*" This is inaccurate. As per Table 78 in the CS, this footnote is associated with alemtuzumab only.	Please remove this footnote from the teriflunomide row. Its presentation next to the administration costs of alemtuzumab in this table is appropriate and should be maintained.	The current statement is factually inaccurate.	We have removed this footnote.
Page 137 of the ERG report summarises ICERs versus comparators. These results represent [redacted], and therefore the values stated are [redacted].	Please amend this wording to the following: "*The ICER for the comparison between ofatumumab and alemtuzumab was approximately* [redacted]*. In the other*	The current statement is factually inaccurate. The CIC marking currently provided is insufficient to prevent inference of the cost-effectiveness results for	We have amended the wording. We have also updated the CIC markings.

	comparisons except with cladribine, the ICERs were [redacted].” Please additionally update the CIC marking to this sentence as provided.	ofatumumab versus its comparators	

Table 55 on Page 149 of the ERG report provides the ERG preferred values for the management costs of SPMS, derived from TA624:

EDSS	Management costs for SPMS[5] (ERG preferred values)
0	£1,301
1	£1,340
2	£1,071
3	£4,360
4	£2,285
5	£3,644
6	£4,750
7	£11,955
8	£28,637
9	£22,982
10	£0

Costs for EDSS states 0–6 are consistent with the values presented in TA624, which were obtained from TA320 and inflated to the cost year 2017/18 as presented in Section 5.3.11.2 of the CS in TA624. The values for EDSS 7–9 are not consistent with the values presented in TA624. Therefore, the values

Please update these costs to costs derived by inflating the original data from TA320 to the correct cost year (2018–2019):

EDSS	Management costs for SPMS (original values from TA320)	Management costs for SPMS (inflated to the 2018-2019 cost year)
0	£1,217	£1,339
1	£1,254	£1,380
2	£1,002	£1,103
3	£4,079	£4,489
4	£2,138	£2,353
5	£3,409	£3,751
6	£4,444	£4,890
7	£11,185	£12,308
8	£26,793	£29,483
9	£21,502	£23,661
10	-	£0

The current values are factually inaccurate, both with respect to TA320 and with respect to the model cost year.

The company states here that the values for EDSS ≥ 7 are not consistent with those reported in TA624.

However, it should be noted that there is a <£5 difference between these values and those reported in TA624 and would not make a difference to the results. However, we do accept that the management costs are reported in 2017/18 prices.

We thank the company for inflating the management costs for SPMS to current prices for which we have now used to update our analyses.

reported are factually inaccurate. In addition, and more importantly, the values from TA624 do not relate to the same cost year as presented in the CS (2018/19). This makes the use of the ERG figures itself a factual inaccuracy as they have not been aligned to the model cost year.	These costs have been inflated as explained in the CS, Section B.3.5.2: these data were inflated to 2014–2015 values using the Pay and Price Index, and subsequently inflated for the remaining years to 2018–2019 values using the NHSCII index. Further detail on this inflation process are presented in the CS appendices document (Table 160, Appendix M.5.4).		
Page 178 of the ERG report states: "*In this scenario NMA,* [redacted]." This statement is inaccurate. Ocrelizumab was [redacted] in the base case and scenario analysis using the OPERA-aligned CDW outcome, as shown in Tables 16 and 2 (Appendix C) of the ERG report. Alemtuzumab was [redacted].	Please amend this wording: "*In this scenario NMA,* [redacted]."	The current statement is factually inaccurate.	We have amended the text as requested.

Issue 2 General Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue number 4 in Table 1 on Page 12 of the ERG report states:	Please amend this wording to add this context:	The current statement is ambiguous.	Not a factual error, no change made to the text.

"*The ERG consider the clinical effectiveness evidence for both ofatumumab and relevant comparators to be very limited*." This statement is ambiguous as it misses the context that the evidence in the HA and RES RRMS subgroups is limited.	"*The ERG consider the clinical effectiveness evidence for both ofatumumab and relevant comparators* ***in these subgroups*** *to be very limited*."		
Pages 24 and 89 of the ERG report state: *"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."* In relation to the NMA results, "confidence intervals" is incorrect and should instead refer to "credible intervals".	Please amend this wording to the following: *"The volume of evidence is limited for many of the linking comparisons in the evidence network resulting in wide* ***credible*** *intervals for some of the estimates."*	The current statement is incorrect.	We have amended the text as requested.
Page 43 of the ERG report states: "*In ASCLEPIOS I, 927 patients were randomised, and 465 received 20 mg ofatumumab while 462 received 14 mg teriflunomide; [redacted] ([redacted]%) of those randomised took at least one dose of treatment (CS Document B, Table 7, pg.33).*" "*In ASCLEPIOS II, 955 patients were randomised: 481 the 20mg ofatumumab group and 474 to the 14mg teriflunomide group; [redacted] ([redacted]%) took at least one dose (CS Document B, Table 7, pg.33).*" The values reported for those randomised who took at least one dose of treatment are incorrect. The values reported here relate to patients in the per-protocol set, who as well as receiving at	Please amend the data values to the following: "*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).*" "*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).*"	The current data are incorrect.	We have updated the text as requested.

least one dose of study treatment, also had no major protocol deviations. Patient numbers given in CS Document B, Table 7, pg. 33 for the safety set reflect patients who took at least one dose of treatment. Please note that AIC highlighting has been added to the above quotation as these data are not in the public domain.			
Page 46 of the ERG report states: *"In ASCLEPIOS I, the CSR reports that [redacted]."* The value reported for ASCLEPIOS I is incorrect (ASCLEPIOS I CSR, Page 705).	Please amend the data value for ASCLEPIOS I to the following: *"In ASCLEPIOS I, the CSR reports that [redacted]."*	The current datum is incorrect.	The [redacted], and therefore the statement was correct for individual treatment groups. No change made to the text.
Page 56 of the ERG report states: "*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 corotate the CS statement that this represents a clinically meaningful difference*." This sentence requires an edit to remove use of the word "corotate", which the company believes has been used in error and which leaves the meaning of the sentence unclear.	Please review this sentence and revise it as applicable. The edit should make clear that the company maintain these differences do *not* represent clinically meaningful differences, as per the appendices document of the CS.	The current statement is unclear and needs review.	We have amended the text as follows: Page 56 of the ERG report states: "*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."
Page 61 of the ERG report states: "*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 was [redacted].*" The wording in the last part of the sentence is ambiguous as it is unclear whether it is referring to a comparison between the treatment arms of ASCLEPIOS I (ofatumumab versus teriflunomide), or between the overall rates of SAEs between ASCLEPIOS I and ASCLEPIOS II.	Please amend this wording to the following: "*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 [redacted].*"	The current statement is ambiguous.	We have amended the text as suggested to improve clarity.
Page 63 of the ERG report states: "*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 this based on the approach adopted in a published NMA, 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*".*	Please amend this wording to the following whilst maintaining the integrity of the quoted wording: "*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 this based on the approach adopted in a published NMA, which stated that*	The current statement is ambiguous.	Not a factual error, but ERG has revised the text to improve clarity: "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**

This wording is misleading, since it can be read that "these trials" in the quoted wording is referring to RCTs with a duration of ≥48 weeks, whereas it refers to RCTs with a duration of less than 48 weeks.	***these trials with a shorter duration*** *"*~~these trials~~ were not designed to study clinical outcomes and were therefore considered too different from the other trials for inclusion in NMAs*".*		**exclusion of trials with shorter duration** based on the approach adopted in a published NMA, 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".
Page 64 of the ERG report states: "*These yielded 103 references related to 88 unique studies which were examined by the ERG*." The number of unique studies is incorrect. As per Section D.1.3 of the appendices document of the CS, the original and update clinical SLRs identified 84 unique studies.	Please amend this data value to the following: "*These yielded 103 references related to 84 unique studies which were examined by the ERG*."	The current datum is incorrect.	The number of 88 studies was obtained by ERG's own mapping based on information provided in separate tables in the CS and its appendices. As the company has not provided a unifying list of the 84 studies, the ERG cannot verify the accuracy of this number. Not factual error. No amendment is required.
Page 78 of the ERG report states: "*6 RCTs had one or more domains judged to be of unclear risk*." As per Table 40 in the appendices document, 11 studies had one or more domains judged to be of unclear risk.	Please amend this data value to the following: "***11*** *RCTs had one or more domains judged to be of unclear risk*."	The current datum is incorrect.	We have revised the text to clarify that the number refers to studies without any domain being judged to be of high risk: "6 RCTs had one or more domains judged to be of unclear risk (but had no

			domain judged to be of high risk)."
Table 17 on Page 82 of the ERG report provides the scenario NMA results using the pre-defined criteria for CDW. It reports the CDW-3 HR (95% CrI) as "[redacted] *(*[redacted]*)"* for IFN beta-1b SC 250. The lower credible interval data value is incorrect. It also reports the CDW-6 HR (95% CrI) as "[redacted] *(*[redacted]*)"* for natalizumab. The lower credible interval data value is incorrect.	Please amend the first data value to "[redacted] *(*[redacted]*)"* and the second data value to "[redacted] *(*[redacted]*)"*.	The current data are incorrect.	Proposed amendments accepted We have updated the text accordingly.
Page 83 of the ERG report states: "*Figure 16 of CS Appendix D presents the network of this all-cause discontinuation NMA, which included 29 RCTs and covered 17 different treatments (including placebo)*." This is not correct. As per Table 26 in Section D.1.6 of the appendices document of the CS, 30 trials were included in the all-cause discontinuation NMA. Novartis acknowledges that this error was reported in the footnote of the all-cause discontinuation network diagram (Figure 16, Section D.1.6 of the appendices document of the CS) which states 29 trials were included and apologise for this.	Please amend this wording to: "*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)*."	The current datum is incorrect.	We note the Company's error. We have corrected the text in the document.

Figures 2 and 3 on Page 87 of the ERG report present the ERG comparison of ratio of ARRs and CDW-6, respectively, between the FAS and the HA RRMS and RES RRMS subgroups in the ASCLEPIOS trials. Specifically: • Figure 2 presents the FAS ASCLEPIOS I ES (95% CI) as "[redacted] *([redacted], [redacted])*". • Figure 3 presents the HA RRMS ES (95% CI) as "[redacted] *([redacted], [redacted])*". • Figure 3 presents the RES RRMS ES (95% CI) as "[redacted] *([redacted], [redacted])*". The reported credible intervals are incorrect.	Please amend these data values to the following: • Figure 2 presents the FAS ASCLEPIOS I ES (95% CI) as "[redacted] *([redacted], [redacted])*". • Figure 3 presents the HA RRMS ES (95% CI) as "[redacted] *([redacted], [redacted])*". • Figure 3 presents the RES RRMS ES (95% CI) as "[redacted] *([redacted], [redacted])*".	These current data are incorrect.	The ERG constructed the Figures based on the point estimates and credible intervals reported in the CS. This process resulted in slight discrepancies of no more than 0.01 between the credible intervals reported and some of the values shown in the forest plots. These differences are negligible and have no practical relevance. Not factual error. No text amendments required. However, we added AIC markings to Figure 2 and 3.
Page 116 of the ERG report states: "*However, there is indirect benefit on mortality because DMTs delay progression to more severe EDSS health states, which is associated with a higher risk of dying*." This wording is ambiguous. The higher risk of dying is associated with more severe EDSS health states, not with delayed progression.	Please amend this wording to the following: "*However, there is indirect benefit on mortality because DMTs delay progression to more severe EDSS health states, which* ***are*** ~~*is*~~ *associated with a higher risk of dying*."	The current statement is ambiguous.	We have updated the text to improve clarity.
Page 124 of the ERG report states: "*It was assumed that for each AE, [redacted]% were non-serious and [redacted]% were serious events*." The percentage of non-serious AEs is incorrect.	Please amend this figure to the following: "*It was assumed that for each AE,* ***89.87%*** *were non-serious and 10.13% were serious events*."	The current datum is incorrect on Page 124. AIC highlighting is no longer needed for these data.	We have made the requested change and removed AIC highlighting from (Pages 124 and 134).

	Additionally, please note that as these data have now been published, AIC highlighting can now be removed from these data at any point where they occur in the report (Pages 124 and 134).		
Page 140 of the ERG report presents two tornado plots of deterministic sensitivity analysis for ofatumumab versus ocrelizumab in the RRMS population in the Company base case: impact on NMB (Figure 5) and impact on ICER (Figure 6). In Figure 6, given that [redacted], interpretation of the impact on ICER for this analysis is significantly ambiguous and produces a result for disability worsening of ocrelizumab that does not include a lower estimate. This figure contains no information that is not captured in Figure 5.	Please remove Figure 6 (*Tornado plot of deterministic sensitivity analysis: impact on ICER for ofatumumab versus ocrelizumab in the RRMS population, using list price for ocrelizumab and PAS for ofatumumab*) from the ERG report.	This figure is ambiguous and contains no data that is not captured within Figure 5.	The ERG does not agree with this suggestion. Therefore, we have not removed Figure 6.
Page 159 of the ERG report presents two tornado plots of deterministic sensitivity analysis for ofatumumab versus ocrelizumab in the RRMS population in the ERG-preferred bases case: impact on NMB (Figure 9) and impact on ICER (Figure 10). In Figure 9, given that [redacted], interpretation of the impact on ICER for this analysis is significantly ambiguous and produces a result for disability worsening of ocrelizumab that does not include a lower estimate. This	Please remove Figure 10 (*ERG Tornado plot of deterministic sensitivity analysis: impact on NMB results for ofatumumab versus ocrelizumab in the RRMS population, using list price for ocrelizumab and PAS for ofatumumab*) from the ERG report.	This figure is ambiguous and contains no data not captured within Figure 9.	The ERG does not agree with this suggestion. Therefore, we have not removed Figure 10.

figure contains no information that is not captured in Figure 10.			

Issue 3 Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Issue number 4 in Table 1 on Page 12 of the ERG report states: "*The use of full ASCLEPIOS trial results and relevant NMAs were used inform cost–effectiveness estimates for HA RRMS and RES RRMS subgroups*."	Please update this wording to remove typographical errors: "~~*The use of*~~ *Full ASCLEPIOS trial results and relevant NMAs were used* ***to*** *inform cost–effectiveness estimates for HA RRMS and RES RRMS subgroups*	There are two typographical errors.	We have updated the text accordingly.
Page 21 of the ERG report contains a typographical error: *"By making this change, the ERG would expect that that total mean costs and incremental costs to remain unchanged, and there to be a decrease in total QALYs, with the incremental QALYs remaining unchanged."*	This sentence should be corrected to the following: *"By making this change, the ERG would expect* ~~*that that*~~ *total mean costs and incremental costs to remain unchanged, and there to be a decrease in total QALYs, with the incremental QALYs remaining unchanged."*	This is a typographical error.	We have updated the text accordingly.
Page 30 of the ERG report contains a typographical error: *"Annualised cost of ofatumumab at with-PAS price for Year 1: [redacted] and Year 2+: [redacted]."*	This sentence should be corrected to remove the additional punctuation: *"Annualised cost of ofatumumab at with-PAS price for Year 1: [redacted] and Year 2+: [redacted]****."***	This is a typographical error.	We have updated the text accordingly.

