NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission summary** from Celgene/BMS
2. **Clarification questions and company responses**
3. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRIG)
4. **Patient group, professional group and NHS organisation submissions** from:
    a. Multiple Sclerosis Trust
        i. Tracy Nicholson, patient expert, endorses this submission.
    b. Association of British Neurologists
        i. The Royal College of Physicians and Dr Victoria Williams, clinical expert, endorses this submission.
5. **Expert personal perspectives** from:
    a. Dr Eli Silber - clinical expert, nominated by Multiple Sclerosis Trust
    b. Lorraine Hazlehurst – patient expert, nominated by Multiple Sclerosis Society
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6. **Company Submission addendum** (submitted July 2020)
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12. **Technical engagement responses from consultees and commentators:**
    a. MS Trust
    b. Biogen
    c. Novartis

13. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group (LRIG)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

November 2019

File name	Version	Contains confidential information	Date
Ozanimod for treating relapsing–remitting multiple sclerosis [ID1294]	**V1**	**Yes**	**4th November 2019**

Instructions for companies

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

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

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

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

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Abbreviations

ABN	Association of British Neurologists
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AR	Annualised Relapse
ARR	Annualised Relapse Rate
AV	Atrioventricular
BBB	Blood brain barrier
BC	British Columbia
BCMS	British Columbia Multiple Sclerosis
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
BVL	Brain volume loss
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete blood count
CD	Crohn's disease
CDP	Confirmed disability progression
CE	Cost effectiveness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
CS	Corticosteroids
CSR	Clinical study report
DIC	Deviance information criterion
DIS	Dissemination in space
DIT	Dissemination in time
DLCO	Diffusing capacity of the lungs for carbon monoxide
DMF	Dimethyl fumarate
DMT	Disease modifying therapy
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOW	Every other week
EQ-5D	EuroQoL-5 dimension
ERG	Evidence Review Group
EU	European Union
EXP	Exponential
FS	Functional system
FVC	Forced vital capacity
GA	Glatiramer acetate
GP	General practitioner
HA	Highly active
HCHS	Hospital and community health services
HCRU	Healthcare resource utilization
HR	Hazard ratio
HSU	Health-state utility
HTA	Health technology assessment

ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IR	Incidence rate
ISE	Integrated summary of efficacy
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LCLA	Low-contrast letter acuity
LFT	Liver function test
LN	Natural logarithm
LOCF	Last observation carried forward
LY	Life year
MA	Marketing authorisation
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSQOL	Multiple sclerosis quality of life
NEDA	No evidence of disease activity
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analyses
NSAIDs	Non-steroidal anti-inflammatory drugs
OLE	Open label extension
PAS	Patient access scheme
PASAT	Paced auditory serial addition test
PASLU	Patient Access Scheme. Liaison Unit
PD	Pharmacodynamics
PFT	Pulmonary function test
PICOS	Population Intervention Comparison Outcome Study design
PK	Pharmacokinetics
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred Items for Systematic Reviews and Meta-Analysis
PSA	Probabilistic sensitivity analysis
PSS	Prescribed Specialised Services
PSSR	Personal Social Services Research
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
QT	Q wave T wave
RCT	Randomised clinical trial
RES	Rapidly-evolving severe
RFT	Renal function test
RMS	Relapsing multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
RSS	Risk-sharing scheme
SAP	Statistical analysis plan
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SE	Standard error
SLR	Systematic literature review
SMR	Standardized mortality ratios
SOC	Standard of care
SOT	Sub optimal treatment
SPMS	Secondary progressive multiple sclerosis

STA	Single technology appraisal
SW	South-west
SY	Subject years
T25-FW	Timed 25-Foot Walk
TEAE	Treatment-emergent adverse events
UC	Ulcerative colitis
UK	United Kingdom
US	United States
WTP	Willingness to pay

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

B.1.1 Decision problem

The final NICE scope identifies the relevant patient population as adult patients diagnosed with relapsing-remitting multiple sclerosis (RRMS). This is aligned with the anticipated marketing authorisation of ozanimod, which is expected to be for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS). CHMP opinion is expected in March 2020, and marketing authorisation (MA) by the EMA in May 2020. This submission and the decision problem for ozanimod is therefore adult patients with active RRMS.

The current pharmacological management of RRMS includes disease-modifying therapies (DMTs) to reduce the frequency, severity of and rate of disease progression. Currently, NICE recommends the following treatment options:

- **Interferon beta-1a** (Rebif® and Avonex®) and **glatiramer acetate** (Copaxone®) for RRMS and **interferon beta-1b** (Extavia®) for RRMS with 2 or more relapses within the last 2 years. Generic versions of glatiramer acetate are also available including Brabio®, Mylan (NICE TA527) (NICE 2018b)
- **Teriflunomide** (Aubagio®) and **dimethyl fumarate** (Tecfidera®) for active RRMS, only if people do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA303 and TA320 respectively) (NICE 2014e, NICE 2014d)
- **Alemtuzumab** (Lemtrada®) for active RRMS (NICE TA312) (NICE 2014a)
- **Ocrelizumab** (Ocrevus®) for active RRMS only if alemtuzumab is contraindicated or otherwise unsuitable (NICE TA533) (NICE 2018c)
- **Fingolimod** (Gilenya®) for highly active RRMS in adults who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (NICE TA254) (NICE 2012b)
- **Natalizumab** (Tysabri®) for rapidly evolving severe RRMS (NICE TA127) (NICE 2007b)
- **Cladribine** (Mavenclad®) for treating highly active MS only for rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT (NICE TA493) (NICE 2017a)

Alemtuzumab is currently under review by the EMA due to safety concerns. As a result, the EMA committee advises that during the review alemtuzumab should only be started in adults with RRMS that is highly active despite treatment with at least two disease-modifying therapies, or when other disease-modifying therapies cannot be used.

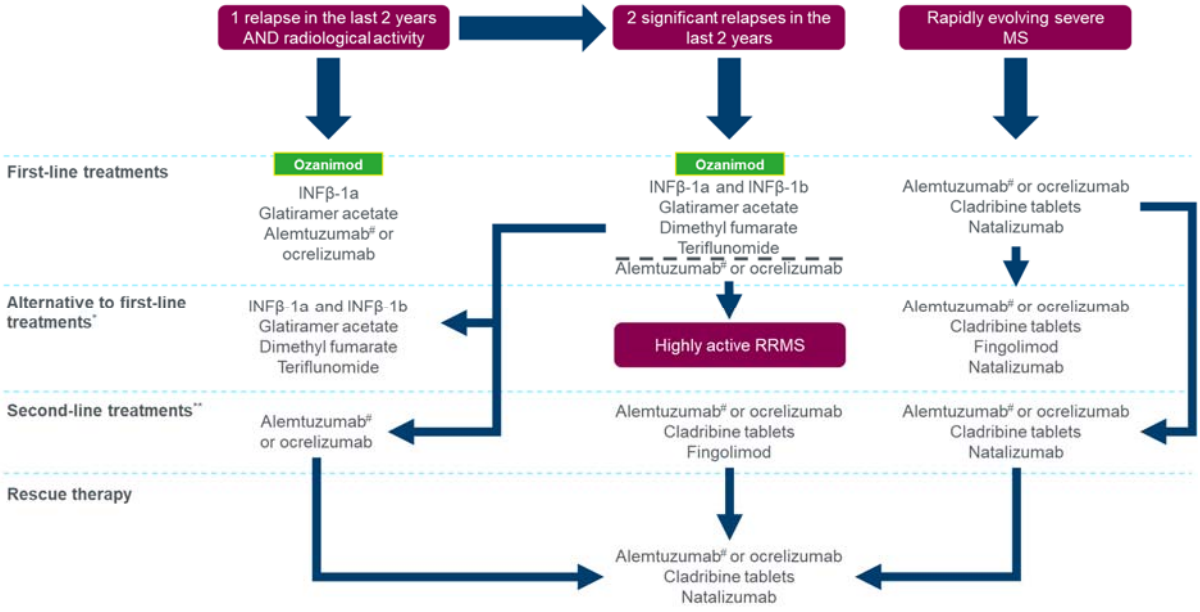
The NICE guidance on this technology will be considered for review when the EMA concludes its review into the safety of alemtuzumab. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators. Due to the expected use of ozanimod in UK clinical practice as a therapy to treat patients with active RRMS (and not highly active and/or rapidly evolving severe RRMS), alemtuzumab is not considered a relevant comparator to ozanimod. Furthermore, since ocrelizumab is only recommended by NICE to be used in patients where alemtuzumab is contraindicated or otherwise unsuitable, it is also not considered a relevant comparator.