Table 3, Page 35 contains a typographical error, where text copied from Table 1, Page 15 of CS Document B has been omitted: *"The population of 'is included in 'For people with RRMS' (see Comparators row above)."*	This sentence should be corrected to include the text from Table 1, Page 15 of CS Document B that has been omitted here: *"The population of 'people who could not tolerate previous treatment' is included in "For people with RRMS" (see Comparators row above)."*	This is a typographical error.	We have updated the text accordingly.
The ERG report misspells *"ASCLEPIOS"* as *"ASCELPIOS"* on Pages 49 and three times on Page 184, as "*ASCLPIOS*" on Page 50, as *"ACLEPIOS"* on Page 56, as *"ASCLEPISO"* on Page 62 and as *"ASCLEPIO"* on Page 184.	These instances of the incorrect spelling of *"ASCLEPIOS"* should be corrected.	This is a typographical error.	We have updated the text accordingly.
Page 53 of the ERG report references Tables 135 and 136 in the CS Appendix L to Pages 535–536 of the appendices document.	These page references should be correct to Pages 540–541.	This is a typographical error.	We have updated the text accordingly.
The ERG report misspells "*RRMS*" as "*RRNS*" in Table 11, Pages 66–69 and as *"RRM"* on Page 191.	These instances of the incorrect spelling of *"RRMS"* should be corrected.	This is a typographical error.	We have updated the text accordingly.
Table 12 on Pages 70–71 of the ERG report misspells "*Rebif*" as "*Rabif*".	"*Rabif*" should be corrected to "*Rebif*".	This is a typographical error.	We have updated the text accordingly.
The ERG report references an incorrect table on Page 80: "*The network for ARR is shown in Figure 19 of the CS (page 84) and the results are presented*	*"Table 17"* should be corrected to *"Table 16".*	This is a typographical error.	We have updated the text accordingly.

in Table 17."			
Page 91 and the caption of Table 69 on Page 157 of the ERG report contain a typographical error, both referring to *"RES MS".* Page 93 of the ERG report contains a typographical error, referring to *"highly active, and rapidly-evolving severe MS populations*." In all cases, *"MS"* should read *"RRMS".*	In all instances, *"MS"* should be corrected to *"RRMS"*.	This is a typographical error.	We have updated the text accordingly.
The ERG report references an incorrect table on Page 106: "*The starting distribution of people in each EDSS level is presented in Table 24*."	*"Table 24"* should be corrected to *"Table 23"*.	This is a typographical error.	We have updated the text accordingly.
Page 114 of the ERG report contains a typographical error: *"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 the ofatumumab used as the reference."*	This sentence should be corrected to the following: *"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 ~~the~~ ofatumumab used as the reference."*	This is a typographical error.	Typographical error corrected.
Page 122 of the ERG report contains a typographical error: *"Across both MS (RRMS and SPMS), the health state values derived from the ASCLEPIOS trials were higher than those obtained from Orme et al., 2007 alone."*	This sentence should be corrected to the following: *"Across both **types of** MS (RRMS and SPMS), the health state values derived from the ASCLEPIOS trials*	This is a typographical error.	We have updated the text accordingly.

	were higher than those obtained from Orme et al., 2007 alone."		
The ERG report misspells *"from"* as *"form"* on Page 123.	*"Form"* should be corrected to *"from"*	This is a typographical error.	We have updated the text accordingly.
The ERG report references an incorrect table on Page 133: "*see the third column of Table 42*."	"*Table 42*" should be correct to "*Table 41*".	This is a typographical error.	We have updated the text accordingly.
Page 136 of the ERG report states: *"The pairwise deterministic results are presented in Table 45 for ofatumumab versus all included parameters for the RRMS population."*	"*Parameters*" should be corrected to "*comparators*".	This is a typographical error.	Typographical error corrected.
Page 139 of the ERG report contains a typographical error: *"Where possible, lower and upper bounds were, according to confidence intervals, reported in the literature."*	The sentence should be corrected to the following: *"Where possible, lower and upper bounds were **used**, according to confidence intervals, reported in the literature."*	This is a typographical error.	Typographical error corrected.
Table 58 on Page 151 of the ERG report contains an unformatted reference "*{#102}*".	The reference list should be updated to produce a formatted reference.	This is a typographical error.	We removed the text accordingly.
The ERG report misspells *"MRI scans"* as *"MRI sans"* in Table 3 on Page 181.	*"Sans"* should be corrected to *"scans"*	This is a typographical error.	We have updated the text accordingly.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **1 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of ASCLEPIOS trial populations	Yes	Novartis considers the ASCLEPIOS trial population to be generalisable to the population who would be eligible for ofatumumab in NHS clinical practice for the following reasons: • The baseline characteristics of the ASCLEPIOS trial population are representative of patients in UK clinical practice. This conclusion is consistent with expert advice provided by MS consultants in an advisory board as well as the clinical advisor to the ERG (Novartis advisory board Data on File,[1] ERG report, page 53). • The trial population for the ASCLEPIOS global studies was well balanced across different geographical regions with patients from Eastern Europe accounting for [redacted]% of participants.[2, 3] In relation to MS trials for other DMTs, this proportion of patients from Eastern Europe is similar, or significantly lower than some.[4-7] • Subgroup data by region provided by Novartis in response to the concerns of the ERG regarding the proportion of Eastern European patients show that the baseline characteristics across all regions are similar with no substantial differences (see Appendix Document, Section 1). • Subgroup analyses on the ASCLEPIOS I & II trial outcomes by region found that point estimates in ARR (by trial) and CDW-3 and CDW-6 (pooled across trials, as pre-specified) favour ofatumumab versus teriflunomide in all regional subgroups and identified no evidence for treatment by subgroup interaction. The treatment effect of ofatumumab versus teriflunomide in regional subgroups differed by trial, with no indication of a consistently larger or smaller effect in the Eastern Europe subgroup than in the Western Europe subgroup, and the region heterogeneity test was consistently non-significant for these outcomes. Together, these results suggest random

		variation is the cause of the observed differences, rather than geographic region being a treatment effect modifier. The results of these subgroup analyses are presented in full in the Appendix Document, Section 1. Therefore, Novartis considers the ASCLEPIOS trial population to be representative of UK patients and has identified no significant effect of geographical region on the treatment effect of ofatumumab versus teriflunomide.
Key issue 2: Trials included in the company network meta-analysis (NMA)	Yes	As discussed in the CS (Document B, Sections B.2.9.2 and B.2.9.3), Boiko et al., 2018a, was excluded from the network as a non-inferiority trial comparing different formulations of the same DMT (two formulations of glatiramer acetate), while Etemadifar et al., 2006, did not directly report ARR.[8, 9] Novartis acknowledges the concerns of the ERG regarding exclusion of these studies from the ARR network. In order to address these concerns, Novartis has performed a scenario analysis in which these two studies and the GOLDEN study (see response to Issue 3) were included in the ARR network (including an estimated ARR for Etemadifar et al., 2006). The results are presented in full in Section 2 of the Appendix Document and are discussed further in response to Issue 3.
Key issue 3: Lack of transparency in the process of selecting studies from systematic literature review (SLR) into the NMA	Yes	The SLR of clinical evidence was performed to identify studies of DMTs in patients with relapsing multiple sclerosis (RMS). The SLR identified 731 publications on 84 unique studies of DMTs in RMS which met the eligibility criteria for inclusion in the SLR (as presented in CS, Appendices Document, Table 8). Of these, 37 trials met the eligibility criteria for inclusion in the NMA (as presented in CS, Document B, Table 28). The BECOME study had a mixed population which comprised 79% patients with RRMS and 21% patients with clinically isolated syndrome (CIS).[10] As per the SLR eligibility criteria, this trial was included in the SLR due to having a mixed population that included more than 70% RMS patients. However, as per the NMA eligibility criteria (CS, Document B, Table 28) which specify exclusion of studies with patients with MS types other than RMS, such as patients with CIS, it was excluded from the NMA as it does not report results for the RRMS population separately. Therefore, Novartis considers the exclusion of the BECOME study from the NMA to be systematic and methodologically consistent with the NMA eligibility criteria presented. More broadly, Novartis considers inclusion of

		CIS patients in the study population to be an appropriate basis for study exclusion from the NMA given that patients with CIS have a significantly distinct disease trajectory as compared with patients with RMS, with many CIS patients never developing MS.[11] The GOLDEN trial was excluded because it was not designed or powered to study comparative treatment effects.[12] Although exclusion of this study is in alignment with the criteria presented in Table 28 of Document B of the CS, which specified exclusion of non-comparative studies, Novartis acknowledges the concerns of the ERG regarding exclusion of this trial from the ARR network. Therefore, Novartis has performed a scenario analysis in which the GOLDEN study is included in the ARR network alongside the two studies also included by the ERG in their scenario analysis for Issue 2. The results of this NMA scenario analysis for the ARR outcome in which Boiko et al., 2018a, Etemadifar et al., 2006, and the GOLDEN study were included are presented in full in Section 2 of the Appendix Document. In alignment with the results produced by the ERG analysis in which the Boiko et al., 2018a, and Etemadifar et al., 2006, studies were included in the ARR network (ERG report, page 19), the differences between the results produced from this NMA scenario and the NMA results presented in the original CS are negligible (see Appendix Document, Section 2, Table 3). Therefore, given the relatively small sample sizes of these three trials and the negligible impact on the ARR rate ratios produced (as acknowledged by the ERG in the ERG report, page 12), the Novartis base case NMA remains unchanged following consideration of this issue. Furthermore, Novartis agrees with the conclusions of the ERG that the impact of considering these results in the economic model would be expected to be very small and that no change to the economic analyses presented is needed (ERG report, pages 12 and 19). As such, Novartis does not present a scenario of the cost-effectiveness analyses in which these NMA results are considered in the economic model given that the minimal changes in some of the ARR rate ratios in this scenario are expected to have a negligible effect on the cost-effectiveness results and would not affect cost-effectiveness conclusions.

Key issue 4: Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS	No	Novartis agrees with the ERG that comparative effectiveness evidence for HA RRMS and RES RRMS is limited and welcomes the conclusion of the ERG in agreeing with Novartis' approach of using full results from the ASCLEPIOS trials to estimate treatment effects (ERG report, page 19). Furthermore, Novartis agrees with the conclusion of the ERG that this approach is unlikely to introduce substantial bias in favour of ofatumumab, and that it is a [redacted] approach for CDW-6 and [redacted] ofatumumab (ERG report, page 87).
Key issue 5: Inclusion of disease management costs associated with treating people with SPMS	No	In the original economic model, disease management costs by EDSS state for people with SPMS were included, but Novartis acknowledges the preference of the ERG for these costs to be SPMS-specific and agrees that the costs derived from TA320 and inflated to the 2018/19 cost year are an appropriate and reasonable source for these (ERG report, last column of Table 41, page 132). Following this feedback, Novartis has updated the Company's preferred base case following technical engagement to include these disease management costs specific to people living with SPMS. As presented in Table 1 of this response document, the effect of using SPMS-specific disease management costs is relatively small and all cost-effectiveness conclusions remain unchanged as compared with the original base case analysis.
Key issue 6: Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis	No	Novartis acknowledges the availability of alternative transition probabilities derived from TA624 and that these probabilities have been used in prior MS appraisals, as noted by the ERG (ERG report, page 20). However, the source employed in the company base case, derived from TA254, has also been previously used and accepted by NICE. The Company Submission for TA624 states that the transition probabilities used in that appraisal were derived from the 2002 Assessment Group report for TA32 (TA624, company submission, page 120). The Company Submission for TA254 states that "*In previous analyses, the London Ontario transition matrices did not include adjustments for active or benign forms of relapsing MS and, as a result, may have under- or over-estimated the cost-effectiveness of DMT treatment. By excluding patients who have less progressive forms of relapsing*

(SPMS)		*MS we have adjusted the natural history transition matrices to fully represent patients who are eligible for DMT treatment*." (TA254, company submission, page 203). Therefore, given that the values from TA254 are from a more recent analysis of the London Ontario dataset undertaken to address specific criticisms of the older analysis, than those in TA624 (which refers to TA32), Novartis does not agree that the transition probabilities suggested by the ERG represent a more reasonable source than those included in the company base case. Noting that the alternative transitions have nonetheless been accepted in other NICE appraisals, Novartis considers them to be a reasonable scenario for consideration alongside the company base case. The economic model has been updated to include an option to use the transition probabilities derived from TA624 in order to conduct this scenario analysis. In this scenario, the effect of using the alternative set of transition probabilities on the ICERs is relatively small. The conclusions of the cost-effectiveness in all populations and versus all comparators are unchanged in this scenario versus the base case analysis.
Key issue 7: Source of annualised relapse rates (ARR)	No	Novartis acknowledges the preference of the ERG to utilise relapse frequency values reported in TA527, particularly given the face validity of these values which show decreasing annual relapse rates as EDSS level increases. Following this feedback, Novartis has updated the Company's preferred base case following technical engagement in line with the preference of the ERG. As presented in Table 1 of this response document, the effect of using these relapse frequency values is relatively small and all cost-effectiveness conclusions remain unchanged as compared with the original base case analysis. This is in alignment with the expectation of the ERG, given that this parameter was not identified to be a key driver of the model (ERG report, page 21).
Key issue 8: Source of health state utility values	Yes	In the original economic model, health state utility values (HSUVs) for RRMS and SPMS by EDSS state were derived from the ASCLEPIOS trials (EDSS states 0–6) and supplemented by values from Orme et al., 2007 (EDSS states 7–9). Novartis has not changed this approach to the modelling of RRMS HSUVs, following agreement of its suitability by the ERG in their report (ERG report, page 122) and in the technical engagement video conference on 11th November 2020, but acknowledges the

		preference of the ERG for the use of SPMS-specific HSUVs for SPMS health states in the model. Novartis considers the SPMS-specific utility values derived from the EXPAND trial supplemented by Orme et al., 2007, to be more appropriate for use than Orme et al., 2007, values alone. The EXPAND trial is the pivotal trial evaluating the efficacy and safety of siponimod in patients with SPMS which provides a recent source of HSUVs for SPMS states EDSS 3–7.[13] The EXPAND trial was the preferred source of HSUVs in the siponimod NICE appraisal, which is the most relevant NICE appraisal of a DMT in SPMS.[14] Although the licence and NICE recommendation for siponimod is specific to people with SPMS with active disease, the EXPAND trial included a broader SPMS population. Novartis considers it most appropriate to use utility values from the broader SPMS population (the intention to treat population of the EXPAND trial) given that in the economic model, these utilities are applied to all patients following progression from RRMS to SPMS, regardless of disease activity. Furthermore, derived from an SPMS population of [redacted] patients, the EXPAND trial represents the largest such utility dataset and is therefore more robust than Orme et al., 2007, in which SPMS-specific HSUVs were derived from the 37.2% of the overall population with data suitable for analysis (approximate population size of 762).[15] The values derived from the EXPAND trial maintain face validity. They consistently decrease with each progressive EDSS state which aligns with clinical expectation of reduced quality of life with increased disability; conversely, in Orme et al., 2007, the HSUV for SPMS state EDSS 3 is lower (0.529) than SPMS state EDSS 4 (0.565), suggesting a better quality of life in more disabled patients. This lack of face validity in the Orme et al., 2007, values was highlighted in the original company submission for this appraisal (Document B, Section B.3.4.1) and by the NICE technical team in the siponimod appraisal. Furthermore, the EXPAND SPMS-specific HSUVs are consistently lower than the utility associated with the same EDSS state in RRMS patients, as derived from the ASCLEPIOS trials (full HSUVs for RRMS patients by EDSS state are presented in the CS, Section B.3.4.1, Table 72) which supports their face validity and aligns with the expectation of the clinical advisor to the ERG (ERG report, page 122). Therefore, in line with the source used for people with SPMS in the siponimod appraisal, Novartis has updated the Company's preferred base case following technical engagement to include SPMS-specific HSUVs from EXPAND and supplemented by Orme et al., 2007. These new data are provided

		in Section 3 of the Appendix Document. As presented in Table 1 of this response document, the use of these SPMS-specific HSUVs does not affect any cost-effectiveness conclusions as compared with the original company base case analysis.
Key issue 9: Inclusion of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)	No	In response to ERG clarification question B18, scenario analyses were presented in which waning of treatment efficacy was considered. As discussed further in that response, an assumption in which effectiveness is modelled to wane in a tapered fashion with a 25% reduction after 5 years and then a 50% reduction after 8 years is conservative given that it applies to all patients in the model who are still on treatment at that point, and assumes treatment continuation despite loss of benefit. Furthermore, waning from Year 5 in this scenario can be considered arbitrary and conservative given that the published long-term data available for ocrelizumab, the DMT with the most similar mechanism of action, shows no evidence of a marked drop in efficacy at 5 years.[16, 17] Novartis does not support the validity of including treatment effect waning in the base case for the following reasons: • As acknowledged by the ERG in their report and in the technical engagement video conference on 11th November 2020, the additional analyses presented in response to ERG clarification question B18 support that there is "no evidence of treatment waning" (ERG report, page 120). • The ERG suggests that inclusion of an assumption of efficacy waning would increase consistency with other recent MS technology appraisals. Novartis highlights that the ocrelizumab appraisal (TA533) represents the most relevant MS appraisal to ofatumumab given the very similar mechanism of action (anti-CD20 monoclonal antibodies).[18] As discussed further in response to clarification question B18, the committee in that appraisal (TA533) concluded that "*rate of stopping treatments could have acted as a proxy to account for treatment waning in the absence of evidence for a waning effect for ocrelizumab*."[18] Therefore, we understand consideration of all-cause discontinuation as a proxy for treatment waning to be the approach most consistent with the most relevant, recent MS NICE appraisal. • Neurologists consulted by Novartis have consistently agreed that should efficacy waning occur in an RRMS patient, the patient would no longer remain on that treatment and, as such, any

		observation of efficacy waning would be captured through discontinuation rates. This supports the validity of using all-cause discontinuation as a proxy for treatment waning. Therefore, Novartis does not support the plausibility of waning scenarios for reimbursement decision making in RRMS given that there is no evidence of efficacy waning and that inclusion of waning on top of all-cause discontinuation would lead to significant double-counting of a potential loss of efficacy.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Novartis has not identified additional issues in the ERG report for consideration.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

<table>
<tr><th>Key issue(s) in the ERG report</th><th>Company's base case before technical engagement</th><th>Change(s) made in response to technical engagement</th><th>Impact on the company's base-case ICER</th></tr>
<tr><td>Issue 5: Inclusion of disease management costs associated with treating people with SPMS</td><td>EDSS state-specific management costs were assumed to be equal for RRMS and SPMS and were derived from UK MS survey costs presented in TA527.</td><td>The base case has been updated to use the SPMS-specific management costs suggested by the ERG in Table 41 of the ERG report (last column), in which costs are derived from TA320 and inflated to the cost year 2018/19.</td><td rowspan="3">Please see Table 1 below.</td></tr>
<tr><td>Issue 7: Source of annualised relapse rates</td><td>ARR sourced from Patzold 1982 and UK MS survey for RRMS, and from EXPAND, Patzold 1982 and UK MS survey for SPMS.</td><td>The base case has been updated to use ARR sourced from TA527 for RRMS and SPMS in line with the preference of the ERG.</td></tr>
<tr><td>Issue 8: Source of health state utility values (HSUVs)</td><td>HSUVs for RRMS and SPMS sourced from ASCLEPIOS trials [EDSS 0–6] and supplemented by Orme et al., 2007 [EDSS 7–9].</td><td>The base case has been updated to use SPMS HSUVs derived from EXPAND [EDSS 3–7] supplemented by values from Orme et al., 2007 [EDSS 0–2, 8–9]. RRMS values remain unchanged from the original base case.</td></tr>
<tr><td>Company's preferred base case following technical engagement</td><td colspan="3">
<table>
<tr><th rowspan="2">Comparator</th><th rowspan="2">Technologies</th><th colspan="2">Incremental costs</th><th colspan="2">Incremental QALYs</th><th colspan="2">ICER (£/QALY)</th></tr>
<tr><th>Updated</th><th>Change v. original</th><th>Updated</th><th>Change v. original</th><th>Updated</th><th>Change v. original</th></tr>
<tr><td colspan="8">All RRMS</td></tr>
<tr><td rowspan="2">Avonex®</td><td>Avonex® (IFN β-1a)</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Ofatumumab</td><td>[redacted]</td><td>[redacted]</td><td>0.55</td><td>−0.01</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="2">Dimethyl fumarate</td><td>Dimethyl fumarate</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Ofatumumab</td><td>[redacted]</td><td>[redacted]</td><td>0.49</td><td>−0.02</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="2">Glatiramer acetate</td><td>Glatiramer acetate</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Ofatumumab</td><td>[redacted]</td><td>[redacted]</td><td>0.72</td><td>−0.02</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
</table>

Ocrelizumab	**Ocrelizumab**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	−0.06	0	[redacted]	[redacted]
Rebif® 44	**Rebif® 44 (IFN β-1a)**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	0.59	−0.02	[redacted]	[redacted]
Teriflunomide	**Teriflunomide**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	0.75	−0.02	[redacted]	[redacted]
HA RRMS							
Alemtuzumab	**Alemtuzumab**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	−0.32	0.01	[redacted]	[redacted]
Cladribine	**Cladribine**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	0.12	0	[redacted]	[redacted]
Fingolimod[b]	**Fingolimod**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	0.5	−0.02	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	−0.06	0	[redacted]	[redacted]
RES RRMS							
Alemtuzumab	**Alemtuzumab**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	−0.36	+0.01	[redacted]	[redacted]
Cladribine	**Cladribine**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	0.11	−0.01	[redacted]	[redacted]
Natalizumab	**Natalizumab**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	−0.05	0	[redacted]	[redacted]
Ocrelizumab	**Ocrelizumab**	-	-	-	-	-	-
	Ofatumumab	[redacted]	[redacted]	−0.06	0	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.
Abbreviations: HA: highly active; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis.