A comparison of ozanimod versus alemtuzumab, ocrelizumab, and other NICE approved therapies used to treat patients with highly active and/or rapidly evolving severe RRMS is presented in Appendix L.

Celgene expects ozanimod to be used by UK clinicians in patients with active RRMS. As such, ozanimod would be positioned in the treatment algorithm as indicated in

Figure 1 (NHS England; 2019). Therefore, the most relevant comparators for ozanimod are interferon beta-1a (INFβ-1a), interferon beta-1b (INFβ-1b), glatiramer acetate (GA), dimethyl fumarate and teriflunomide; i.e. treatments for active RRMS, according to the NICE scope.

Figure 1. NHS England treatment algorithm for the current management of RRMS



Adapted from: (NHS England; 2019)

* Alternative first-line therapies due to intolerance **for patients experiencing disease activity whilst on first-line treatment #Alemtuzumab is currently under review by the EMA due to safety concerns. As a result, the EMA committee advises that during the review alemtuzumab use should only be started in adults with RRMS that is highly active despite treatment with at least two disease-modifying therapies, or when other disease-modifying therapies cannot be used. Ocrelizumab is recommended in cases where alemtuzumab is contraindicated or unsuitable.

Abbreviations: IFN: Interferon; MS: Multiple Sclerosis; RRMS: Relapsing remitting multiple sclerosis

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsing-remitting MS	As per scope	
Intervention	Ozanimod	Ozanimod 1 mg daily oral	
Comparator(s)	For patients with active RRMS: • Alemtuzumab* • Beta-interferon • Dimethyl fumarate • Glatiramer acetate • Teriflunomide • Ocrelizumab** (only if alemtuzumab is contraindicated or otherwise unsuitable) • Peginterferon beta-1a (subject to ongoing NICE appraisal) For patients with highly active (HA) RRMS despite previous treatment: • Alemtuzumab* • Cladribine tablets • Fingolimod • Ocrelizumab** (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with rapidly-evolving severe (RES) RRMS: • Alemtuzumab* • Cladribine tablets	For patients with active RRMS: • Alemtuzumab* • Beta-interferons • Glatiramer acetate • Dimethyl fumarate • Teriflunomide • Ocrelizumab** (only if alemtuzumab is contraindicated or otherwise unsuitable) • Peginterferon beta-1a (subject to ongoing NICE appraisal)	*Alemtuzumab is currently under review by the EMA due to safety concerns. As a result, the EMA committee advises that during the review alemtuzumab use should only be started in adults with RRMS that is highly active despite treatment with at least two disease-modifying therapies, or when other disease-modifying therapies cannot be used. Due to the expected use of ozanimod in UK clinical practice as a therapy to treat patients with active RRMS (and not highly active RRMS) alemtuzumab is not considered a relevant comparator to ozanimod. **Since ocrelizumab is only recommended by NICE to be used in patients where alemtuzumab is contraindicated or otherwise unsuitable, it is also not considered a relevant comparator to ozanimod. Due to the expected use of ozanimod in UK clinical practice as a therapy to treat patients with active RRMS, this submission will not consider ozanimod for the treatment of patients with either HA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Natalizumab • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)		or RES RRMS.
Outcomes	• Relapse rate • Severity of relapse • Disability (e.g. EDSS) • Symptoms of MS (e.g. fatigue, cognition and visual disturbance) • Freedom from disease activity (e.g. lesions on MRI scans) • Mortality • Adverse effects of treatment • Health-related quality of life	• Relapse rate • Disability • Freedom from disease activity • Mortality • Adverse effects of treatment • Health-related quality of life • Brain atrophy (brain volume) • Radiological (MRI) measurements of disease activity (T2 and Gd-E T1 brain lesion)	RADIANCE and SUNBEAM did not explore severity of relapse, and symptoms in their trial design endpoints. Freedom from disease activity has been reported as no evidence of disease activity 3 (NEDA-3) and 4 (NEDA-4).
Subgroups to be considered	If the evidence allows the following subgroups will be considered (in addition to those specified above for comparators): • People who could not tolerate previous treatment	• No subgroups will be considered	

Abbreviations: EDSS: Expanded Disability Status Scale; EMA: European Medicines Agency; Gd-E; Gadolinium-enhancing: HA: Highly active; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; NICE: National Institute for Health and Care Excellence; NEDA: No evidence of disease activity: RES: Rapidly-evolving severe; RRMS: Relapsing-remitting multiple sclerosis

B.1.2 Description of the technology being appraised

A summary of the technology to be appraised is presented in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Ozanimod
Mechanism of action	Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5. Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration (namely of circulating B and T lymphocytes) into the central nervous system (CNS), thereby modulating immunity. Ozanimod is 27-fold more selective to $S1P_1$ relative to $S1P_5$ and has little activity on other S1P receptors ($S1P_2$, $S1P_3$, and $S1P_4$) (Scott 2016). Pharmaceutical activation of sphingosine 1-phosphate receptor 1 (S1P1R) by ozanimod induces internalisation and degradation of S1P1R from the cell surface. The resulting reduction of surface expressed S1P1R causes transient retention of the T cell in the lymph nodes (Subei 2015).
Marketing authorisation/CE mark status	Ozanimod does not currently have a MA in the UK. An application for a MA was submitted to the European Medicines Agency in March 2019. CHMP opinion is expected in March 2020, and MA in May 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated licence for ozanimod is for the treatment of adult patients with RRMS.
Method of administration and dosage	Ozanimod hydrochloride 1 mg (equivalent to ozanimod 0.92 mg) is administered orally once daily. The titration regimen for ozanimod consists of 0.25 mg ozanimod hydrochloride (equivalent to ozanimod 0.23 mg) starting on Day 1 for 4 days, then 0.5 mg ozanimod hydrochloride (equivalent to ozanimod 0.46 mg) starting on Day 5 for 3 days, followed by the assigned treatment level beginning on Day 8. Please note that throughout this submission the term ozanimod 1 mg, 0.5 mg and 0.25 mg will be used to refer to ozanimod hydrochloride 1 mg, 0.5 mg and 0.25 mg.
Additional tests or investigations	The introduction of ozanimod would not require additional tests, investigations or administration beyond those that are currently required for all patients with MS.
List price and average cost of a course of treatment	£343.00 per 7 tab initiation pack (4 x 0.23 mg and 3 x 0.46 mg); £1,373.00 per 28 tab 0.92 mg pack (£17,910.00 pa).
Patient access scheme (if applicable)	[redacted]*

Source: Identified in table

Abbreviations: CNS: Central nervous system; S1P: sphingosine 1-phosphate; S1P1R: Sphingosine 1-phosphate receptor 1; RRMS: Relapsing-remitting multiple sclerosis *[redacted]

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

B.1.3.1. Disease overview

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating condition of the central nervous system (CNS) leading to the formation of focal confluent lesions of primary demyelination in the white and grey matter, as well as diffuse damage and neurodegeneration in the entire brain (Lassmann 2007, Lassmann 2018). This production of lesions, and atrophy of the brain, optic nerves, and spinal cord results in severe physical and mental disability (Tullman 2013, Giovannoni 2016). The symptoms of MS can include pain, disturbance to muscle tone including weakness and spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, numbness, visual disturbance and cognitive impairment (Gross 2017).

MS is a disease continuum with four main presenting phenotypes based on the relative presence and clinical dominance of either episodic active neuroinflammation with associated disability, or disability progression independent of acute inflammatory events (Lublin 2014a). MS is defined according to the 2017 McDonald criteria (see Appendix D1.4), and is grouped based on clinical course as follows (Lublin 2014b, Thompson 2018):

- Clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS)
- Relapsing-remitting MS (RRMS)
- Secondary progressive MS (SPMS)
- Primary progressive MS (PPMS)

Approximately 85% of people with MS are first diagnosed with RRMS and 15% are diagnosed with PPMS (Kamm 2014, National MS Society 2019). Patients with RRMS experience unpredictable and recurring clinical episodes of acute neurological dysfunction (relapses) that are driven by acute neuroinflammation. This is followed by a recovery of function (remission), although studies have shown that some patients will have residual disability following a relapse (Confavreux 2000). A relapse is a clinically evident 'attack' of neuroinflammation and demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, either completely or partially (Rolak 2003, Kalincik 2015).

Patients with RRMS could be further classified as having highly active (HA) disease, or rapidly evolving severe (RES) disease based on clinical and imaging features. RES is defined as two or more disabling relapses in one year, and one or more gadolinium-enhancing (Gd-E) lesions on brain magnetic resonance imaging (MRI), or a significant increase in T2 lesion load compared with a previous MRI (NHS England 2019). Patients with HA RRMS are defined as those with an unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year despite treatment with at least one DMT (NHS England 2019). Based on feedback from UK clinicians, ozanimod is expected to be used in clinical practice to treat patients with active RRMS (and not HA or RES RRMS). Therefore, this submission will only focus on an active RRMS patient population.

In absence of treatment, approximately 50% of patients with RRMS eventually develop SPMS within 10 years after being diagnosed, and up to 90% within 20-25 years (Gross 2017). SPMS is a period of steady disease progression with less distinguishable clinical signs of acute neuroinflammation, after an initial period of neuroinflammatory-driven relapses and remission. Occasional relapses as well as periods of stability may occur in SPMS patients, however disability gradually increases over time (Gross 2017).

Relapses in MS are associated with an influx of inflammatory T-cells into the CNS, leading to breakdown of the blood-brain barrier (BBB), followed by entry of B-cells and macrophages, all of which result in demyelination and axonal damage (Hauser 2006, Tullman 2013). Although the exact pathophysiology remains elusive, research suggests a key role of the sphingosine-1-phosphate 1 receptor (S1P1R) in the development and progression of MS, as it mediates lymphocyte trafficking (Scott 2016). The influx of inflammatory cells and the subsequent damage creates lesions on the brain which can be measured using magnetic resonance imaging (MRI). Repeat bouts of relapses and remittance leads to a build-up of lesions and brain atrophy, which result in significant disease progression and a worsening of MS symptoms.

MRI scans further reveal the level of extensive damage of the brain and spinal cord in patients with MS, even in patients that initially seem symptomless and clinically silent, and are therefore crucial in the diagnosis of MS, and MS disease monitoring processes (Ge 2006, Siva 2013). Acute inflammatory lesions and relapses impair cognitive function (DeLuca 2015), and absence of MRI activity, new T2 lesions, or enlarging T2 lesions have been associated with less cortical and subcortical grey matter atrophy (Damasceno 2016).

With the advancement in MRI technology, the importance of white matter, grey matter, cortical volume, and thalamic volume in the pathogenesis of MS has increased greatly (Kern 2015). Thalamic involvement in patients with MS occurs relatively early in the course of the disease; it has been detected in patients with CIS suggestive of MS (Kern 2015). The thalamic grey matter atrophy is directly associated with cognitive impairment and can be used for prediction of disease progression (Kern 2015). Changes in the thalamus occur early in the MS disease course, particularly in patients who are more likely to have more rapid disease progression, and concluded that greater decrease in thalamic and cortical volume, during the first 10 years after the onset of MS, influences disability progression (Zivadinov 2013). In terms of RRMS, a correlation has been found between the rate of thalamic volume loss and a change in the EDSS score during a 2 year follow-up (Filippi 2013).

There are a number of factors that are associated with reduced brain volume; Radue et al. determined that increasing age, disease duration, T2 lesion volume, T1-hypointense lesion volume, and disability were all significantly associated with reduced brain volume (Radue 2015). Confirmed disability progression was most frequent in patients with the greatest brain volume loss (BVL). Fritz et al. have shown that lower thalamic volume was directly correlated and had a significant association with reports of lower physical quality of life, as well as higher pain severity scores (Fritz 2016). In addition to physical disability, cognitive impairment has also shown a correlation with regional, cortical, and total grey matter volume (Jeffery 2016, Favaretto 2018).

In a study conducted on the predictive value of MRI-parameters for domains of cognitive function in MS, cortical volume was the strongest predictor of overall cognitive function and efficiency (Pinter 2015). T2-lesions load was also identified as an important predictor of overall cognition, cognitive efficiency, and memory function. Normalised thalamic volume was also determined to be a strong predictor of overall cognition (Pinter 2015).

The burden created from the number and the location of lesions, as well as repeating relapses influences the extent and type of functional disability; for example, coordination impairment has been linked to lesion location in areas such as the limbic and prefrontal cortex (Charil 2003).

B.1.3.2. Diagnosis and measurement of disease state

In the absence of a definitive diagnostic test, the 2017 McDonald diagnostic criteria are widely used in clinical practice for the diagnosis of MS, making use of advances in MRI techniques to allow diagnosis to be made at an earlier stage (Thompson 2018). The McDonald criteria

allow for a combination of diagnostic evidence such as MRI and clinical symptoms to satisfy both dissemination in time (DIT) (CNS damage detected in ≥2 distinct points in time) and dissemination in space (DIS) (two or more CNS regions affected) requirements.

In clinical practice, disability progression is measured by the accumulation of permanent disability according to the Expanded Disability Status Scale (EDSS) (Kurtzke 1983). EDSS scores range from 0 (no disability) to 10 (death), in incremental units of 0.5 (after EDSS 1). Scoring is based on measures of impairment in eight functional systems: pyramidal (weakness or difficulty in moving limbs); cerebellar (ataxia, loss of coordination, or tremor), brain stem - problems with speech, swallowing, and nystagmus (involuntary eye movement); sensory (numbness or loss of sensations); bowel and bladder function; visual function; cerebral (or mental) functions and other (neurologic findings) (Kurtzke 1983). An accurate and reliable evaluation of confirmed disease progression (CDP) is important and should include two consecutive examinations carried out by the same physician at least 6 months apart, in order to effectively gauge the rate of decline in health over this time period.