Table 1: Impact on ingoing base case ICERs of each update made in the updated base case

Comparator	Impact on ingoing base case ICER (£/QALY)		
	SPMS management costs (Issue 5)	Source of ARR (Issue 7)	Source of SPMS HSUVs (Issue 8)
All RRMS			
Avonex®	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Rebif® 44	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
HA RRMS			
Alemtuzumab	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod[b]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
RES RRMS			
Alemtuzumab	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]

[redacted]

[b] As a Novartis product, the PAS for fingolimod is known and was taken into account during analyses.
Abbreviations: ARR: annualised relapse rate; HA: highly active; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; RES: rapidly-evolving severe; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

References

1. Novartis (Data on File): Multiple Sclerosis Advisory Board. 2020.
2. Novartis (Data on File): ASCLEPIOS I Clinical Study Report Appendix 16.1.9.
3. Novartis (Data on File): ASCLEPIOS II Clinical Study Report Appendix 16.1.9.
4. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:247-56.
5. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis. New England Journal of Medicine 2011;365:1293-1303.
6. Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014;13:657-65.
7. EMA. Lemtrada (alemtuzumab): European Public Assessment Report. Available at: https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf [Last accessed: 28th February 2020].
8. Boiko AN, Bosenko LP, Vasilovskii VV, et al. A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Interferon β-1a Formulations for S.C. Administration in Patients with Remitting Multiple Sclerosis: First-Year Results. Neuroscience and Behavioral Physiology 2018;48:883-889.
9. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006;113:283-7.
10. Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology 2009;72:1976-83.
11. Novakova L, Skoog B, Runmarker B, et al. Clinically isolated syndromes with no further disease activity suggestive of multiple sclerosis at the age of population life expectancy. Mult Scler 2014;20:496-500.
12. Comi G, Patti F, Rocca MA, et al. Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study). J Neurol 2017;264:2436-2449.
13. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018;391:1263-1273.
14. National Institute for Health and Care Excellence (NICE). Siponimod for treating secondary progressive multiple sclerosis: Technology appraisal guidance [TA656]. Available at: https://www.nice.org.uk/guidance/ta656 [Last accessed: 20th November 2020].
15. Orme M, Kerrigan J, Tyas D, et al. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.
16. Hauser SL, Kappos L, Arnold DL, et al. Five-years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. Neurology 2020.
17. Giovannoni G, Kappos L, Hauser S, et al. Long-term reduction of relapse rate and confirmed disability progression after 6 years of ocrelizumab treatment in patients with relapsing multiple sclerosis. Presented at ECTRIMS, 11-13 September 2019, Stockholm (Sweden). P1015. 2019.

18. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing–remitting multiple sclerosis: Technology appraisal guidance [TA533]. Available at: https://www.nice.org.uk/guidance/ta533 [Last accessed: 20th November 2020].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Company Technical Engagement Response Appendix: Additional supporting data for the technical engagement

December 2020

File name	Version	Contains confidential information	Date
Company Technical Engagement Response Appendix	1	Yes	1st December 2020

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Contents

Tables

Figures

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1. Generalisability of ASCLEPIOS trial populations to NHS practice

Following feedback from the ERG raising a potential concern regarding the generalisability of the patient population in the ASCLEPIOS trials due to the proportion of Eastern European patients, Novartis has conducted subgroup analyses by region for the baseline characteristics (Table 1) and relative efficacy estimates for the annualised relapse rate (ARR) (Figure 1–Figure 3), three month confirmed disability worsening (CDW-3) (Figure 4–Figure 6) and six month confirmed disability worsening (Figure 7–Figure 9). For simplicity of presentation and given the focus of the ERG's comment on the Eastern Europe subgroup, the baseline characteristics are presented for the Eastern Europe, Western Europe and ITT populations only. The baseline characteristics of the two other regional subgroups can be found in the reference pack.[1]

As discussed further in response to Issue 1 in the Technical Engagement Response Form, these data suggest no region-specific variation in baseline characteristics as compared with the overall population, and region was not found to show a significant interaction in efficacy analyses, supporting use of the ITT population data in the appraisal as generalisable to NHS patients.

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Table 1: Baseline characteristics of patients in the Eastern Europe, Western Europe and ITT populations of the ASCLEPIOS trials

Characteristic		Eastern Europe subgroup			Western Europe subgroup			ITT		
		ASCLEPIOS I (N=[redacted])	ASCLEPIOS II (N=[redacted])	Pooled (N=[redacted])	ASCLEPIOS I (N=[redacted])	ASCLEPIOS II (N=[redacted])	Pooled (N=[redacted])	ASCLEPIOS I (N=[redacted])	ASCLEPIOS II (N=[redacted])	Pooled (N=[redacted])
Age (years), mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of MS since first symptom	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previously treated patients, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapses in the 12 months prior to screening, mean (SD)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EDSS	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total volume of T2 lesions	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	cm^3, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients free of Gd-enhancing T1 lesions, n (%)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gd-enhancing T1 lesions	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Number, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Randomisation was stratified by six regions, of which three (Asian Pacific, Latin America, and Others) were combined for statistical analyses due to the small number of patients and events, resulting in four regional subgroups.[2, 3] For simplicity of presentation, data are presented for the two European regions and ITT population only. The baseline characteristics of the two other regional subgroups (North America and Australia; Others) can be found in the reference pack.[1]

Abbreviations: EDSS: Expanded Disability Status Scale; Gd: gadolinium; ITT: intention-to-treat population; MS: multiple sclerosis; N: number of patients in full analysis set; n: number of patients with non-missing values; SD: standard deviation.

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Figure 1: ARR forest plot by subgroup based on region (ASCLEPIOS I and II, pooled)

[1] Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for study, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for the subgroup analysis. The natural log of the time-in-study was used as offset to annualise the relapse rate.
* Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: ARR: annualised relapse rates; OMB: ofatumumab; TER: teriflunomide; N: Total number of patients included in the analysis.

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Figure 2: ARR forest plot by subgroup based on region (ASCLEPIOS I)

[1] Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for study, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for the subgroup analysis. The natural log of the time-in-study was used as offset to annualise the relapse rate. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: ARR: annualised relapse rates; OMB: ofatumumab; TER: teriflunomide; N: Total number of patients included in the analysis.

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Figure 3: ARR forest plot by subgroup based on region (ASCLEPIOS II)

[1] Obtained from fitting a negative binomial regression model with log-link to the number of relapses, adjusted for study, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for the subgroup analysis. The natural log of the time-in-study was used as offset to annualise the relapse rate. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: ARR: annualised relapse rates; OMB: ofatumumab; TER: teriflunomide; N: Total number of patients included in the analysis.

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Figure 4: Time to CDW-3 forest plot by subgroup based on region (ASCLEPIOS I and II, pooled)

[1] Using a Cox regression with study as stratum, and treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: CDW-3: 3-month confirmed disability worsening; KM: Kaplan-Meier; n: Total number of events included in the analysis; N: Total number of patients included in the analysis; OMB: ofatumumab; TER: teriflunomide.

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Figure 5: Time to CDW-3 forest plot by subgroup based on region (ASCLEPIOS I)

[1] Using a Cox regression with study as stratum, and treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: CDW-3: 3-month confirmed disability worsening; KM: Kaplan-Meier; n: Total number of events included in the analysis; N: Total number of patients included in the analysis; OMB: ofatumumab; TER: teriflunomide.

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Figure 6: Time to CDW-3 forest plot by subgroup based on region (ASCLEPIOS II)

[1] Using a Cox regression with study as stratum, and treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: CDW-3: 3-month confirmed disability worsening; KM: Kaplan-Meier; n: Total number of events included in the analysis; N: Total number of patients included in the analysis; OMB: ofatumumab; TER: teriflunomide.

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Figure 7: Time to CDW-6 forest plot by subgroup based on region (ASCLEPIOS I and II, pooled)

[1] Using a Cox regression with study as stratum, and treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: CDW-6: 6-month confirmed disability worsening; KM: Kaplan-Meier; n: Total number of events included in the analysis; N: Total number of patients included in the analysis; OMB: ofatumumab; TER: teriflunomide.

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Figure 8: Time to CDW-6 forest plot by subgroup based on region (ASCLEPIOS I)

[1] Using a Cox regression with treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: CDW-6: 6-month confirmed disability worsening; KM: Kaplan-Meier; n: Total number of events included in the analysis; N: Total number of patients included in the analysis; OMB: ofatumumab; TER: teriflunomide.

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Figure 9: Time to CDW-6 forest plot by subgroup based on region (ASCLEPIOS II)

[1] Using a Cox regression with treatment as factor for the overall analysis, with additional co-factors of subgroup, and treatment by subgroup interaction for the subgroup analysis. * Indicates statistical significance (2-sided) at the 0.05 level. [a] P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).
Abbreviations: CDW-6: 6-month confirmed disability worsening; KM: Kaplan-Meier; n: Total number of events included in the analysis; N: Total number of patients included in the analysis; OMB: ofatumumab; TER: teriflunomide.

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2. Trials included in the company NMA

To address uncertainty identified by the ERG in Issues 2 and 3 regarding the trials selected for inclusion in the ARR network, Novartis performed a scenario analysis in which Boiko et al., 2018a, Etemadifar et al., 2006, and the GOLDEN trial were included in the ARR network.

The relative effectiveness of ofatumumab at reducing ARR versus other DMTs and placebo in this scenario is summarised in the league table in Figure 10. The forest plot in Figure 11 summarises the relative rate ratio (RR) of the DMTs versus placebo, and mean surface under the cumulative ranking curve (SUCRA) scores are presented in Table 2. A summary of the ARR rate ratios for the base case NMA and new scenario NMA is presented in Table 3.

In alignment with the original submission, the results of this scenario analysis identified ofatumumab to be the [redacted].
The inclusion of the three additional trials had a negligible impact on the estimates of relative efficacy as compared with the base case analysis.

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Figure 10: ARR league table in scenario including Boiko et al., 2018a, Etemadifar et al., 2006, and the GOLDEN study

All values displayed as rate ratio for all comparisons (95% credible interval). Pink denotes comparisons that exclude unity.
Abbreviations: ALEM: alemtuzumab IV 12 mg; BID: twice a day; CLAD 3.5: cladribine PO 3.5 mg/kg; DMF: dimethyl fumarate PO 240 mg BID; FIN: fingolimod PO 0.5 mg QD; GA 20: glatiramer acetate SC 20 mg QD; 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 14: teriflunomide PO 14 mg QD; TIW: three times a week.

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Figure 11: ARR forest plot in scenario including Boiko et al., 2018a, Etemadifar et al., 2006, and the GOLDEN study

All rate ratios are versus placebo.
Abbreviations: ARR: annualised relapse rate; DMT: disease-modifying therapy; IFNB-1a: interferon β-1a; IFNB-1a: interferon β-1b; IM: intramuscular; SC: subcutaneous.

Table 2: ARR SUCRA and P-Best in scenario including Boiko et al., 2018a, Etemadifar et al., 2006, and the GOLDEN study

Treatment	Mean SUCRA (%)	Mean P-Best (%)	Trial Name(s)
Alemtuzumab IV 12 mg	[redacted]	[redacted]	CAMMS223; CARE-MS I; CARE-MS II
Cladribine PO 3.5 mg/kg	[redacted]	[redacted]	CLARITY
Dimethyl fumarate PO 240 mg BID	[redacted]	[redacted]	CONFIRM; DEFINE
Fingolimod PO 0.5 mg QD	[redacted]	[redacted]	ASSESS; FREEDOMS; FREEDOMS II; *GOLDEN*; TRANSFORMS
Glatiramer acetate SC 20 mg QD	[redacted]	[redacted]	ASSESS; BEYOND; *Boiko et al. (2018a)*; Bornstein et al. (1987); Calabrese et al. (2012); CombiRx; CONFIRM; Copolymer 1 MS trial; REGARD
IFN β-1a IM 30 µg QW	[redacted]	[redacted]	BRAVO; Calabrese et al. (2012); CombiRx; *Etemadifar et al. (2006)*; EVIDENCE; MSCRG; Stepien et al. (2013); TRANSFORMS
IFN β-1a SC 22 µg TIW	[redacted]	[redacted]	PRISMS
IFN β-1a SC 44 µg TIW	[redacted]	[redacted]	Calabrese et al. (2012); CAMMS223; CARE-MS I; CARE-MS II; *Etemadifar et al. (2006)*; EVIDENCE; OPERA I; OPERA II; PRISMS; REGARD; TENERE
IFN β-1b SC 250 µg Q2D	[redacted]	[redacted]	BEYOND; *Etemadifar et al. (2006); GOLDEN;* IFNB MS; Stepien et al. (2013)

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Treatment	Mean SUCRA (%)	Mean P-Best (%)	Trial Name(s)
Natalizumab IV 300 mg Q4W	[redacted]	[redacted]	AFFIRM
Ocrelizumab IV 600 mg	[redacted]	[redacted]	OPERA I; OPERA II
Ofatumumab SC 20 mg Q4W	[redacted]	[redacted]	ASCLEPIOS I; ASCLEPIOS II
Teriflunomide PO 14 mg QD	[redacted]	[redacted]	ASCLEPIOS I; ASCLEPIOS II; TEMSO; TENERE; TOWER
Placebo	[redacted]	[redacted]	ADVANCE; AFFIRM; *Boiko et al. (2018a);* Bornstein et al. (1987); BRAVO; CLARITY; CONFIRM; Copolymer 1 MS trial; DEFINE; FREEDOMS; FREEDOMS II; GALA; IFNB MS; MSCRG; PRISMS; TEMSO; TOWER

Abbreviations: ARR: annualised relapse rate; BID: twice a day; IFNB: interferon beta; IM: intramuscular; IV: intravenous; P-Best: probability of being best; PO: oral; Q2D: every other day; Q4W: once every four weeks; QD: once a day; QW: once a week; SC: subcutaneous; SUCRA: surface under the cumulative ranking curve; TIW: three times a week.

Table 3: ARR rate ratios for base case and scenario analysis including Boiko et al., 2018a, Etemadifar et al., 2006, and the GOLDEN study

Treatment	ARR (RR, 95% CrI)	
	Base case	Scenario
Alemtuzumab	[redacted]	[redacted]
Cladribine 3.5 mg/kg	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]
IFN β-1a (Avonex®) SC 22 µg	[redacted]	[redacted]
IFN β-1a (Avonex®) SC 44 µg	[redacted]	[redacted]
IFN β-1a IM	[redacted]	[redacted]
IFN β-1b (Rebif®) SC	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]

All rate ratios are versus placebo.
Abbreviations: ARR: annualised relapse rate; CrI: credible interval; IFNB-1a: interferon β-1a; IFNB-1a: interferon β-1b; IM: intramuscular; RR: rate ratio; SC: subcutaneous.

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3. Source of SPMS health state utility values

In the original submitted model, health state utility values (HSUVs) for RRMS and SPMS were derived from the ITT population of the pooled ASCLEPIOS I and II trials (EDSS 0–6) and supplemented by values from Orme et al., 2007.[4]

Novartis maintains this approach for modelling RRMS HSUVs but acknowledges the preference of the ERG to implement SPMS-specific HSUVs in the model and for these to be derived from Orme et al., 2007. However, as discussed further in response to Issue 8 in the Technical Engagement Response Form, Novartis consider SPMS-specific HSUVs derived from the intention to treat (ITT) population of EXPAND, the pivotal trial on the efficacy and safety of siponimod in people with SPMS, to be the most appropriate source of HSUVs for SPMS states EDSS 3–7:[5]

- The ITT population of the EXPAND trial represents the largest, most recent and therefore more robust SPMS utility dataset among options available: utilities in EXPAND were derived from [redacted] people with SPMS as compared with derivation from an approximate population size of 762 in Orme et al., 2006.[12] Derivation of values from the broader EXPAND ITT population, rather than from people with SPMS with active disease, is appropriate given that these utilities are applied to all patients in the economic model following transition from RRMS to SPMS regardless of disease activity.
- These values maintain face validity with increasing disability consistently associated with decreased utility, unlike values from Orme et al., 2007, and with consistently lower utility associated with SPMS than RRMS in each EDSS state.

Novartis has updated their preferred base case to include SPMS-specific HSUVs from EXPAND (SPMS states EDSS 3–7) supplemented by values from Orme et al., 2007 (SPMS states EDSS 0–2 and 8–9). The HSUVs implemented in the original company base case and the updated base case are presented in Table 4 alongside the HSUVs suggested for use by the ERG, for completeness.

Table 4: SPMS health state utility values employed in the original and updated base case

EDSS	Original base case: ASCLEPIOS and Orme et al., 2007		ERG-preferred values: Orme et al., 2007		Updated base case: EXPAND and Orme et al., 2007	
	Utility	SE	Utility	SE	Utility	SE
0	[redacted]	[redacted]	0.8250	0.0607	0.8250	0.0607
1	[redacted]	[redacted]	0.7540	0.1087	0.7540	0.1087
2	[redacted]	[redacted]	0.6600	0.1084	0.6600	0.1084
3	[redacted]	[redacted]	0.5290	0.1125	[redacted]	[redacted]
4	[redacted]	[redacted]	0.5650	0.1084	[redacted]	[redacted]
5	[redacted]	[redacted]	0.4730	0.1077	[redacted]	[redacted]
6	[redacted]	[redacted]	0.4130	0.1082	[redacted]	[redacted]
7	0.2520	0.0941	0.2520	0.1100	[redacted]	[redacted]
8	−0.0940	0.0952	−0.0940	0.1110	−0.0940	0.1110
9	−0.2400	0.1191	−0.2400	0.1350	−0.2400	0.1350

Abbreviations: EDSS: Extended Disability Status Score; ERG: Evidence Review Group; ITT: intention-to-treat population; SE: standard error.

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References

1. Novartis (Data on File): Regional Subgroup Data.
2. Novartis (Data on File): ASCLEPIOS I Clinical Study Report Appendix 16.1.9.
3. Novartis (Data on File): ASCLEPIOS II Clinical Study Report Appendix 16.1.9.
4. Orme M, Kerrigan J, Tyas D, et al. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.
5. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018;391:1263-1273.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ofatumumab for treating relapsing multiple sclerosis (ID1677)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **1 December 2020.**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with multiple sclerosis and current treatment options	
About you	
1.Your name	**Emma Meadows**
2. Are you (please tick all that apply):	☒ a patient with multiple sclerosis? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with multiple sclerosis? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	MS Trust
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with multiple sclerosis? If you are a carer (for someone with multiple sclerosis) please share your experience of caring for them.	Multiple Sclerosis can be an unpredictable condition which I have at times found to be challenging and has on occasions made me feel very vulnerable. I have invisible symptoms which means that others do not necessarily understand the impact of the condition on my everyday life and when I have tried to explain my symptoms to others, many people find it hard to relate to them as they are so different to their usual experiences. Due to the unpredictable nature of MS, it can be difficult to plan too far ahead as its impossible to know how you may be feeling or what you may be experiencing on any given day.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for multiple sclerosis on the NHS?	My experience has been positive – I am looked after by a dedicated MS nurse specialist team and have appointments with a member of the team every six months. I am also aware that I could have potentially chosen any of the current treatments available as the hospital makes them all available to you, though I did choose to do the ASCLEPIOS II trial. I am aware the treatments come in a variety

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	of forms – injections, tablets and infusions. I haven't discussed treatment options with many other MS sufferers to have gained their views on the current treatments, though I do know someone who also had various treatment options made available to her and she considered several avenues before making her choice.
8. If there are disadvantages for patients of **current NHS treatments** for multiple sclerosis (for example how ofatumumab is given or taken, side effects of treatment etc) please describe these	It may be difficult for people to carry out their own injections depending on the individual's dexterity and frequency of injections. It may also be time-consuming and inconvenient to have to visit the hospital every four weeks for an infusion as this would probably mean taking time off work. Some people may also struggle to remember to take tablets at the same time/s every day. Due to Covid, routine appointments have taken place virtually, but some treatments have to be administered at the hospital, mainly infusions. A treatment that can be taken at home would be more advantageous at this time under the current circumstances.
Advantages of this treatment	
9a. If there are advantages of ofatumumab over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	While Ofatumumab is still a subcutaneous injection, you are only required to inject once every four weeks and this is done at home. This means that, in between those times, I have been able to carry on working and carrying out other activities without having to remember to take a daily treatment or having to visit the hospital for treatment. I can plan my holidays and any other events around it easily so I don't need to take my treatment in a cooler box with me, as there is a leeway of a couple days either side of the due date to deliver the injection. In between treatments (which takes only a few seconds at a time) I can just carry on with life as normal as the treatment has been effective and delivering the treatment is not burdensome. Life very much carries on as normal in between, which is a great advantage to me. I think the fact you can carry on as normal, only having to make very minimal allowance to deliver the drug at the right time every month at home, is the greatest

9c. Does ofatumumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	advantage. Ofatumumab has the advantage of being delivered at home by the patient – given the current circumstances, visits to hospitals have been greatly reduced due to the risks and this treatment removes the need to visit hospitals for treatment. This gives the patient more of their own time back and causes less inconvenience to them. As ofatumumab only needs to be administered once a month, fewer injections need to be kept by the patient and stored as required, i.e. in the fridge.
Disadvantages of this treatment	
10. If there are disadvantages of ofatumumab over current treatments on the NHS please describe these? For example, are there any risks with ofatumumab? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	As part of both the ASCLEPIOS II trial and the current extension study, I was provided with a list of the side effects noted in Ofatumumab alongside how common or uncommon they may have been. I personally have not experienced any side effects caused by the drug itself and I was not overly concerned by the potential side effects that featured in the list, as I am aware that all drugs, including all MS treatments, carry risks. I would have felt it was riskier to not take any treatment at all in my case as I didn't want to continue experiencing relapses or worrying that the next one may just be round the corner. In my personal experience, I have not found this drug to be a disadvantage as it is very convenient; I have not experienced any relapses since I started using it in April 2017, nor have I experienced any side effects that I have noted.
Patient population	
11. Are there any groups of patients who might benefit more from ofatumumab or any who may benefit less? If so, please describe them and explain why.	Ofatumumab would probably be quite good for people who have busy, demanding jobs, family commitments and lifestyles as it is easy to set a reminder to administer the injection once a month and plan to just take a very small amount of time to deliver it. It would also help those who struggle to attend at the hospital every month due to their mobility/condition or logistics around travel, work, family etc. In my opinion, being able to deliver the treatment at home would assist a lot of MS sufferers to carry on as normal.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The only people I think who may not benefit are those who would already have struggled with the idea of injections (perhaps due to phobia), whether self-administered or not, or have difficulties with the delivery of injections due to dexterity or other causes.
Equality	
12. Are there any potential equality issues that should be taken into account when considering multiple sclerosis and ofatumumab? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition?	I am aware that the ASCLEPIOS II trial compared ofatumumab against teriflunomide, a licensed MS treatment.
14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition?	From personal experience, a lot of the tests seemed to be relevant to fairly standard neurological assessments, particularly related to rating disability, where the EDSS is used.
14c. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	Allows you to carry on with your life as normal in between treatments. Can be administered in the comfort of your own home – no need for extra hospital visits. Only needs to be taken once every four weeks. Treatment can be administered quickly, it only takes seconds to do.
d. What are the benefits of this treatment for carers?	The fact it can be administered at home without hospital visits means that patient and carer do not need to visit the hospital frequently, which is far more convenient and again allows people to carry on as normal as much as possible. The frequency of the treatment would also be helpful for carers, especially if they were to administer it for the patient.

15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Taking ofatumumab as my MS treatment has allowed me to carry on with my life as normal as far as possible.
- The frequency of administering the injection is incredibly convenient, I can easily plan my life around it.
- Administering the treatment at home is quick and easy and means a reduction in hospital visits for patients.
- Ofatumumab would offer a suitable alternative treatment option which isn't already available – there are injections available and monthly treatments to treat MS, but the current injections are more frequent and the monthly treatments generally involve hospital visits. In my opinion this treatment offers a good alternative, a middle ground between the options already available.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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……

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **1 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Multiple Sclerosis Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of ASCLEPIOS trial populations	**NO**	**Yes, we believe so. We note that for ASCLEPIOS I and II, 1882 participants were recruited from 385 sites in 37 countries in Europe and Northern America. Of these, 120 were recruited from the United States, representing the largest national subgroup. The majority of the remaining participants were recruited from Europe. Given that all participants met the inclusion criteria we do not believe that this population would have a different course of relapsing remitting MS compared to those seen in NHS practice.**
Key issue 2: Trials included in the company network meta-analysis (NMA)	**NO**	**ERG acknowledges that including these two missing studies will have minimal effect on cost-effectiveness estimates as trials concerned had relatively small sample sizes (p18 ERG report).**
Key issue 3: Lack of transparency in the process of selecting studies from systematic literature review (SLR) into the NMA	**NO**	**No comment.**
Key issue 4: Paucity of evidence for comparative effectiveness of treatments for	**NO**	**The ERG and committee expressed similar reservations for the ocrelizumab appraisal [TA533]. The committee concluded that, although there was a lot of**

Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS		**uncertainty in the clinical-effectiveness data, the ICERs generated by the economic model for treating highly active and rapidly evolving severe multiple sclerosis represented a cost-effective use of NHS resources. We are unable to comment further as ICERs have been redacted in the ofatumumab ERG report.**
Key issue 5: Inclusion of disease management costs associated with treating people with SPMS	**NO**	**For consistency, we would agree that the same source of costs should be used in this appraisal as was used in the ocrelizumab appraisal [TA533], the most relevant recent MS appraisal addressing a similar decision problem.**
Key issue 6: Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis (SPMS)	**NO**	**For consistency, we would propose using the same transition probabilities as used for the ocrelizumab appraisal [TA533].**
Key issue 7: Source of annualised relapse rates (ARR)	**NO**	**For consistency, we would propose using the same approach to determining ARR as used for the ocrelizumab appraisal [TA533].**
Key issue 8: Source of health state utility values	**NO**	**Again, as far as possible, the same approach to source health state utility values used for the ocrelizumab appraisal should also be used for ofatumumab.**
Key issue 9: Inclusion of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)	**NO**	**Ofatumumab is a fully human antibody; data in the company submission are not available in the redacted version (p107 of company submission) but overall incidence of anti-drug antibodies is described as low in both ASCLEPIOS trials. Consequently long-term treatment waning due to formation of neutralising antibodies is considered unlikely with ofatumumab.**

		There is no clinical evidence to support the ERG's preferred waning of 25% after 5 years, then 50% after 8 years. We would propose that treatment discontinuation is used as a proxy for treatment waning as for ocrelizumab appraisal [TA533].

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Clinical expert statement & technical engagement response form

Ofatumumab for treating relapsing multiple sclerosis (ID1677)

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved, or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **1 December 2020**

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Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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PART 1 – Treating a patient with multiple sclerosis and current treatment options	
About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**
3. Job title or position	**Consultant Neurologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	☒ yes

submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment with ofatumumab is to reduce the relapse rate in relapsing forms of multiple sclerosis (MS). The primary end point in the two phase 3 randomised controlled trials of ofatumumab versus teriflunomide (ASCLEPIOS I and ASCLEPIOS II) was the annualised relapse rate. Secondary endpoints included time to disability progression confirmed at three and six months respectively, confirmed disability improvement at 6 months, gadolinium enhancing T1 lesions, number of new or enlarging T2 lesions, serum levels of neurofilament light chain (NfL), and rate of brain volume loss By reducing the number of relapses the treatment aims to reduce the accumulation of disability due to MS. This is referred to as disability progression in the clinical trials.
9. What do you consider a clinically significant treatment response? (For example, a	A clinically significant reduction in relapse rate for a treatment in MS would be a minimum reduction in relapses by a third compared to placebo. This is the efficacy of the least effective currently licensed treatments for relapsing MS. A higher reduction in relapse rate with an active comparator, e.g. licensed first line treatments such as

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	teriflunomide, would be expected in new treatments for MS. In the ofatumumab trials there was a greater than 50% reduction in relapse rate when compared to an active comparator.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need for people with relapsing MS to have access to effective treatments with a better safety profile than some of the currently approved treatments. There is also a need for treatments which have less impact on people living with MS in terms of frequency of treatment, intensity of monitoring and hospital attendances
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Relapsing forms of MS are treated with licensed disease modifying treatments (DMTs) approved for use in the NHS using the NHSE Algorithm (Date published: 04 September 2018; Updated 8 March 2019).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHSE Algorithm NICE TAs for natalizumab TA127, fingolimod TA254, teriflunomide TA 303, alemtuzumab TA312, dimethyl fumarate TA320, beta interferons and glatiramer acetate TA527, ocrelizumab TA533, cladribine TA 616, peginterferon beta-1a TA624 ABN/NICE – joint summary of treatment options for relapsing–remitting multiple sclerosis (2019) - attached
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	A NHSE algorithm has been developed for prescribing DMTs in relapsing MS (RMS). The NHSE algorithm allows for different DMT choices for different disease definitions and at different time points in the evolution of RMS. The choice of DMT is a shared decision making process between the professionals and the person with MS and takes into account the individual's life situation and priorities eg reproductive issues. The use of high

from outside England.)	efficacy DMTs has to be approved by the multidisciplinary team. There is variation in prescribing across the UK as evidenced by the prescribing data in the Bluteq system
• What impact would the technology have on the current pathway of care?	Ofatumumab is a fully humanised antiCD20 drug given by subcutaneous injection on a monthly basis at home. This avoids the need for attendance at an infusion centre / day-case unit in a hospital setting. This may be of particular relevance in the context of the Covid-19 pandemic and any subsequent local lockdowns or further waves of Covid-19. It will require MS Specialist nurse support for training on self-injection. This training is delivered for other MS DMTs for example interferons and glatiramer acetate
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in MS treatment centres with MS specialist neurologists and MS specialist nurses. Injectable treatments for MS are already used in clinical practice. MS nurses are skilled in training people with MS to safely self-inject DMTs.
• How does healthcare resource use differ between the technology and current care?	There will be no requirement for day-case/infusion unit admissions compared to ocrelizumab 6 monthly admissions, natalizumab.4-6 weekly admissions, alemtuzumab 5 days Year 1 and 3 days Year 2 admissions. MS Specialist Nurse time will be required for training patients in self-injection. This training is already delivered for interferons and glatiramer acetate
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment will be prescribed by MS specialist neurologists and will be delivered by subcutaneous self-injection at home

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be no requirement for day-case/infusion unit admissions compared to ocrelizumab 6 monthly admissions, natalizumab.4-6 weekly admissions, alemtuzumab 5 days Year 1 and 3 days Year 2 admissions. MS Specialist Nurse time will be required for training patients in self-injection. This training is already delivered for interferons and glatiramer acetate.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Although there are other DMTs with similar efficacy available, this is the only high efficacy monoclonal antibody DMT which does not require hospital admission for administration.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	There may be an increase in quality of life compared to other less effective DMTs.eg the comparator drug teriflunomide was less effective in the RCTs. Monthly subcutaneous injections are less burdensome than some of the other DMTs for example daily injections or tablets or monthly infusions in a hospital setting. This may have less adverse impact on employment and time away from work for people with MS and less impact on home life and any caring responsibilities.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general	The technology would be more appropriate for confirmed relapsing remitting MS and so-called active MS or rapidly evolving severe MS. These categories of RRMS have now been superceded by the joint ABN/NICE summary of treatment options for relapsing remitting MS (Categories 1-4)

population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Ofatumumab is delivered by monthly subcutaneous injection. This will be easier to deliver than the infusion treatments for MS as it can be given at home by self-injection. This avoids the need for attendance at hospitals or day case infusion units. This may be particularly relevant in the context of Covid-19. In some NHS hospitals infusions for people with MS were significantly delayed and infusion units were closed or re-purposed. This had unintended adverse consequences for PwMS Some PwMS may prefer a monthly treatment rather than more frequent injectable treatments on alternate days or 3 times weekly or daily oral treatments.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are defined starting, stopping or switching criteria for all DMTs in MS. These would apply to this technology which would be included in the NHSE Treatment Algorithm for MS DMTs.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The impact of reduced relapse rate on continued employment for people with MS should be considered. The short-term impact in terms of convenience and reduced time off work to attend hospital for either treatment or monitoring should also be considered.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is innovative in its mode of delivery as a subcutaneous injection. Ocrelizumab which is a licensed anti-CD20 monoclonal antibody is delivered by 6 monthly infusions. B cell repopulation after treatment with ofatumumab is reported to be more rapid than following treatment with ocrelizumab. The median time to B cells repletion to the lower limit of normal (LLN) with ofatumumab is predicted to be 40 weeks in comparison with a median repletion time of 72 weeks with ocrelizumab. This may be a significant advantage if there are further waves of Covid-19 or localised Covid-19 outbreaks and for the efficacy of future vaccines. The faster repletion of the B cell repopulation may also allow more women of child-bearing age to access anti-CD20 therapy. Currently in the UK women with MS are advised to use contraception for 12 months after the last infusion with ocrelizumab. The current recommendation for ofatumumab is for the use of effective contraception for 6 months after treatment (**KESIMPTA®**