Despite being the most commonly used measure of MS disease progression, the EDSS scale has a number of limitations, including but not limited to, failing to capture QoL, relying on walking as the main measure of disability, and being a predominantly subjective examination open to investigator bias (Bosma 2013, Meyer-Moock 2014, van Munster 2017). CDP is defined as an increase in EDSS score over a period of time, typically 3 or 6 months, and although it is often used as an endpoint in MS clinical trials, it has been regarded as inaccurate in the measurement of disease progression in MS, due to its basis in the EDSS score, which in itself has the limitations outlined earlier.

It is recognised that the EDSS does not adequately assess upper limb function and cognitive impairment and is open to physician bias. Therefore, additional neurological rating scales, quantitative neurological performance tests (e.g. MSFC) are often used as secondary measurements of disability. The advantages and disadvantages of the EDSS in assessing disability in MS are well-known, and thus there is a recognised need for the development of alternative sensitive scales that assess disability (Bosma 2013, Meyer-Moock 2014, van Munster 2017).However, there are no specific recommendations regarding the acceptability of alternative scales, and although alternative scales are still under development, there is a need for them to be validated. To fully capture the impact of disease progression on patients, the ozanimod clinical trial programme also included other tool for assessing disease impairment, including the timed 25-Foot Walk (T25-FW), SDMT, PASAT and MRI data of Gd lesions, T2 lesions, and brain volume. The cumulative findings from these measures should also be used when evaluating the potential therapeutic effect of a drug, in order to better evaluate the impact of the drug on MS disease progression. These measures of MS activity are as follows:

- Gd-E is a marker for BBB breakdown and histologically correlates with the inflammatory phase of lesion development, therefore an increase in Gd-E lesions relates to disease progression (Pitteri 2016)
- T2 lesion formation, which is also measured on MRI, mirrors a complex sequence of inflammatory, degenerative and reparative processes. The formation of T2 lesions is a marker of inflammatory activity and repair mechanisms, i.e. relapses and recovery (Mostert 2010, Rovira 2013)
- Brain volume and its association with disease severity in MS is currently being explored in the MS research community. BVL occurs at a higher rate in patients with MS (Chard 2002, De Stefano 2010), starting in the earliest stages of MS, and occurring throughout the disease course at a rate considerably greater than in the general population: the average rate of BVL in MS patients ranges from 0.5% to 1.3% (median 0.7-0.8%) versus 0.1% to 0.3% in healthy gender and age matched controls (median 0.2%) (Radue 2015, Tsivgoulis 2015, Favaretto 2018). BVL has been shown to be correlated

to and predictive of disability progression and cognitive decline over the patient's lifetime (Fisher 2002, Popescu 2013)

- Grey matter volume reduction is associated with long-term disability, and MS patients tend to show significantly smaller cortical and deep grey matter volume compared with healthy people. Volume loss, in deep grey matter, tends to be faster than volume loss in other areas of the brain across all clinical MS phenotypes, and tends to be the only region associated with disability accumulation (Eshaghi 2018). One study found that patients with a smaller grey matter volume at baseline had a shorter time to EDSS progression (Eshaghi 2018)
- Cortical volume has long been correlated with disability and cortical atrophy in MS; patients with high cortical lesion loads tend to have higher EDSS increases (Calabrese 2012)
- Cortical damage tends to differ between the various clinical phenotypes, and it has been shown to correlate better with clinical disability and cognitive impairment than measures of T2 lesion load or white matter damage (Calabrese 2012). Epilepsy and fatigue are also likely to be related to cortical involvement (Filippi 2013)
- No evidence of disease activity (NEDA) is a composite endpoint comprised of CDP, MRI outcomes, and annualised relapse rate (ARR). It is believed to be able to predict MS disease activity, disease progression, and treatment efficacy. There are currently eight levels of NEDA, with NEDA-3 and NEDA-4 regarded as the most commonly utilised tools in MS. NEDA-3 is defined by no relapses, no increase in disability, and no new or active (enhancing) lesions on MRI scans (Hegen 2018). NEDA-4 is defined as no evidence of relapses, new or enlarged T2 lesions and 6-month CDP (as defined in NEDA-3), and a mean annualised rate BVL of less than 0.4% (Kappos 2016).

B.1.3.3. Clinical pathway of care

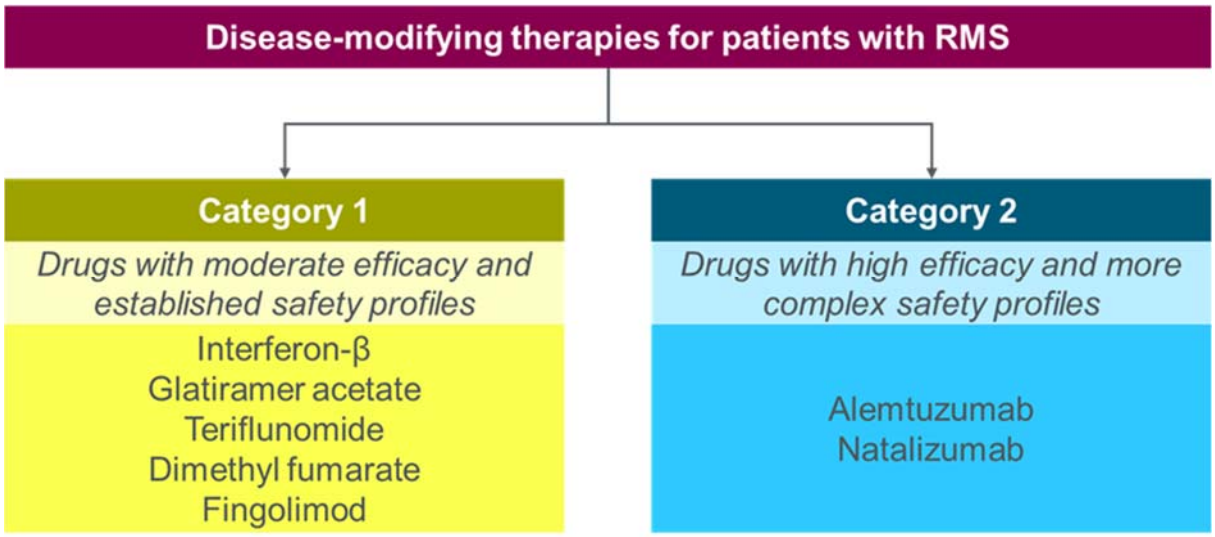
DMTs recommended by NICE in the UK for the treatment of RRMS include interferon beta (IFNβ) therapies [IFNβ-1a (Rebif® and Avonex®) and IFNβ-1b (Extavia®)] (NICE 2018b), glatiramer acetate (GA; Copaxone®) (NICE 2018b), teriflunomide (Aubagio®) (NICE 2014e), dimethyl fumarate (DMF; Tecfidera®) (NICE 2014d), natalizumab (Tysabri®) (NICE 2007b), fingolimod (Gilenya®) (NICE 2012b), alemtuzumab (Lemtrada®) (NICE 2014a), ocrelizumab (Ocrevus®) (NICE 2018c), and cladribine tablets (Mavenclad®) (NICE 2017a). The choice of DMT prescribing in UK for RRMS is largely driven by an informed discussion and consensus between the prescribing clinician and the patient based on the level of disease activity, patient risk tolerance, patient preference and patient lifestyle considerations such as family planning. Patient preference for the route and frequency of administration also varies. Real world studies of MS patients have repeatedly shown that adherence among patients taking an oral DMT is better than in patients taking injectable DMTs (Agashivala 2013, Bergvall 2014).

According to the NHS England treatment algorithm published in September 2018 (as depicted in Figure 1), IFNβ and GA are used as first-line treatments, with teriflunomide and DMF also recommended in this patient population (NHS England; 2019). Although alemtuzumab could also be used as a first-line treatment option, it was noted to be a high-risk treatment associated with increased burden of monitoring. Alemtuzumab is currently under review by the EMA due to safety concerns; as a result, EMA has restricted its use to 'adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least 2 DMTs, or when other DMTs cannot be used' (EMA 2019).

Treatments such as natalizumab, cladribine tablets, alemtuzumab, fingolimod and ocrelizumab are typically used in highly active, rapidly evolving severe or sub-optimally treated patient populations. Autologous stem cell therapy is currently been used as rescue therapy.

The Association of British Neurologists (ABN) have also issued guidance on the prescribing of DMTs for MS (Figure 2). The ABN classifies the treatments into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles) (Scolding 2015). Celgene believes that ozanimod fits into category 1, i.e. drugs with moderate efficacy and established safety profiles. Therefore, ozanimod is likely to be used as a first-line therapeutic in the treatment pathway of MS, and therefore, the most relevant comparators are IFNβ, GA, teriflunomide and dimethyl fumarate.

Figure 2. Categorisation of DMTs in accordance with the ABN guidelines



Source: Adapted from (Scolding 2015)
Abbreviations: ABN: Association of British Neurologists; DMT: Disease-modifying treatment; RMS: Relapsing multiple sclerosis

B.1.4 Equality considerations

No equality issues have been identified for ozanimod.

B.2. Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify clinical trials relevant to the NICE decision problem. This systematic review assessed the efficacy, safety, and tolerability outcomes associated with key interventions in the treatment of relapsing-remitting forms of multiple sclerosis (RRMS). Studies identified in the SLR were used to inform the Network Meta-Analysis (NMA). The final NICE scope identifies the relevant patient population as adult patients diagnosed with RRMS. The proposed population for this technology submission is aligned with the marketing authorisation and will focus on the RRMS population only.

The protocol, search strategy and details of the methodology used to identify the clinical evidence are summarised in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The systematic literature review identified two Phase III RCTs, RADIANCE Part B (RPC01-201B) and SUNBEAM (RPC01-301)), and one Phase II RCT, RADIANCE Part A (RPC01-201A)), relevant to the decision problem.

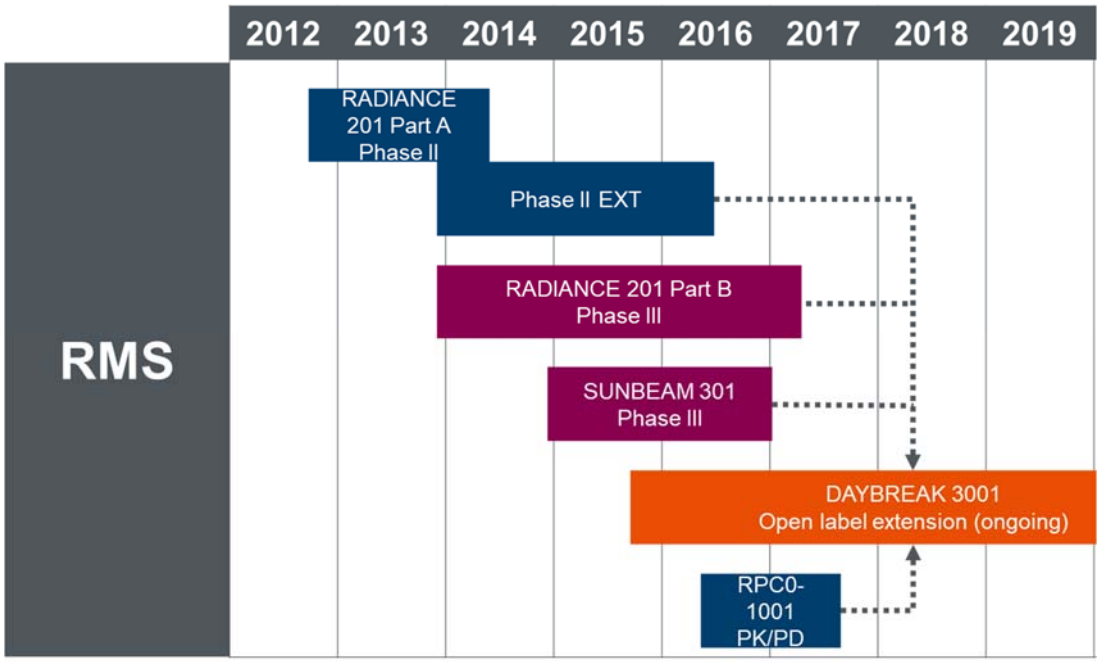
The two pivotal Phase III head-to-head trials versus IFN β-1a, along with the Phase II placebo-controlled RADIANCE Part A trial, are part of the ozanimod clinical trial programme, designed to demonstrate the safety and efficacy of ozanimod. Please note that while the target of this submission is active RRMS, the recruited population in the RADIANCE Part B and SUNBEAM also consisted of a small number of patients with SPMS (1.8% of the ITT population in both Phase III trials) in addition to patients with RRMS, hence the target population of the trial has been referred to as RMS (an overarching term including patients with RRMS and SPMS).

B.2.2.1. Ozanimod clinical trial programme

The ozanimod clinical trial programme in MS involves five key overlapping clinical trials, as depicted in Figure 3. These include the Phase I study RPC01-1001 (a randomised, open-label study to evaluate the multi-dose pharmacokinetics [PK] and pharmacodynamics [PD] of ozanimod), one Phase II trial including a dose-blinded extension (RPC01-201A, RADIANCE Part A), two Phase III head-to-head trials (RPC01-201B, RADIANCE Part B and RPC01-301, SUNBEAM), and an ongoing Phase III open label trial (RPC01-3001, DAYBREAK) that is an extension of RPC01-1001, RADIANCE Part A and B, and SUNBEAM.

The evidence base for ozanimod in this submission is comprised of two pivotal Phase III RCTs (RADIANCE Part B and SUNBEAM), a Phase II RCT (RADIANCE Part A) and an open label extension trial, DAYBREAK.

Figure 3. Ozanimod clinical trial programme



Note: Arrows depict movement of suitable patients from the trial they were initially enrolled and involved in, into the Phase III open label extension trial, DAYBREAK
Abbreviations: PD: pharmacodynamics; PK: pharmacokinetics; RMS: relapsing multiple sclerosis

B.2.2.2. Patient eligibility

The criteria used for the recruitment of patients into the RADIANCE Part A and Part B and SUNBEAM trials was as follows:

- Adult subjects with RMS aged 18 to 55 years, inclusive
- Meeting the revised McDonald 2010 criteria
- EDSS (expanded disability status scale) score between 0 and 5.0 at baseline
- At least 1 documented relapse within the last 12 months, or at least 1 documented relapse within the last 24 months plus at least 1 Gd-E lesion within the last 12 months, prior to randomization
- No history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening through randomisation
- Positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation

Exclusion criteria:

- PPMS
- Disease duration greater than 15 years and an EDSS of 2.0 or less
- Previous inability to tolerate IFN-β
- Specific cardiovascular conditions (e.g., recent myocardial infarction, stroke, or prolonged Fridericia-corrected QT interval [QTcF])
- Resting heart rate less than 55 beats per min (bpm) at screening
- Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers

- Any active infection

The population used for the Phase I PK/PD study were adult subjects with RMS which include the RRMS population which is the focus of this technology submission.