• Is the technology a 'step-change' in the management of the condition?	The technology has similar efficacy to other approved treatments
• Does the use of the technology address any particular unmet need of the patient population?	More flexible high efficacy treatment delivered in -the home setting. There is an unmet need for people with MS to have access to a new effective treatment without a high risk of PML or autoimmune conditions.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse events which occurred in >10% of participants treated with ofatumumab were injection-related reactions, nasopharyngitis, headache, injection-site reaction, upper respiratory tract infection and urinary tract infection. The infection rates were similar in the teriflunomide treated participants. Appendicitis was reported in 8 ofatumumab participants and 2 teriflunomide participants Injection related systemic reactions were more common in the ofatumumab group particularly with the first injection. There were no reported episodes of anaphylaxis. In the Asclepios trials the first 4 injections were supervised at the trial site: Days 1,7,14 and Month1. This would require MS Specialist Nurse supervision on 4 occasions/patient in a hospital/outpatient department setting.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The ASCLEPIOS I and II studies (NCT02792218 and NCT02792231) were identical design, flexible duration (up to 30 months), double-blind, randomized, multi-centre Phase III studies evaluating the safety and efficacy of ofatumumab 20mg monthly subcutaneous injections versus teriflunomide (Aubagio®) 14mg

	oral tablets taken once daily in adults with a confirmed diagnosis of RMS. The studies enrolled 1,882 patients with MS, between the ages of 18 and 55 years, with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5 The trial population is similar to that of other licensed DMTs in MS. In clinical practice patients with EDSS up to 6.5 are eligible to start treatment. The population in these trials was limited to those up to EDSS 5.5. The age range is restricted to adults under 55 years.
• If not, how could the results be extrapolated to the UK setting?	In the UK setting PwMS up to EDSS 6.5 are currently treated with other licensed DMTs, and there is no restriction on upper age limit.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Annualised relapse rate was the primary end point which is the most important clinical outcome in relapsing MS. Reduction in sustained disability progression is less meaningful at 3 months. In these trials it was measured at 3 and 6 months. Confirmed disability improvement was also measured at 6 months which is a useful additional clinical outcome.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MRI surrogate outcome measures were appropriate including gadolinium enhancing T1 lesions, number of new or enlarging T2 lesions, and rate of brain volume loss. These measures are representative of the surrogate outcomes used in other trials of MS DMTs. Serum levels of neurofilament light chain (NfL) were also measured. The implications for long-term clinical outcomes are less well-established.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The FDA issued black box warnings (26/09/2013) for rituximab and ofatumumab for 'the potential to cause reactivation of hepatitis B virus (HBV) as well as fulminant and fatal HBV infection in HBV carriers who have not had any prior instances of HBV virus activation'. Ofatumumab was used in refractory cases of chronic lymphocytic leukaemia (CLL) There was a case report in 2014 of a progressive multifocal leukoencephalopathy (PML) death associated with ofatumumab. treatment for chronic leukaemia: Progressive Multifocal Leukoencephalopathy Associated with Ofatumumab presenting as Alexia without Agraphia: A Case Report (P4.319) Jose Avila, Jennifer Han, Islam Zaydan Neurology Apr 2014, 82 (10 Supplement) P4.319 A FDA black box warning was issued for ofatumumab for Progressive multifocal leukoencephalopathy

	(PML) resulting in death.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA616	No
23. How do data on real-world experience compare with the trial data?	There is no real-world experience available yet.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Equitable access to MS Specialist Neurologists, MS Specialist Nurses and Neuro-pharmacists across different regions of England to deliver this treatment.
24b. Consider whether these issues are different from issues with current care and why.	These issues are applicable to delivery of all DMTs and lack of access to comprehensive MS Specialist services in the NHS results in health inequalities for people with MS.
Topic-specific questions	

Is ofatumumab considered an appropriate treatment in the NHS for people with active secondary progressive multiple sclerosis (SPMS) as well as for people with relapsing remitting multiple sclerosis (RRMS)? Are people with highly active (HA) RRMS and people with rapidly evolving severe (RES) RRMS considered appropriate subgroups in which to classify people receiving treatment with ofatumumab or is ofatumumab considered to be suitable for people with both active symptoms of multiple sclerosis as well as those who are in a remitting state?	Asclepios I and Asclepios II only included a very small population of people with secondary progressive MS; 93.9% and 94.9% respectively had RRMS. The current evidence base is thus in the RRMS population and this would be the most appropriate treatment population in the NHS. Siponimod has now been approved by NICE (FAD 18/11/2020) for active secondary progressive MS. This would now need to be a comparator for ofatumumab in any analysis of the SPMS population. As outlined above the ABN and NICE have jointly developed a new categorisation of treatment options for relapsing-remitting MS. The definitions of highly active (HA) and rapidly evolving severe (RES) RRMS have been derived from previous NICE TAs and these definitions are not routinely used in clinical practice. We would recommend using the new categorisation (attached) when considering the appropriate population of people with MS to receive treatment with MS. Both the ‘highly active’ population with failure of first line treatment and the ‘RES’ population are represented in the categories and would be appropriate populations for ofatumumab treatment.

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PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key Issue 1: Generalisability of ASCLEPIOS trials (the focus for company discussion)	The ABN does not have any specific concerns about the sites involved in the ASCLEPIOS trials or differences in the health care systems of different sites. Ofatumumab is a self-administered treatment delivered at home. The participants in both trials were similar to the populations of other RRMS Phase III studies.
Key Issue 2: Trials included in the company network meta-analysis (NMA)	Reasonable criteria for selection of the trials included in the NMS. Agree that trials included should be of at least 48 weeks duration. We're not aware of the exclusion of any relevant trials.
Key Issue 3: Lack of transparency in the process of selecting studies	37 trials were selected for the NMA. We note that 30 trials were selected for the NMA in the Ocrelizumab TA process.

from systematic literature review (SLR) into the NMA	
Key Issue 4: Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS	See above for comments on these categories. We agree that there is a paucity of comparative trials of high efficacy treatments. The trials have in general been designed with lower efficacy comparators to show superiority.
Key Issue 5: Inclusion of disease management costs associated with treating people with SPMS	See above comments about the small population of SPMS in the ASCLEPIOS I and II trials.
Key Issue 6: Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis	Previous epidemiological evidence suggested 50% transition to SPMS within 10 years of diagnosis of RRMS with 80-90% within 25 years. More recent real world evidence from the MS BASE group suggests a lower rate of transition. This was in a population with 85% treated with DMTs and a transition rate to SPMS of only 10%. Identifying transition can be difficult with no clear diagnostic criteria. The diagnosis of SPMS may also be delayed due to the restrictions on prescribing current DMTs in this group.

(SPMS):	
Key Issue 7: Source of annualised relapse rates (ARR)	
Key Issue 8: Source of health state utility values	
Key Issue 9: Inclusion of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years	The rates of immunogenicity are thought to be lower with the newer anti-CD20 drugs such as ofatumumab compared to rituximab. The association between anti-drug antibodies and lack of efficacy is not consistent. In the ocrelizumab studies anti-drug antibodies were detected in 0.4%. Stopping or switching treatment due to lack of efficacy rather than side effects has been used as a proxy for treatment waning. These waning levels seem high and it would be useful to see the evidence for this. We note that the ERG found no evidence of waning of the treatment effect.
Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement:	

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- Ofatumumab is an effective new treatment for relapsing MS
- Two large phase III trials have shown a significant reduction in annualised relapse rate compared to an active comparator.
- The treatment is given by monthly subcutaneous injection at home which may be more convenient for some people with MS than other approved DMTs.
- The delivery of treatment at home avoids the needs for hospital attendances and access to day-case unit facilities.
- There is evidence of faster B cell repletion and reconstitution of humoral immunity than with intravenous anti-CD20 treatments. This is important in preparation for vaccinations eg potential Covid-19 vaccines .

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Technical engagement response form

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **1 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Biogen Idec Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Generalisability of ASCLEPIOS trial populations	**NO**	The ASCLEPIOS trials applied inclusion and exclusion criteria which correspond to drug eligibility criteria in the UK. Based on the available information on baseline characteristics presented in Table 6 of the company submission, Biogen expects the patients in the trials to be comparable to those patients treated in the NHS.
Key issue 2: Trials included in the company network meta-analysis (NMA)	**Yes**	Biogen does not agree with the ERG that Boiko et al. 2018 and Etemadifar et al. 2006 should have been included in the company NMA. Studies that directly report the outcomes listed in Table 28 of the company submission: inclusion criteria in the NMA, should be included in the evidence network. The results reported in Boiko et al. 2018 for trial NCT02727907 does not directly report outcomes listed in Table 28 unless further calculations are undertaken to derive ARR. Biogen does not believe calculating the ARR based on the mean number of relapses per patient (as done so by Melendez-Torres et al. TA527) is a justified assumption. Hereunder, the following studies: Etemadifar et al. 2006, Bornstein et al. 1987, Boiko et al. 2018 and PRISMS (Ebers et al. 1998), do not directly report ARR as an outcome, and should be excluded from the company NMA base case.

		Bornstein MB, Miller A, Slagle S et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med 1987;317:408-14. Boiko AN, Bosenko LP, Vasilovskii VV et al. A comparative placebo-controlled clinical trial of the efficacy and safety of interferon β-1a formulations for S.C. administration in patients with remitting multiple sclerosis: first-year results. Neurosci Behav Physiol 2018;48(7):883-9. Ebers GC, PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998;352:1498-504. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006;113:283-7.
Key issue 3: Lack of transparency in the process of selecting studies from systematic literature review (SLR) into the NMA	**NO**	Biogen notes that GOLDEN is an open label study and would not have been included based on the inclusion criteria (manufacturer submission Table 28: Eligibility criteria for inclusion in the NMAs). Without access to Appendix D: eligibility criteria for inclusion in the clinical systematic literature review, we are unable to comment on the process of selecting studies at this stage of the process. Biogen would welcome an explanation for not including BECOME (Cadavid et al. 2009) in the SLR and NMA. BECOME trial has a relevant population, and relevant clinical outcome: ARR (≥ 12 months) with intent to treat analysis. Without access to Appendix D: eligibility criteria for inclusion in the clinical systematic literature review, it can only be presumed that Cadavid et al. 2009 was not identified or did not pass the inclusion criteria for the clinical systematic literature review process.

		Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, Kamin SS, Pachner AR, Halper J, Cook SD. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009 Jun 9;72(23):1976-83.
Key issue 4: Paucity of evidence for comparative effectiveness of treatments for Highly Active (HA) RRMS and Rapidly Evolving Severe (RES) RRMS	**NO**	In estimating the comparative effectiveness for the comparators in the subgroups, it is important to note the need to match and adjust to the comparator trial populations to produce results. HA and RES RRMS data should be used wherever possible, as use of full RRMS data may underestimate the efficacy in the subgroups and would not accurately reflect the population who would be treated with ofatumumab in clinical practice. With a lack of trial data and infeasibility to conduct NMA in the HA and RES RRMS, the assumption that the treatment effect is the same in the whole RRMS as the subgroup populations has inherent limitations. Where possible subgroup data should be used and only when not available, data for the whole RRMS population is considered.
Key issue 5: Inclusion of disease management costs associated with treating people with SPMS	**YES**	For clarification, there is variation in the use of the UK MS Survey data (2005) cited in TA527, TA147 and Tyas et al. 2007. Both the cost data in TA147, and Tyas et al. 2007 use data from the same survey. The company submission uses model inputs for health state management costs derived from TA527. These costs have been taken from the TA527 AG re-estimated 2014/15 costs (Table 27 UK MS Survey health state management costs) which did not stratify costs by RRMS/SPMS state. The AG in appraisal TA527 cite the UK MS Survey as the preferred source for EDSS health state costs, using data from TA147 to estimate 2014/15 prices. Biogen notes that the source of the data reported in Table 27 (UK MS Survey health state management costs) of the TA527 ERG report cites TA147. However, TA147 does not present costs stratified by RRMS and SPMS (Table 8, TA147), and Tyas et al. 2007

		includes covariates in the model including estimating health states costs within SPMS; costing an additional £280. It would be expected that disease management costs increase with disease severity. This has been in past appraisals. As such, Biogen agrees with the ERG approach that management costs for RRMS and SPMS differ, as has been used in past appraisals (TA312, TA320, TA303, TA533, TA624) and that Tyas et al. 2007 should be used for estimating disease management health state costs. NICE, TA527 Beta interferons and glatiramer acetate for treating multiple sclerosis. Published date: 27 June 2018. Table 27 UK MS Survey health state management costs p849 of 959 . Retrieved from https://www.nice.org.uk/guidance/ta527/documents/committee-papers NICE, TA127 Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. Published date: 22 August 2007. p150 of 269. Retrieved from https://www.nice.org.uk/guidance/TA127/documents/multiple-sclerosis-natalizumab-manufacturer-submissions-biogen-idec-uk-and-elan-pharma-international-ltd-joint-development-agreement-confidential-information-removed2
Key issue 6: Probability of progressing from Relapsing Remitting Multiple Sclerosis (RRMS) to Secondary Progressive Multiple Sclerosis (SPMS)	YES	Novartis cites TA254 as the source for the conversion rates. In TA254, the RRMS-SPMS transitions uses exponential distributions, implying rates at which transitions between EDSS states occur are constant over time. This observation predicts that with EDSS progression there is acceleration upon conversion from RRMS to SPMS. The manufacturer was unable to justify the assumptions for estimating the transitions in the appraisal and the TA254 ERG subsequently did not consider the model to have been validated against the trial data or against other published studies.

		Biogen agrees with the ERG that it is more appropriate to use the conversion rates from RRMS to SPMS based on the RRMS-SPMS transition probabilities estimated by ScHAAR. This is described in the TA441 ERG report, where the probabilities were calculated from patient level data of the London Ontario dataset presented in the ScHAAR report appendix. The ScHAAR RRMS-SPMS conversion rates have since been used in previous appraisals including TA533 and TA624.
Key issue 7: Source of annualised relapse rates (ARR)	**YES**	Biogen agrees relapse rates should be considered dependent on EDSS, and that the ERG preferred values of the ARR in TA527 assessment for a natural history cohort should be used in the base case, and Patzold et al. 1982 be considered in sensitivity analysis. Based on the available information, Biogen recommends using published data due to the uncertainty raised by the ERG on the low ARR in people with SPMS from the EXPAND trial.
Key issue 8: Source of health state utility values	**Y**ES	Biogen agrees with the ERG preferred source for utilities for people living with SPMS. Patients that have progressed to SPMS are recognised to have a more progressive form of MS, it would be inappropriate to use data where the reported utilities are equal for RRMS and SPMS as proposed by the company. This implicitly assumes that while clinically the SPMS state is more severe than RRMS state, based patient preference the health state utility value of SPMS as no more severe than RRMS, which is not consistent with preferred committee assumptions from prior technology appraisals, or studies published on the effect of disease and functional status in multiple sclerosis on health utilities (Orme et al. 2007). Additionally, with a small sample size in ASCLEPIOS trials indicating numerically equivalent utility values for EDSS health state irrespective of RRMS/SPMS state –

<table>
<tr><td></td><td></td><td>Biogen considers this dataset not representative of the general population of people living with SPMS.

Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007 Jan-Feb;10(1):54-60. doi: 10.1111/j.1524-4733.2006.00144.x. PMID: 17261116.</td></tr>
<tr><td>Key issue 9: Inclusion of waning of the treatment effect (25% reduction after 5 years, then 50% reduction after 8 years)</td><td>YES</td><td>Evidence of waning associated with disease modifying therapies in the treatment of multiple sclerosis is very limited.

For consistency in decision making, Biogen agrees with the ERG to take a precautionary approach applied in past appraisals and to use an assumption of waning of the treatment effect.
Biogen notes the ERG recommendation states the waning 25% reduction after 5 years, then 50% reduction after 8 years is based on “consistency with other recent MS technology appraisals and due to lack of long-term follow-up evidence for ofatumumab” – this is incorrect. Past appraisals have not considered this assumption. Table 1 presents the treatment waning effect assumptions used in past technical appraisals.
In line with the majority of previous submissions, Biogen considers consistency should be applied to applying the treatment waning effect – using a 25% reduction after 2 years, and 50% after 5 years.

Table 1. Treatment waning effect used in economic analysis in previous NICE technology appraisals
<table>
<tr><td>Factor</td><td colspan="11">Previous appraisals*</td></tr>
<tr><td></td><td>TA32</td><td>TA127</td><td>TA254</td><td>TA303</td><td>TA312</td><td>TA320</td><td>TA441</td><td>TA493</td><td>TA527</td><td>TA533</td><td>TA624</td></tr>
<tr><td>Treatment waning effect</td><td>Not applied</td><td>Not applied</td><td>50% waning after 5 years</td><td>25% waning after 2 years and 50% after 5 years</td><td>25% waning after 2 years and 50% after 5 years, time-dependent</td><td>25% waning after 2 years and 50% after 5 years</td><td>25% waning after 2 years and 50% after 5 years</td><td>25% waning after 2 years and 50% after 5 years</td><td>25% waning after 2 years and 50% after 5 years</td><td>25% waning after 2 years and 50% after 5 years</td><td>25% waning after 2 years and 50% after 5 years</td></tr>
</table>
</td></tr>
</table>

		rate of retreatment * The values for TA32, TA127, TA254, TA303, TA312, TA320, and TA441 are based on the committee papers of TA493 (Table 59) and TA533 (Table 25). The values for TA493, TA527, TA533 and TA624 reflect the preferences of the assessment groups and are based on the committee papers for each submission.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Trials included in the company network meta-analysis (NMA)	ERG Report: Section 3.3.3.1, p76	Yes	Biogen does not agree that the study INCOMIN should be excluded from the comparative efficacy in the base case network in the NMA based on the justification: an outlier not reflective of clinical practice and aligning to the past appraisal TA533 and published NMAs excluding INCOMIN. INCOMIN has been used for comparative efficacy in past appraisals including TA254, TA493, TA527 and TA624. Methods applied in the systematic review should be consistent. Unless further assessment is undertaken on the bias and study results, to exclude INCOMIN - with a number of past appraisals using INCOMIN trial for comparative efficacy data, Biogen consider INCOMIN should be included in the base case networks.