Patients who completed one of the parent studies (RADIANCE Part A extension, RADIANCE Part B, SUNBEAM, or the Phase I PK/PD study in RMS patients) were eligible to enter the ongoing open-label extension study DAYBREAK (Figure 3). All patients were required to undergo dose titration at the start of DAYBREAK, except those entering the trial from either the blinded extension of RADIANCE Part A, or the RPC01-1001 study. If the duration between the last dose of ozanimod in either of these two parent studies and the first dose in the open-label extension (OLE) exceeded 14 days, then dose escalation and cardiac monitoring were required (Celgene 2019d).

Trial overview

The RADIANCE Part A, Part B and SUNBEAM trials explored the efficacy and safety of orally administered 0.5 mg ozanimod and 1 mg ozanimod, with the marketing authorisation expected to be only for the 1 mg ozanimod dosage in adult patients with RRMS. As such this submission will present efficacy data only for the ozanimod 1 mg dosage, however, both ozanimod 0.5 mg and ozanimod 1 mg safety data will be presented to support the overall safety profile of the intervention. The outcomes for the three trials are presented separately in this submission, as well as pooled analyses of RADIANCE Part B and SUNBEAM to support the efficacy of ozanimod 1 mg administered orally in the RRMS patient population to reduce relapse rates, disability, and disease activity.

RADIANCE Part A (RPC01-201A) was a 24-week, Phase II, multi-centre, randomised, double-blind, placebo-controlled trial with a blinded extension of 24 months. The primary endpoint of the core study was the mean cumulative total number of Gd-E lesions from Week 12 to Week 24. Outcomes from the Phase II trial, including the blinded extension, will be presented as supplementary data to support the efficacy trial data from RADIANCE Part B and SUNBEAM.

RADIANCE Part B (RPC01-201B) was a 24-months multi-centre, randomised, double-blind, double-dummy, active-controlled parallel group Phase III trial where the efficacy and safety of ozanimod compared to IFNβ-1a (Avonex®) was explored in subjects with RMS.

SUNBEAM (RPC01-301) was a 12-months multi-centre, randomised, double-blind, double-dummy, active controlled, parallel group Phase III study to evaluate the efficacy and safety of ozanimod compared to IFNβ-1a (Avonex®) in subjects with RMS (Section B.2.3.1).

A summary of the clinical evidence for ozanimod is presented in Table 3.

Table 3. Clinical effectiveness evidence for efficacy and safety of ozanimod

Study name	RADIANCE Part A	RADIANCE Part B	SUNBEAM	DAYBREAK OLE
Study code	**RPC01-201A**	**RPC01-201B**	**RPC01-301**	**RPC01-3001**
Study design	A 24-week placebo-controlled treatment period and 96-week blinded extension period for a total of 120 weeks (Cohen 2019a)	A Phase III, 24-month, randomised, multi-centre, double-blind, double-dummy, active-controlled parallel group study	A Phase III, 12-month, randomised, multi-centre, double-blind, double-dummy, active-controlled parallel group study	An ongoing, single-arm, Phase III, multi-centre, open label extension study
Population	RRMS patients diagnosed using the revised 2010 McDonald criteria exhibiting a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS. Patients were required to have an EDSS score between 0 and 5.0 at baseline and meet one of the following disease activity criteria: • At least 1 documented relapse within the last 12 months prior to screening, or • At least 1 documented relapse occurred within the last 24 months prior to screening and documented evidence of at least 1 Gd-E lesion on brain MRI within the last 12 months prior to randomization			• Completed one of the parent trials: RADIANCE Part A or B, SUNBEAM, or the Phase I PK/PD trial RCP01-1001 • Does not have a condition that would require withdrawal from one of the parent trials (RADIANCE Part A and B, SUNBEAM, or RCP01-1001) • Has no conditions requiring treatment with a prohibited concomitant medication
Intervention(s)*∞	• Ozanimod 0.5 mg oral daily • Ozanimod 1.0 mg oral daily	• Ozanimod 0.5 mg oral daily • Ozanimod 1.0 mg oral daily	• Ozanimod 0.5 mg oral daily • Ozanimod 1.0 mg oral daily	Ozanimod 1.0 mg oral daily
Comparator(s)	Placebo	IFN β-1a (30µg) weekly	IFN β-1a (30µg) weekly	

Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes	No
Indicate if trial used in the economic model	Yes	Yes (pooled analysis with SUNBEAM)	Yes (pooled analysis with RADIANCE Part B)	No
Rationale for use/non-use in the model	Phase II study included in NMA. Outputs used in CE analysis.	Pivotal trial providing clinical data for the economic model	Pivotal trial providing clinical data for the economic model	Data in the economic model is based on the pivotal clinical trials
Reported outcomes specified in the decision problem	• Annualised relapse rate • Adverse events • MRI	• Annualised relapse rate • Disability • Disease activity • Mortality • Adverse events • MRI • Health-related quality of life • Brain atrophy	• Annualised relapse rate • Disability • Disease activity • Mortality • Adverse events • MRI • Health-related quality of life • Brain atrophy	• Adverse events • Annualised relapse rate • Disability

Source: (Celgene 2015c, Celgene 2017a, Celgene 2017b, Celgene 2019d)

Abbreviations: EDSS: Expanded disability status scale; Gd-E: gadolinium-enhanced; IFN: interferon MS: multiple sclerosis; MRI: magnetic resonance imaging; OLE: open-label extension; PK: pharmacokinetics; PD: pharmacodynamics RMS: relapsing multiple sclerosis

* The 0.5 mg dosage was studied in all three Phase III studies (RADIANCE Part A and B, SUNBEAM, DAYBREAK). As it is not the dosage approved, the results for the 0.5 mg dosage arms will only be presented in the safety sections, while the focus of this submission will be the 1 mg dose

∞ The initial study treatment consisted of a 7-day dose titration regimen. For patients randomised to receive treatment with ozanimod, this regimen consisted of 0.25 mg ozanimod starting on Day 1 for 4 days, then 0.5 mg ozanimod starting on Day 5 for 3 days, followed by the assigned treatment level beginning on Day 8. Patients assigned to the INF arm received a dummy up titration to keep the blinding. Patients were screened for protocol eligibility up to 30 days before the baseline visit. Informed consent was obtained after the study was fully explained to each patient as well as before any procedures or assessments were conducted.

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

The clinical trials identified as relevant to the decision problem in Section B2 of this submission, include two Phase III RCTs, RADIANCE Part B (RPC01-201B) and SUNBEAM (RPC01-301)), and one Phase II RCT, RADIANCE Part A (RPC01-201A)).

The methodologies of RADIANCE Parts A and B, and SUNBEAM are summarised in Table 4.