Additional issue 2: Trials included in the company network meta-analysis (NMA)	ERG report: Section 3.3.3.2, p77	Yes	Biogen does not agree ADVANCE should be excluded from comparative efficacy in the NMA for being a clinical outlier and aligning to the past appraisals TA527 and TA533 in excluding peginterferon beta-1a. Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis in adults was appraised in TA624; a subsequent appraisal that followed TA527 and TA533. The clinical data of ADVANCE used as one of the pivotal trials for peginterferon beta-1a was considered appropriate for decision making by the TA624 Appraisal Committee. As such for consistency in appraisals, peginterferon beta-1a / ADVANCE should be included in the base case networks.
Additional issue N: Insert additional issue			Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Public observer slides (redacted)

Ofatumumab for treating relapsing multiple sclerosis [ID1677]

Lead team presentation

Lead team: Megan John, Ed Wilson, Tony Wootton

ERG: Warwick Evidence

Chair: Sanjeev Patel

Technical team: Vicky Gillis-Elliott, Richard Diaz, Henry Edwards

Company: Novartis

ACM 1: 04th February 2021

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Abbreviations

ARR: Annualised relapse rate
CDW-3: 3 months confirmed disability worsening
CDW-6: 6 months confirmed disability worsening
DMT: Disease modifying therapy
EDSS: Extended disability status score
FAS: Full analysis set
HA: Highly active
HSUV: Health state utility value
RES: Rapidly evolving severe
RMS: Relapsing multiple sclerosis
RRMS: Relapsing remitting multiple sclerosis
SPMS: Secondary progressive multiple sclerosis

Key issues

Issues resolved after Technical engagement	Resolved and impact on the ICER
1 Generalisability of ASCLEPIOS trial data	Resolved
2 Lack of transparency for selecting studies into the network meta-analysis (NMA)	Resolved
3 Trials included in the company NMA	Resolved
4 Paucity of evidence for comparative effectiveness of treatments for HA RRMS and RES RRMS	Resolved
Outstanding issues after Technical engagement	
5 Including SPMS- specific costs associated with treating people with SPMS	Small impact on ICER
6 Probability of progressing from RRMS to SPMS	Small impact on ICER
7 Source of annualised relapse rates (ARR)	Small impact on ICER
8 Source of health state utility values	
9: Inclusion of waning of the treatment effect	To discuss

Key questions for committee

- Are the results of the ASCLEPIOS trials generalisable to the NHS?
  What is the significance of the paucity of evidence for MS sub-groups?
- Should treatment waning be applied in the model and how should this be done?

Multiple Sclerosis (MS)

- Chronic, lifelong, neurological disease, resulting in progressive, irreversible disability
- Affects central nervous system:
  - immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves
- 85% of MS is relapsing-remitting (RRMS): episodes of relapses (neurological worsening) separated by remission (periods of stability)
- Associated with pain, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Onset typically between 25 and 35 years of age
- Approximately 110,000 people in the UK have MS, and about 5,000 people are newly diagnosed each year
- Treatment (disease-modifying therapies): decrease frequency and severity of relapses, reduce accumulation of lesions, slow accumulation of physical and mental disability, maintain or improve patient quality of life

Types of multiple sclerosis

Primary progressive MS
- Gradual disability progression from onset with no obvious relapses or remission
- Limited treatment options

Relapsing-remitting MS (RRMS)
- 85% of people at diagnosis
- Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment

50% in 20 years

Secondary progressive MS (SPMS)
- Steady progression of neurological damage with or without relapses
- Treatment might be restricted to secondary progressive disease *with relapses*

Subgroups of RRMS

1. Active RRMS with no prior disease-modifying therapy
2. Active RRMS with prior disease-modifying therapy
3. Highly active (HA), with disease activity on first line therapy
4. Rapidly evolving severe (RES)

NICE

Patient and professional comments

Patient:

Impact on daily life:

- MS can be unpredictable and at times can be challenging and difficult to plan too far ahead. Experience of current treatment and care with MS MDT has been positive

Experience of ofatumumab:

- Greatest advantage of ofatumumab is only having to make minimal allowance to deliver drug at right time each month
- Ofatumumab injected by patient once every 4 weeks at home
- Difficult for some people with dexterity complications to carry out injections and time-consuming to visit hospital every 4 weeks for infusion
- Personal experience not found ofatumumab to be disadvantage as very convenient; no relapses since starting treatment in April 2017, nor experienced any side effects

Patient and professional comments

NHS England commissioning expert:

MS treatment approaches:

- Current variation in approach to treatment: Some clinicians start with drugs of lower toxicity and efficacy and escalate if disease breaks through. Others favour early treatment with more potent/toxic therapies. NHS England introducing national algorithm based on NICE guidance and this clinical practice due to be published shortly
- Ofatumumab would have relatively small impact on current pathway of care as several treatments available for RRMS

	Final scope	Company submission	Company rationale if submission different from DP
P	People with relapsing MS	*Adults with RRMS*	*Anticipated licence for ofatumumab is only for adult patients* Small proportion with active SPMS and data not sufficient to perform meaningful indirect comparisons or robust cost-effectiveness analyses
C	**For people with active RRMS** beta interferon; dimethyl fumarate; glatiramer acetate; teriflunomide; ocrelizumab; peginterferon beta-1a; ozanimod **For people with HA RRMS despite previous treatment:** alemtuzumab; cladribine; fingolimod; ocrelizumab[1]; ozanimod **For people with RES MS:** alemtuzumab; cladribine; natalizumab; ocrelizumab[1]; ozanimod[2] **For people with active SPMS:** peginterferon beta-1b or other DMTs used outside their MA; siponimod[2]	All relevant apart from ozanimod and siponimod	Ozanimod not a comparator as not established clinical practice at time of submission Cladribine is a comparator but used in tablet form only Siponimod not relevant- No comparators included for SPMS as company not making a case for this population

RRMS: relapsing remitting MS; HA: Highly active; RES: Rapidly evolving severe; SPMS: secondary progressive MS
[1] Only if alemtuzumab is contraindicated or otherwise unsuitable; [2] Subject to ongoing NICE appraisal

ERG agree with company rationale

	Final scope	Company submission (CS)
O	• 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	• Relapse rate and severity: ARR, time to first relapse, relapse severity • Disability and disease progression: 3- and 6-month CDW and 6-month CDI by EDSS • Symptoms of MS: 6-month CDW by Timed 25 Foot Walk (T25FW)) • Freedom from disease activity using composite scores that include MRI, relapse rate and brain volume • Adverse effects • Patient-reported outcomes: • Health- related quality of life: EQ-5D-5L

Outcomes in CS were in alignment with final scope

CDW: confirmed disability worsening; CDI: confirmed disability improvement

NHS England treatment algorithm and company positioning

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and *alternatives for intolerance to first-line therapy in italics and underline*)		
• *Interferon beta-1a* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Ozanimod* [c] • **Ofatumumab?**	• *Beta interferons (1a and 1b)* • *Dimethyl fumarate* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Teriflunomide* • *Ozanimod* [c] • **Ofatumumab?**	• *Alemtuzumab* • *Cladribine* • Natalizumab • *Ocrelizumab* [b] • *[Fingolimod, only as alternative to natalizumab]* • **Ofatumumab?**

NICE [a] N.B Peginterferon beta-1a on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable, [c] Proposed positioning, appraisal in development

NHS England treatment algorithm and company positioning

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and *alternatives for intolerance to first-line therapy in italics and underline*)		
• *Interferon beta-1a* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Ozanimod* [c] • **Ofatumumab?**	• *Beta interferons (1a and 1b)* • *Dimethyl fumarate* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Teriflunomide* • *Ozanimod* [c] • **Ofatumumab?**	• *Alemtuzumab* • *Cladribine* • Natalizumab • *Ocrelizumab* [b] • *[Fingolimod, only as alternative to natalizumab]* • **Ofatumumab?**
Second-line therapy, when disease activity on 1st line therapy (highly active [HA] RRMS)		
• Alemtuzumab or ocrelizumab [b] • Cladribine • Fingolimod • *Ozanimod* [c] • **Ofatumumab?** *Patients developing RES receive second-line therapy for RES*		• Alemtuzumab or ocrelizumab [b] • Cladribine • Natalizumab • **Ofatumumab?**

NICE [a] N.B Peginterferon beta-1a on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable, [c] Proposed positioning, appraisal in development

NHS England treatment algorithm and company positioning

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)

1st line therapy (and *alternatives for intolerance to first-line therapy in italics and underline*)

- *Interferon beta-1a*
- *Glatiramer acetate*
- Ocrelizumab [b]
- Peginterferon beta-1a
- *Ozanimod* [c]
- **Ofatumumab?**

- *Beta interferons (1a and 1b)*
- *Dimethyl fumarate*
- *Glatiramer acetate*
- Ocrelizumab [b]
- Peginterferon beta-1a
- *Teriflunomide*
- *Ozanimod* [c]
- **Ofatumumab?**

- *Alemtuzumab*
- *Cladribine*
- Natalizumab
- *Ocrelizumab* [b]
- *[Fingolimod, only as alternative to natalizumab]*
- **Ofatumumab?**

Second-line therapy, when disease activity on 1st line therapy (highly active [HA] RRMS)

- Alemtuzumab or ocrelizumab [b]
- Cladribine
- Fingolimod
- *Ozanimod* [c]
- **Ofatumumab?**

Patients developing RES receive second-line therapy for RES

- Alemtuzumab or ocrelizumab [b]
- Cladribine
- Natalizumab
- **Ofatumumab?**

Third-line therapy

- Alemtuzumab or ocrelizumab [b]
- Cladribine
- Autologous haematopoietic stem cell treatment (AHSCT)

Patients developing RES receive third-line therapy for RES

- Alemtuzumab or ocrelizumab [b]
- Cladribine
- Natalizumab
- AHSCT

NICE

[a] N.B Peginterferon beta-1a on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable, [c] Proposed positioning, appraisal in development

Position of ofatumumab in current pathway

Position of ofatumumab anticipated license

Position of ofatumumab in Company submission

RRMS treatment options	HA treatment options	RES treatment options	Active SPMS treatment options
interferon beta 1a and 1b **(TA527)**	alemtuzumab **(TA312)**	alemtuzumab **(TA312)**	siponimod **(TA656)**
peginterferon beta 1a **(TA624)**	cladribine tablets **(TA616)**	cladribine tablets **(TA616)**	
dimethyl fumarate **(TA320)**	fingolimod **(TA254)**	natalizumab **(TA127)**	
teriflunomide **(TA303)**	ocrelizumab **(TA533)**	ocrelizumab **(TA533)**	

Company suggest ofatumumab is positioned as same line of therapy as ocrelizumab. Do clinicians agree?

NICE

Company positioning of ofatumumab

- Company suggest there is unmet need for high-efficacy therapy for all RRMS patients that can be initiated in a timely manner and self-administered by patients at home

- Ocrelizumab is only other B-cell therapy currently recommended by NICE for use in patients with RRMS
  - administered in hospital via infusion lasting several hours

- Ofatumumab monthly subcutaneous injection self-administration at home by patients or their carers

Ofatumumab (Kesimpta, Novartis)

Marketing authorisation	• Anticipated UK marketing authorisation wording: Ofatumumab for treatment of adult patients with relapsing forms of multiple sclerosis (RMS)
Mechanism	Monoclonal antibody that binds to CD20 on cell surface of B lymphocytes targeting cells for destruction
Administration and dose	• Subcutaneous injection 20 mg in 0.4 mL solution Administered at Weeks 0, 1 and 2 and monthly dosing at Week 4 • Self administration, but first injection performed under guidance of healthcare professional
Proposed place in the MS	Adult patients with RRMS
Cost of treatment	list price is [redacted] (exc. VAT) per 1-unit pack (pre-filled autoinjector pen), Simple Patient Access Scheme applied for

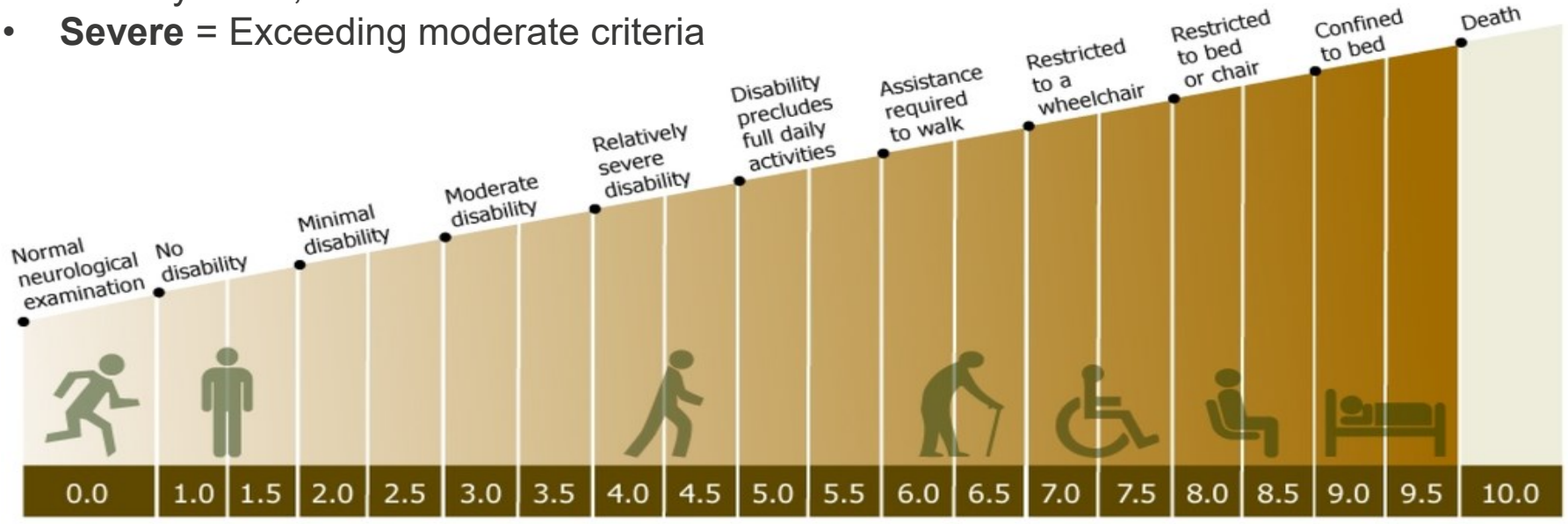
Clinical effectiveness

Definition of outcomes in trials

- **Relapse**: Patient reported new, reoccurring or worsening neurological symptoms assessed by investigator within 7 days
- **Confirmed relapse**: Relapse accompanied by “clinically relevant” change in Extended disability status score (EDSS)
  - 0.5 point EDSS increase
  - 1 point EDSS increase on two functional scores or 2 point increase on one functional score compared to previous EDSS rating

Relapse severity:

- **Mild** = 0.5 point EDSS increase or 1 point functional score change in 1–3 systems;
- **Moderate** = 1–2 points EDSS increase or 2 point change in 1–2 systems or 1-point change in ≥4 systems;
- **Severe** = Exceeding moderate criteria



Source: *https://www.msonetoone.eu/managing-ms/monitoring-symptoms*

Key outcome definition-disability progression

- **Current appraisal**
- Disability worsening based on EDSS change from baseline:
- Baseline EDSS = 0:
  - Disability worsening at least 1.5-point increase in EDSS
- Baseline EDSS = 1–5:
  - Disability worsening at least 1-point increase in EDSS
- Baseline EDSS at least 5.5:
  - Disability worsening at least 0.5-point increase in EDSS
- Death due to MS considered confirmed disability worsening regardless of bEDSS.