Table 4. Comparative summary of trial methodology

Trial	RADIANCE Part A	RADIANCE Part B	SUNBEAM
Duration	**24 weeks (6 months)**	**24 months**	**> 12 months**
Trial design	A Phase II 24-week placebo-controlled treatment period and 96-week blinded extension period for a total of 120 weeks (Cohen 2019a)	Randomised, multi-centre, double-blind, double-dummy, active-controlled parallel group Phase III	Randomised, multi-centre, double-blind, double-dummy, active-controlled parallel group Phase III
Eligibility criteria for participants	• Adult subjects with RMS aged 18 to 55 years, inclusive • Meeting the revised McDonald 2010 criteria • EDSS (expanded disability status scale) score between 0 and 5.0 • At least 1 documented relapse within the last 12 months, or at least 1 documented relapse within the last 24 months plus at least 1 GdE lesion within the last 12 months, prior to randomization • No history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening through randomisation • Positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation Exclusion criteria: • PPMS • Disease duration greater than 15 years and an EDSS of 2.0 or less • Previous inability to tolerate IFN-β • Specific cardiovascular conditions (eg, recent myocardial infarction, stroke, or prolonged Fridericia-corrected QT interval [QTcF]) • Resting heart rate less than 55 beats per min (bpm) at screening • Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers • Any active infection		
Settings and locations where the data were collected	• 13 countries (North America and Europe) • 55 study centres	• 21 countries (EU/US/South Africa) • 150 study centres • 16 patients in 6 sites across the	• 18 countries (North America/Europe/ New Zealand) • 158 study centres

		UK	
Trial drugs – Interventions and comparators	Patients (N=258) were randomised (1:1:1) to receive*: • Ozanimod 1 mg oral daily (n=83) • Ozanimod 0.5 mg oral daily (n=87) • Placebo (n=88)	Patients (N=1313) were randomised (1:1:1) to receive*: • Ozanimod 1 mg oral daily (n=433) • Ozanimod 0.5 mg oral daily (n=439) • IFN β-1a 30µg weekly (n=441)	Patients (N=1346) were randomised (1:1:1) to receive: • Ozanimod 1 mg oral daily (n=447) • Ozanimod 0.5 mg oral daily (n=451) • IFN β-1a 30µg weekly (n=448)
Trial drugs – permitted and disallowed concomitant medication	• Beta-blockers, calcium channel blockers, or Class 1A or Class 3 antiarrhythmics were not permitted during the study • Systemic corticosteroids were not permitted during the study except for subjects experiencing a protocol-defined relapse • Methylprednisolone 1 g per day over 5 consecutive days maximum was permitted as rescue medication in case of protocol-defined relapse • Treatments were permitted for symptoms related to MS such as spasticity, incontinence, pain and fatigue		
Primary outcomes (including scoring methods and timings of assessments)	• Total number of GdE lesions on MRI (weeks 12–24)	• ARR at the end of Month 24	• ARR during the treatment period
Other outcomes used in the economic model/specified in the scope	• ARR • Discontinuation • Adverse events	• Time to onset of disability progression after 3 months and after 6 months • ARR • Discontinuation • Adverse events	• Time to onset of disability progression after 3 months and after 6 months • ARR • Discontinuation • Adverse events
Pre-planned subgroups	• Baseline EDSS score (EDSS ≤3.5 versus EDSS >3.5) • Baseline presence of GdE lesions (lesions present versus lesions absent) • Age at baseline (age ≤40 versus age >40) • Sex (female versus male) • Weight (<median	• Baseline EDSS score (EDSS ≤ 3.5 vs. EDSS > 3.5) • Baseline presence of Gd-enhancing lesions (present vs. Absent) • Prior treatment status (treatment naïve vs. Previously treated)	• Baseline EDSS score (EDSS ≤ 3.5 vs. EDSS > 3.5) • Baseline presence of Gd-enhancing lesions (present vs. Absent) • Prior treatment status (treatment naïve vs. Previously treated)

	versus ≥median) • Number of relapses in the past 12 months (<2, ≥2) for the ARR endpoint only • Regions (North America, Western Europe, and Eastern Europe)	• Age at Baseline (age ≤ 40 vs. Age > 40) • Sex (female vs. Male) • Race (white vs. Non-white) • Weight (< median vs. ≥ median) • Number of relapses in the past 12 months (< 2, ≥ 2) for ARR endpoint only • Regions (North America, Western Europe, Eastern Europe)	• Age at Baseline (age ≤ 40 vs. Age > 40) • Sex (female vs. Male) • Race (white vs. Non-white) • Weight (< median vs. ≥ median) • Number of relapses in the past 12 months (<2, ≥2) for ARR endpoint only • Regions (North America, Western Europe, Eastern Europe, Latin America, New Zealand)
Publications and Presentations	(Cohen 2019a)	(Cohen 2019b) (Comi 2018b) (Comi 2018a) (Cree 2018) (Steven 2018) (Schippling 2019)	(Comi 2019) (Comi 2018b) (Comi 2018a) (Cree 2018) (Steven 2018) (DeLuca 2018)

Source: In table, and (Receptos 2015a, Receptos 2015b, Celgene 2017a, Celgene 2017b, Celgene 2019c, Celgene)

* For all patients, the initial study treatment consisted of a 7-day dose titration regimen. This regimen consisted of 0.25 mg ozanimod starting on Day 1 for 4 days, then 0.5 mg ozanimod starting on Day 5 for 3 days, followed by the assigned treatment level beginning on Day 8. Patients assigned to the INF arm received a dummy up titration to keep the blinding.

Abbreviations: ARR: annualised relapse rate; DMT: disease-modifying therapy; EDSS: Expanded disability status scale; Gd-E: gadolinium-enhanced; IFN: interferon MS: multiple sclerosis; MRI: magnetic resonance imaging; OLE: open-label extension; PK: pharmacokinetics; PD: pharmacodynamics RMS: relapsing multiple sclerosis

B.2.3.1. Trial design

The designs of each study are described in Table 4. Further details of the trial designs are outlined in Appendix D.

B.2.3.2. Drugs and concomitant medications in RADIANCE Part A, RADIANCE Part B, and SUNBEAM

Concomitant treatment with medications with a known impact on the cardiac conduction system (e.g., beta-blockers, calcium channel blockers, or Class 1A or Class 3 antiarrhythmics) were not permitted during the study. Systemic CS were not permitted during the study except for subjects experiencing a protocol-defined relapse. As per protocol, methylprednisolone 1 g per day over 5 consecutive days maximum was permitted as rescue medication. Treatments were permitted for symptoms related to MS such as spasticity, incontinence, pain and fatigue, however a recommendation to the investigators states that they should attempt to keep therapies or treatments reasonably constant throughout the study (Celgene 2015f, Celgene 2019c).

B.2.3.3. Trial outcomes

The pre-specified primary and secondary outcomes for RADIANCE and SUNBEAM are summarised in Table 5.