Company highlighted differences in CDW-3 and CDW-6 criteria between other trials used in NMA

ASCLEPIOS Different criteria for baseline EDSS score of 0 or 5.5

ERG unclear what impact would be they noted adjusting can help, but may not do entirely

CDW-3 defined as increase from baseline in EDSS sustained for at least 3 months

CDW-6 defined as increase from baseline in EDSS sustained for at least 6 months

Abbreviations:
bEDSS; baseline EDSS; ERG: Evidence review group; NMA: Network meta analysis

Clinical evidence: Trial data

Systematic literature review found 2 identical phase 3 double-blind, active-comparator controlled trials

ASCLEPIOS 1 AND 2

(N=1882)

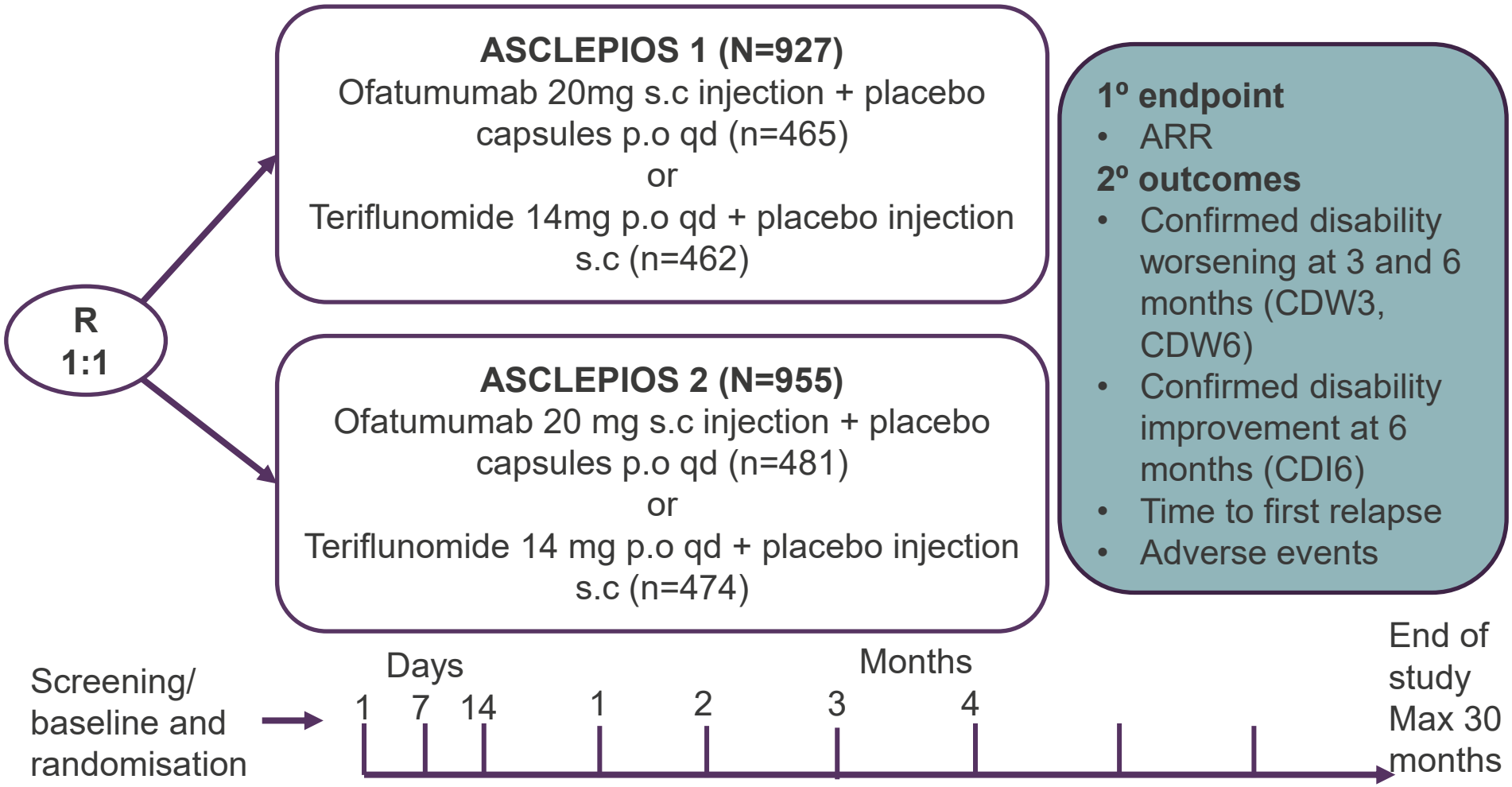
- Ofatumumab 20mg subcutaneous injection and oral placebo vs teriflunomide 14mg orally and subcutaneous injection placebo
- Ofatumumab or matched placebo administered once weekly on Days 1, 7 and 14 and once every 4 weeks at week 4 onwards
- Teriflunomide or matched placebo administered orally once daily

- Key inclusion criteria:
  - Aged 18–55 years
  - RMS (RRMS or SPMS with disease activity)
  - EDSS 0-5.5
  - At least 1 relapse in past year and/or 2 relapses in last 2 years and/or positive GdE MRI scan in last year
- Key exclusion criteria:
  - PPMS or SPMS without disease activity
  - Neuromyelitis optica
  - Disease duration more than 10 years and EDSS score of at least 2

Abbreviations: RMS; relapsing multiple sclerosis, RRMS; relapsing remitting multiple sclerosis, PPMS; primary progressive multiple sclerosis, SPMS; secondary progressive multiple sclerosis; GdE; Gadolinium - enhancing;

ASCLEPIOS 1 and 2: study design

Two Phase 3, international multi-centre, randomised, double-blind, double-dummy, active-controlled parallel group trial



• Abbreviations: p.o. orally; qd once a day; s.c. subcutaneous;

Baseline characteristics of ASCLEPIOS trials (including all RRMS)

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)		5.8 (6.0)	5.6 (6.2)	5.6 (6.4)	5.5 (6.0)
Treatment-naïve patients		191 (41.1)	182 (39.4)	195 (40.5)	181 (38.2)
Previously treated patients, n (%)		274 (58.9)	280 (60.6)	286 (59.5)	293 (61.8)
Type of MS at study entry, n (%)	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)
Relapses in 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 12-24 months prior to screening	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	0.9 (1.0)	0.9 (1.2)	0.7 (1.0)	0.8 (1.0)
EDSS	N	465	461	481	473
	Mean(SD)	3.0 (1.4)	2.9 (1.4)	2.9 (1.3)	2.9 (1.4)

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

NICE Small SPMS population; ERG note data insufficient to allow robust analyses in active-SPMS population: Subsequent results for RRMS only

Proportion of MS subtypes in ASCLEPIOS

- **Relapsing-remitting MS (RRMS)**
- 85% of people at diagnosis
- Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment
- In ASCLEPIOS proportion = [redacted] patients [redacted]

50% in 20 years

Secondary progressive MS (SPMS)

- Steady progression of neurological damage with or without relapses
- Treatment might be restricted to secondary progressive disease *with relapses*
- In ASCLEPIOS proportion = [redacted] patients [redacted]

RRMS Subgroups

1. Active RRMS with no prior disease-modifying therapy
2. Active RRMS with prior disease-modifying therapy

[redacted]

3. Highly active (HA) disease [redacted] patients ([redacted]%)
4. Rapidly evolving severe (RES) [redacted] patients ([redacted]%)

Post-hoc analyses

RRMS subgroups in ASCLEPIOS trials

- **Company submission considered 2 post-hoc sub-groups**

Highly active RRMS
ASCLEPIOS ITT
Population with RRMS and previously treated with any DMT who discontinued last DMT to lack of efficacy

Pooled n of ASCLEPIOS trials
= [redacted]

Rapidly evolving severe RRMS
ASCLEPOS ITT

Population with at least 2 relapses in previous year and at least oneT1 Gd-enhancing lesions on baseline brain MRI
Pooled n of ASCLEPIOS trials
= [redacted]

ERG noted paucity of evidence for subgroups in ASCLEPIOS trials

EDSS, Expanded Disability Status Scale; GdE, gadolinium enhanced; RRMS, relapsing remitting multiple sclerosis. ITT; Intention to treat population, DMT; disease modifying therapy for MS

Key results from ASCLEPIOS trial data:
Annualised relapse rates RRMS population

	ASCLEPIOS 1		ASCLEPIOS 2	
	Full RRMS population			
	20 mg ofatumumab (N=454)	14 mg teriflunomide (N=452)	20 mg ofatumumab (N=469)	14 mg teriflunomide (N=469)
Adjusted ARR (95% CI)	0.11 (0.09, 0.14)	0.22 (0.18, 0.26)	0.10 (0.08, 0.13)	0.25 (0.21, 0.30)
Reduction	-50.5%		-58.5%	
ARR ratio (95%CI)	0.50 (0.37, 0.65)		0.42 (0.31, 0.56)	

Abbreviations: RRMS: Relapsing remitting MS; ARR: Annual relapse rate

Disability and disease progression:
Confirmed disability worsening in ASCLEPIOS Trials

		ASCLEPIOS pooled data Full RRMS population	
		ofatumumab 20 mg (N=944)	teriflunomide 14 mg (N=931)
3- month Confirmed disability worsening	Number of CDW-3 events (%)	88 (9.3)	125 (13.4)
	HR vs TER (95% CI)	0.66 (0.50, 0.86)	
	Risk vs TER	−34.4%	
6- month Confirmed disability worsening	Number of CDW-6 events, n (%)	71 (7.5)	99 (10.6)
	HR vs TER (95% CI)	0.68 (0.50, 0.92)	
	Risk vs TER	−32.5%	

OMB, ofatumumab; TER, teriflunomide; CDW, confirmed disability worsening; HR, Hazard ratio.

Key results from ASCLEPIOS trial data: Relapse rates for HA and RES subgroups

	Pooled ASCLEPIOS trial data		Pooled ASCLEPIOS trial data	
	HA subgroup		RES subgroup	
	20 mg ofatumumab (N=[redacted]	14 mg teriflunomide (N=[redacted]	20 mg ofatumumab (N=[redacted]	14 mg teriflunomide (N=[redacted]
Adjusted ARR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Reduction	[redacted]		[redacted]	
ARR ratio (95%CI)	[redacted]		[redacted]	

Abbreviations: HA: Highly active; RES: Rapidly evolving severe; ARR: Annual relapse rate

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Key results from ASCLEPIOS trial data: Disease worsening for HA and RES subgroups

	Pooled ASCLEPIOS trial data		Pooled ASCLEPIOS trial data	
	HA subgroup		RES subgroup	
	20 mg ofatumumab (N=[redacted]	14 mg teriflunomide (N=[redacted]	20 mg ofatumumab (N=[redacted]	14 mg teriflunomide (N=[redacted]
Number of CDW-3 events n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Reduction	[redacted]		[redacted]	
HR (95%CI)	[redacted]		[redacted]	
Number of CDW-6 events n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Reduction	[redacted]		[redacted]	
HR (95%CI)	[redacted]		[redacted]	

Abbreviations: HA: Highly active; RES: Rapidly evolving severe; CDW-3: 3-month confirmed disability worsening; CDW-6: 6-month confirmed disability worsening; HR Hazard ratio

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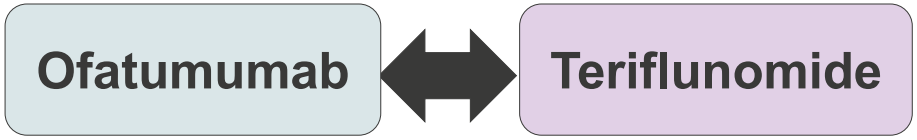
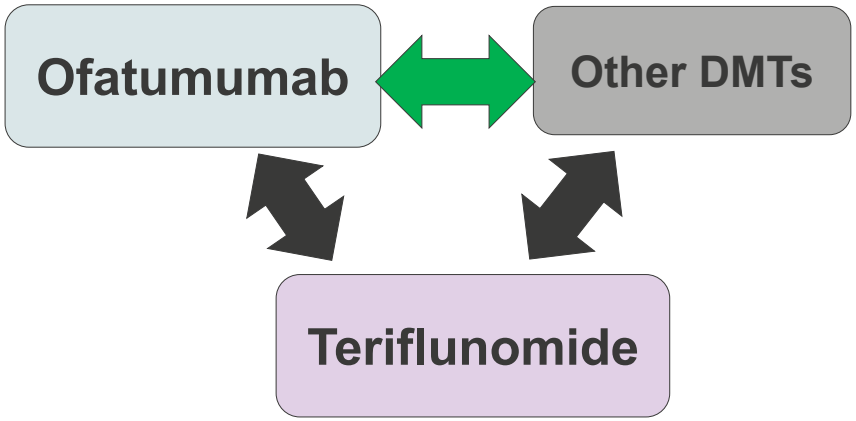
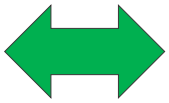
Indirect comparison approaches

Direct comparison

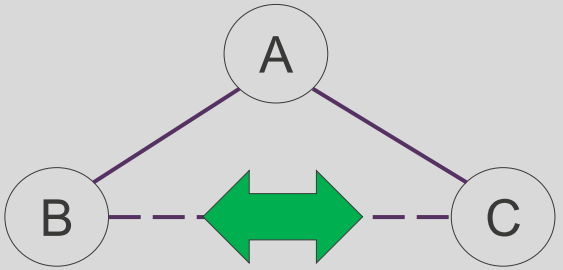


Indirect comparison




Effect of interest (not available from head-to-head trials)

Network meta-analysis (NMA)



- Relies on '**constancy of relative effects**' assumption
  - AB effect in AB study is the same as the hypothetical AB effect in the AC study *if it had included a B arm*

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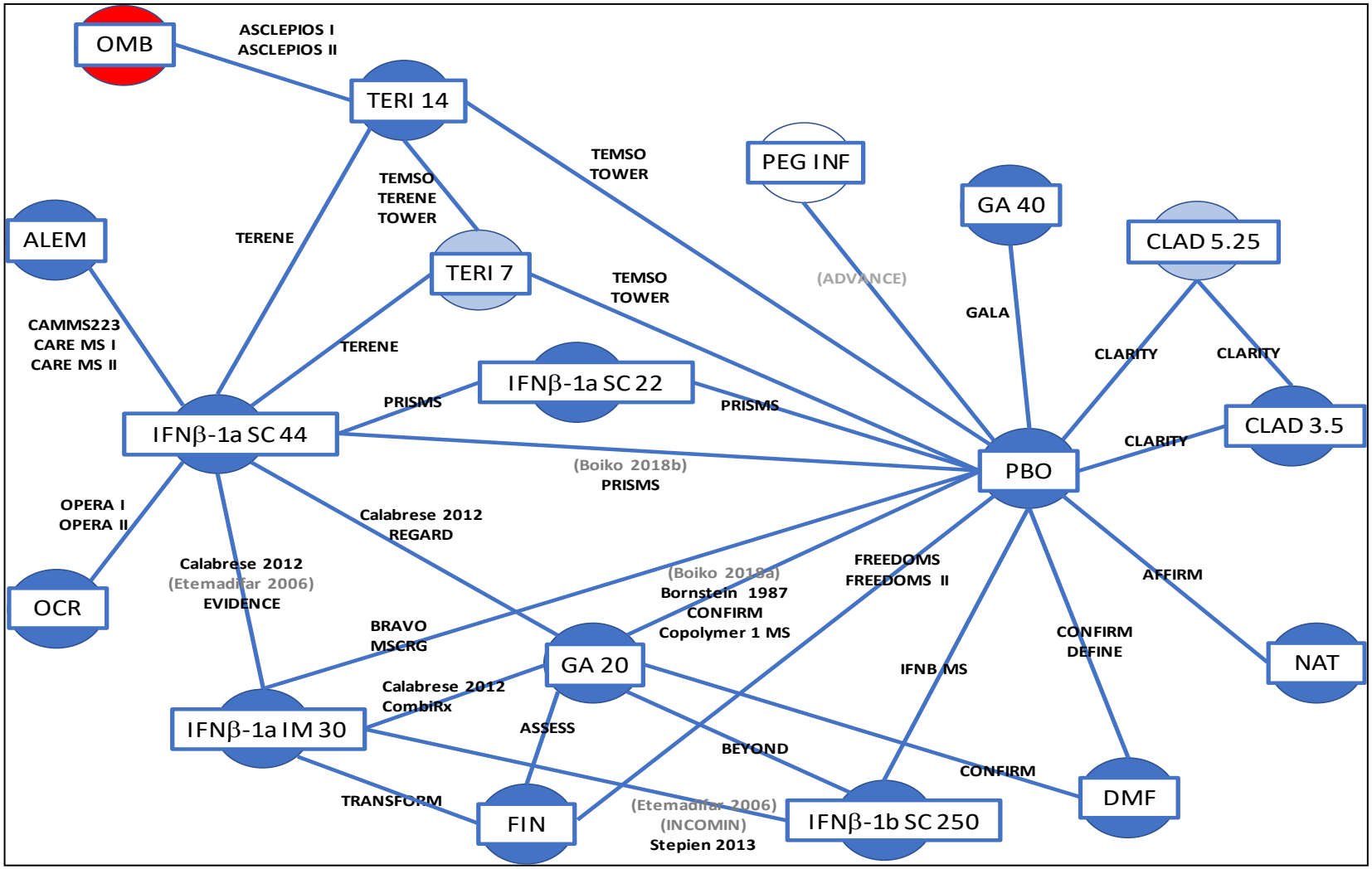
NMA was based on full RRMS population

NMA map ERG mapped network showing all trials included in company's feasibility assessment for NMAs



Trial names listed in grey colour in brackets indicate that the trial was excluded from the company's base case analyses.

Indirect comparisons company and ERG

Company approach	ERG comments
Carried out NMAs for comparison between ofatumumab and other comparators for ARR, CDW-3, CDW-6 and all-cause discontinuation	ERG calculated ARR with additional studies excluded from NMA. Had only small impact on NMA findings and CE analysis.
Considered but concluded NMAs not feasible for HA and RES RRMS subgroups (no RCT data to allow connection from ASCLEPIOS trials to wider network)	Agreed it was unfeasible to conduct NMAs for HA and RES RRMS subgroups
Highlighted differences in CDW-3 and CDW-6 criteria between trials Company used "aligned" CDW criteria in base case NMA to align CDW to definition used in previous trials in network Scenario analyses: "pre-defined criteria" CDW definition in ASCLEPIOS trials	Agree differences in criteria can introduce bias into NMAs; helpful to provide analyses using "pre-defined criteria" and "aligned criteria" but does not completely remove potential bias associated with heterogeneity
Company analysed ASCLEPIOS trials in line with OPERA (ocrelizumab) methodology	Agree "OPERA-aligned" criteria informative but cautious in interpretation of findings (post hoc analyses, lack of clear definition of criteria & other differences in conduct of trials)

Company base case NMA 'aligned' to trials in network

	ARR		CDW-3 (aligned)		CDW-6 (aligned)	
	HR (95% CrI)	Rank	HR (95% CrI)	Rank	HR (95% CrI)	Rank
Ofatumumab vs:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a IM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a SC 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1b SC 250	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14	[redacted]	[redacted]	[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; HR: hazard ratio; CrI: credible interval; IFN: interferon; SC: subcutaneous

Pre-defined criteria: CDW-3 [redacted]

CDW-6 [redacted]

OPERA aligned: CDW-3 [redacted]

CDW-6: [redacted]

Issue 2: Company NMA Base case for ARR

Inclusion of 4 studies identified by the ERG that were not included in the company base case has a minor impact on NMA

ARR: Company base case NMA forest plot

ARR: Company scenario including 4 studies

Cost effectiveness

Summary - technical engagement issues

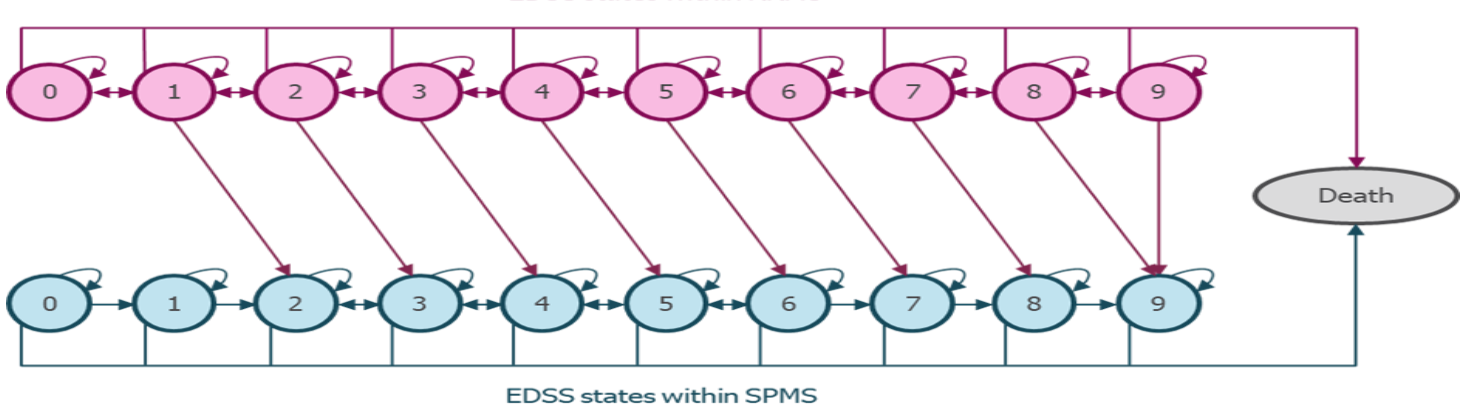
Issues resolved after Technical engagement	Resolved and impact on the ICER
1 Generalisability of ASCLEPIOS trial data	Resolved
2 Lack of transparency for selecting studies into the network meta-analysis (NMA)	Resolved
3 Trials included in the company NMA	Resolved
4 Paucity of evidence for comparative effectiveness of treatments for HA RRMS and RES RRMS	Resolved
Outstanding issues after Technical engagement	
5 Inclusion of SPMS- specific costs associated with treating people with SPMS	Small impact on ICER
6 Probability of progressing from RRMS to SPMS	Small impact on ICER
7 Source of annualised relapse rates (ARR)	Small impact on ICER
8 Source of health state utility values	
9: Inclusion of waning of the treatment effect	Large impact on ICER

NICE

No change
For discussion: minor ICER impact
For discussion: large ICER impact

Company's model structure

Figure source: company's submission document B, Figure 36



Discrete-time cohort Markov model

- 21 health states
  - 10 EDSS states EDSS 0-9 for RRMS
  - 10 EDSS states EDSS 0-9 for SPMS
  - Death
- Annual cycle, lifetime horizon
- Starting mean age [redacted] years; [redacted] female

For each annual cycle:

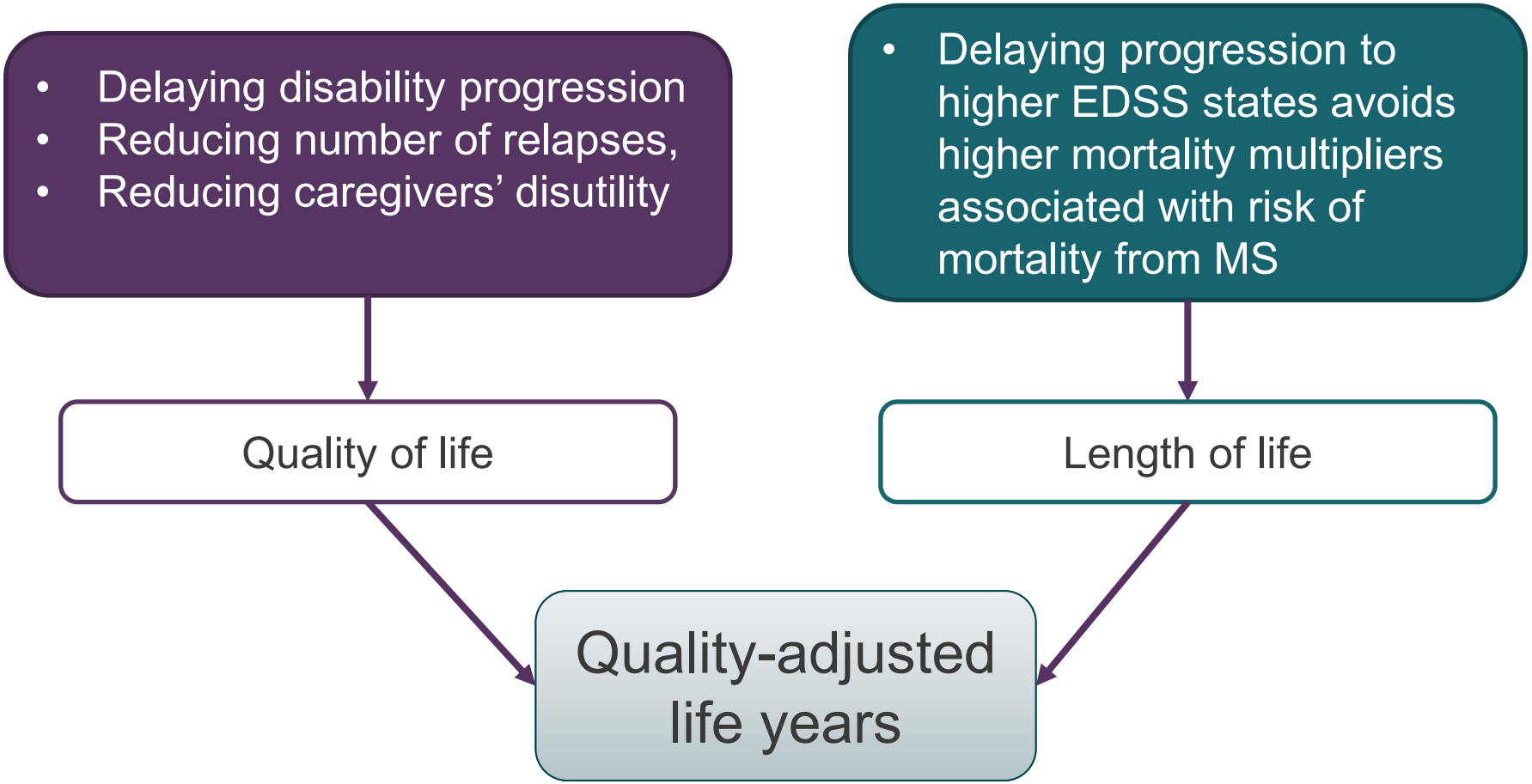
People with RRMS:

- Disability worsening, disability improvement or remain at same disability level; Progress from RRMS to SPMS
- Patients at EDSS scores ≥7 stop disease modifying treatments and switch to best supportive care (BSC)
- Discontinuation for any cause stop disease modifying treatments and move to BSC state
- Relapse event; Adverse events; Mortality event.

People with SPMS:

- Receive BSC plus one of the following:
  - Disability worsening, disability improvement or remain at same disability level
  - Relapse event
  - Mortality event

Overview: how quality-adjusted life years accrue in the model



Company base case assumptions

ERG agree with the following assumptions:

- ASCLEPIOS population representative of NHS population eligible for ofatumumab
- EDSS health state primary determinant of health state costs and utilities
- Patients who discontinue treatment receive BSC
- Patients reaching EDSS treatment threshold (EDSS 7 or above) automatically assumed to discontinue treatment and receive BSC
- Patients transitioning from RRMS to SPMS assumed to discontinue treatment; receive BSC
- Treatment benefits accrued during treatment period; no residual effect modelled on BSC
- Adverse events assumed to occur at constant rate in patients receiving disease modifying therapies and stop after their discontinuation in alignment with the assumption in TA533 (ocrelizumab)

Company base case assumptions	• ERG's base case preferences
• BSC assumed to incur zero cost	• **Costs need to assume change of care over time**
• Treatment effects are not applied to backwards transitions (i.e. disability improvement) nor to the probability of transitioning to SPMS	• **Transition probabilities from RRMS to SPMS from TA624 (peginterferon beta-1a)**
• Any long-term treatment effect waning is captured in all-cause discontinuation	• **Prefer approach using conservative assumption of (25% reduction after 5 years, then 50% reduction after 8 years)**

Issue 5: Inclusion of disease management costs associated with treating people with SPMS

EDSS	Direct medical costs, inflated to 2018–2019 (base-case)	SPMS- specific management costs from TA320* (ERG preferred values)
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

SPMS, secondary progressive multiple sclerosis;
* values were inflated to 2018-19 cost year

- ERG suggest disease management costs associated with treating people with SPMS should be included in economic analysis
- For consistency with other technology appraisals used SPMS-specific costs from TA320 (dimethyl fumarate, inflated to 2018/19 cost year)

Minor

Issue 6: Probability of progressing to SPMS

EDSS	Probabilities	
	fingolimod (TA254) (company base-case)	peginterferon beta-1a (TA624) (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

- Both transition probabilities used in company and ERG's base-case accepted by NICE
- TA624 [peginterferon beta-1a] transition matrices sourced from London Ontario dataset- company rationale: Did not adjust for active or benign forms of relapsing MS - may under- or over-estimate cost-effectiveness of treatment
- TA254 [fingolimod] transition matrices sourced from British Columbia dataset- Company transition matrices adjusted to exclude less progressive relapsing MS to fully represent eligible patients
- Impact on the ICER is small

Issue 7: Source of annualized relapse rates

EDSS	ARR (company base-case), UK MS survey		ARR, using TA527 assessment (ERG preferred)	
	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

- Values are for annual relapse frequency by EDSS for a natural history cohort (in absence of disease modifying treatments).
- Company base case ARR obtained from reported results in the UK MS survey
- Base case for RRMS show steady decrease in ARR for SPMS show at more severe EDSS levels, there is greater frequency of relapses compared to less severe EDSS levels
- ERG values reported in TA527 (beta interferons & glatiramer acetate) show decrease in ARR as EDSS levels increase

Issue 8: Source of health state utility values

EDSS	ASCLEPIOS trials and Orme et al. 2007 (company base-case)		Orme et al., 2007 (ERG preferred values)	
	RRMS	SPMS	RRMS	SPMS
0	[redacted]	[redacted]	0.870	0.8250
1	[redacted]	[redacted]	0.799	0.7540
2	[redacted]	[redacted]	0.705	0.6600
3	[redacted]	[redacted]	0.574	0.5290
4	[redacted]	[redacted]	0.610	0.5650
5	[redacted]	[redacted]	0.518	0.4730
6	[redacted]	[redacted]	0.458	0.4130
7	0.297	0.252	0.297	0.2520
8	-0.049	-0.094	-0.049	-0.0940

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

- ERG consider utility values for SPMS population may not be generalizable due to small sample size
- Company estimated health state utilities, where data was not available for specific EDSS states (EDSS 7–9)
- ERG note TA624 (peginterferon beta-1a) sourced utility values from Orme et al. (2007), Company suggest using alternative from Orme et al. (2007) and EXPAND trial
- ERG noted utility values for EDSS 7 is higher in people with SPMS compared to RRMS using EXPAND trial supplemented by Orme et al.(2007) instead of Orme et al. (2007) and is not in agreement with their clinical expert opinion

Minor

Issue 8: Health state utility values

Company changes to base case

EDSS	Original base case: ASCLEPIOS and Orme et al., 2007		ERG-preferred values: Orme et al., 2007		Updated company base case: EXPAND and Orme et al., 2007	
	Utility	SE	Utility	SE	Utility	SE
0	[redacted]	[redacted]	0.8250	0.0607	0.8250	0.0607
1	[redacted]	[redacted]	0.7540	0.1087	0.7540	0.1087
2	[redacted]	[redacted]	0.6600	0.1084	0.6600	0.1084
3	[redacted]	[redacted]	0.5290	0.1125	[redacted]	[redacted]
4	[redacted]	[redacted]	0.5650	0.1084	[redacted]	[redacted]
5	[redacted]	[redacted]	0.4730	0.1077	[redacted]	[redacted]
6	[redacted]	[redacted]	0.4130	0.1082	[redacted]	[redacted]
7	0.2520	0.0941	0.2520	0.1100	[redacted]	[redacted]
8	−0.0940	0.0952	−0.0940	0.1110	−0.0940	0.1110
9	−0.2400	0.1191	−0.2400	0.1350	−0.2400	0.1350

Issue 9: Waning of treatment effect

Major

Why issue is important	Impact on ICER
Background: Most clinicians agree waning will occur at some point	
Previous appraisals: a variety of approaches with no real consistency	

Current appraisal:
• Company base case assume treatment effect with ofatumumab and all comparators was constant and would not wane over time, ("*waning is already captured within the model via all-cause discontinuation -discontinuing for any reason" noted consistent with TA533; ocrelizumab for relapsing MS*)
• Company carried out analysis to show no evidence of efficacy waning
• Including waning on top of all-cause discontinuation significant double-counting with potential loss of efficacy
• Company provide exploratory scenario analyses:
  • **Conservative scenario** (25% reduction after 5 years; 50% reduction after 8 years)
  • **Extremely conservative scenario** (25% reduction after 2 years; 50% reduction after 5 years)
• ERG: Assumptions in 'conservative scenario' preferred in ERG base case
	ICERs increases significantly when waning is applied.

Major

Waning in previous appraisals (1/2)

TA ref	Company base case/scenarios	ERG preference	Committee conclusion
ocrelizumab (TA533)	**Base case** – no treatment waning • Switch treatment in clinical practice if no longer effective **Scenarios**: • all DMTs 25% loss years 2-5, 50% loss from year 6 • delayed waning for ocrelizumab, 25% loss years 5-7, 50% loss from year 8, other DMTs as above	No changes Company model assume treatment stops after EDSS> 6 reflects clinical practice	• Treatment effect likely to wane in the long term • Stopping treatment could be considered a proxy for waning
alemtuzumab (TA312)	**Base case** - no treatment waning **Scenario** - long-term waning 25% loss or 50% loss after year 5 for all treatments **Updated base case** - alemtuzumab waning at 3 or 5 years	25% loss year 10 and beyond or 25% loss years 6-9, then 50% year 10 onwards	Uncertain on long term so inc. 3 and 5 year waning
Natalizumab (TA127) Waning not applied			
cladribine (TA616)	Based on clinical effectiveness results **cladribine**: 25% loss after 4 years, 50% loss after 5 years **Comparators**: 25% loss after 2 years, 50% after 5 years	Assumed equal weighting of waning for cladribine and all comparators	Insufficient evidence for different treatment waning assumption for cladribine
Note: Unless otherwise stated percentage reduction applied to treatment being considered as well as all comparators			

Waning in previous appraisals (2/2)

TA ref	Company base case/scenarios	ERG preference	Committee conclusion
interferon beta 1a and 1b (TA527)	• Evidence from **risk sharing scheme** provided evidence until year 10 - no waning • 50% loss after 10 years	Assessment group no changes but note assume 5% stopped treatment each year	Longer time-horizon in this current appraisal than previous appraisals so 50% after 10 years appropriate
teriflunomide (TA303)	• **Original base case** assume no waning. Patients benefit - better EDSS state than no treatment. • **Updated base case** 25% loss after 2 years, 50% after 5 years	Explored impact of inc. or exc. waning	Uncertainties whether waning occur most plausible ICER was likely to be between the estimates inc. And exc. waning effect
fingolimod (TA254)	• **Original base case** - 50% or 75% waning after first 2 years • **Update** inc. 50% waning at 5 years	Consider waning over time- 50%, 75%, 100% of original level after 2 and 5 years	• 50% waning after 5 years
peginterferon beta 1a (TA624)	• All treatments wane at same rate • After first 2 years 25% loss • After year 6 : 50% loss	Is waning constant or does it differ for technology and other comparators	Plausible to assume treatment-specific than constant rate
Note: TA32 no treatment waning. Guidance replaced by TA527; Unless otherwise stated percentage reduction applied to treatment being considered plus all comparators			

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include

confidential PAS discounts

Innovation

- Company considers ofatumumab innovative.
- It is not restricted to HA or RES populations
- It can be self-administered at home, enabling its use as first line to all RRMS patients
- Company note comparator (ocrelizumab) is only B cell therapy currently recommended by NICE for use in patients with RRMS and the only high-efficacy DMT able to be used as a first-line treatment (non-RES RRMS). Ocrelizumab is administered in hospital via infusion lasting several hours
- Ofatumumab provided in pre-filled autoinjector-pens for subcutaneous injection which, after being trained by an HCP at the first injection, are intended for monthly self-administration at home by patients or their carers

Abbreviations HA: Highly Active; RES: Rapidly Evolving Severe; RRMS: Relapsing remitting Multiple sclerosis; HCP: Health care professional

Equalities

- Company suggest the technology is unlikely to raise any equality concerns and unlikely to lead to recommendations which differentially impact patients protected by the equality legislation or disabled persons.
- Ofatumumab has potential to increase access to high efficacy treatment avoiding any negative impact of treatment delays, due to home-base, self-administration

Key questions for committee

- Are the results of the ASCLEPIOS trials generalisable to the NHS?
  What is the significance of the paucity of evidence for MS sub-groups?
- Should treatment waning be applied in the model and how should this be done?