Table 5. Pre-planned trial outcomes for RADIANCE and SUNBEAM

Trial	RADIANCE Part A	RADIANCE Part B	SUNBEAM
Trial duration	**24 weeks (6 months)**	**24 months**	**> 12 months**
Primary outcome	Total number of Gd-E lesions on MRI (weeks 12–24)	ARR at the end of Month 24	ARR during the treatment-based period
Secondary outcomes	• The number of Gd-E lesions at week 24 • Total number of new or enlarging hypointense T2-weighted brain MRI lesions from week 12 to week 24 • ARR at the end of week 24 • Safety and tolerability as judged by the site investigator	Key secondary outcomes (rank ordered): • The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months • The number of Gd-E brain MRI lesions at Month 24 • Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months Other secondary efficacy endpoints: • Proportion of subjects who were Gd-E lesion-free at Month 24 • Proportion of subjects who were new or enlarging T2 lesion-free at Month 24 • Percent change in normalised brain volume (atrophy) on brain MRI scans	Key secondary outcomes (rank ordered): • The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months • The number of Gd-E brain MRI lesions at Month 12 • Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months Other secondary efficacy endpoints: • Proportion of patients who were Gd-E lesion-free at Month 12 • Proportion of subjects who were new or enlarging T2 lesion-free at Month 12 • Percent change in normalised brain volume (atrophy) on brain MRI scans from

Trial	RADIANCE Part A	RADIANCE Part B	SUNBEAM
Trial duration	**24 weeks (6 months)**	**24 months**	**> 12 months**
		from baseline to Month 24 • Change in MSFC score from baseline to Month 24 (including the LCLA measurement of visual function as a component) • Change in MSQOL-54 score from baseline to Month 24	baseline to Month 12 • Change in MSFC score from baseline to Month 12 (including the LCLA measurement of visual function as a component) • Change in MSQOL-54 score from baseline to Month 12
Exploratory outcomes	-	Changes from baseline to each MRI visit in other MRI measures: • Number and volume of Gd-E T1 lesions • Volume of T2 lesions • Number of new or enlarging T2 lesions • Volume of unenhancing T1 lesions • Number of new unenhancing T1 lesions • Measures of brain atrophy	

Source: (Celgene 2017a, Celgene 2019b, Celgene 2019d)

Abbreviations: ARR: annualised relapse rate; EDSS: expanded disability status scale; Gd-E: gadolinium-enhanced; LCLA: low-contrast letter acuity; MRI: magnetic resonance imaging; MSFC: multiple sclerosis functional composite; MSQOL: multiple sclerosis quality of life

B.2.3.4. Patient characteristics in Phase III trials, RADIANCE Part B and SUNBEAM

The patient demographic, disease and clinical characteristics were generally well-balanced across treatment groups in both pivotal studies (Table 6.). A patient's age in years was calculated using the date of the informed consent and date of birth or recorded directly on the eCRF. Please note that in this section, only ozanimod 1 mg data is presented to be aligned with the expected marketing authorisation for ozanimod.

Table 6. Baseline characteristics of patients in RADIANCE Part B and SUNBEAM

	RADIANCE Part B		SUNBEAM	
Duration	**24 months**		**> 12 months**	
	IFN β-1a 30 µg (N = 441)	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**
Mean (SD) age, years	35.1 (9.07)	36.0 (8.89)	35.9 (9.11)	34.8 (9.24)

	RADIANCE Part B		SUNBEAM	
Female, n (%)	304 (68.9)	291 (67.2)	300 (67.0)	283 (63.3)
White, n (%)	432 (98.0)	428 (98.8)	447 (99.8)	446 (99.8)
Eastern Europe, n (%)	379 (85.9)	374 (86.4)	419 (93.5)	415 (92.8)
Rest of World	62 (14.1)	59 (13.6)	29 (6.5)	32 (7.2)
Mean (SD) weight, kg	70.14 (16.374)	70.94 (17.014)	69.95 (16.199)	69.70 (15.482)
Mean (SD) BMI, kg/m2	24.28 (5.304)	24.55 (4.958)	24.20 (4.595)	24.06 (4.596)
Mean (SD) time since MS symptom onset, years	6.36 (6.07)	6.92 (6.20)	6.88 (5.88)	6.85 (6.45)
Mean (SD) time since MS diagnosis, years	3.63 (4.61)	3.97 (5.17)	3.71 (4.36)	3.60 (4.19)
Mean (SD) EDSS score	2.49 (1.16)	2.55 (1.15)	2.62 (1.14)	2.61 (1.16)
Mean (SD) number of relapses in the last 12 months, n (%)	1.3 (0.58)	1.3 (0.56)	1.3 (0.55)	1.3 (0.57)
Number of patients with Gd-E T1 Brain MRI Lesions	196 (44.4)	178 (41.1)	216 (48.2)	214 (47.9)
Mean (SD) number of Gd-E T1 brain MRI lesions	1.8 (3.54)	1.6 (3.78)	1.7 (3.22)	1.8 (3.41)
Mean (SD) normalised whole brain volume, cm3	1449.581 (77.156)	1441.949 (79.228)	1443.355 (78.731)	1455.980 (77.941)
Patients with high disease activity, n (%)	104 (23.6)	90 (20.8)	103 (23.0)	102 (22.8)

Source: (Celgene 2019c)

Abbreviations: BMI: body mass index; Gd-E: gadolinium-enhancing; IFN: interferon; MS: multiple sclerosis; SD: standard deviation

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

The primary objective in RADIANCE Part B was to assess whether the clinical efficacy of ozanimod is superior to IFN β-1a in reducing the rate of clinical relapses (expressed as a reduction in ARR) at the end of Month 24 in patients with RMS.

The primary objective in SUNBEAM was to assess whether the clinical efficacy of ozanimod is superior to IFN β-1a in reducing the rate of clinical relapses (expressed as a reduction in ARR) at the end of Month 12 in patients with RMS.

The data for the two controlled Phase III clinical studies (RADIANCE Part B and SUNBEAM) were pooled for integrated efficacy and safety analyses in accordance with a pre-specified statistical analysis plan (SAP). The primary objective of the integrated efficacy analysis was treatment effect estimation and not statistical hypothesis testing, with the notable exception of the pooled evaluation of CDP that was utilised for statistical hypothesis testing for disability progression. The primary analysis for time to first CDP was based on the Cox proportional hazards model with treatment, study, region, age at baseline, and baseline EDSS in which the

handling of tied progression events was accounted for using Efron's method. The hazard ratio, 95% CI, and corresponding p-value for testing a treatment effect (i.e., hazard ratio = 1 under the null hypothesis) were reported.

A summary of the statistical analyses for RADIANCE Part B, SUNBEAM and the integrated summary of efficacy are presented in

Table 7. Summary of statistical analyses

Trial	RADIANCE Part B	SUNBEAM	Integrated summary of efficacy
Duration	**24 months**	**≥ 12 months**	**12 months**
Hypothesis objective	To assess whether the clinical efficacy of ozanimod is superior to IFN β-1a in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS	To assess whether the clinical efficacy of ozanimod is superior to IFN β-1a in reducing the rate of clinical relapses at the end of Month 12 in patients with RMS	To assess the pre-specified primary and secondary efficacy endpoints from RADIANCE Part B and SUNBEAM studies in a pooled analysis
Statistical analysis	• Statistical testing for the primary efficacy endpoint will be made between each ozanimod group and the IFN β-1a group (2 treatment contrasts). To account for multiple comparisons, each of the 2 treatment comparisons will be tested at the alpha = 0.025 level • To control for type 1 error, the 3 key secondary endpoints will be tested in order in a sequential, closed hierarchical testing procedure that ranks the ozanimod 1 mg dose above the ozanimod 0.5 mg dose and the key secondary endpoints in their rank order • Unless specified otherwise, all statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance • The primary analyses will compare the ARRs in each of the ozanimod groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level. The control ARR is assumed to be equal to 0.3		• The primary analysis of ARR will be performed using a Poisson regression model • The natural log transformation of time on study as an offset term • Adjusted relapse rates and their associated 95% CIs for each treatment group, rate ratios comparing treatment groups and their associated 95% CIs, and p-values will be reported
Sample size, power calculation	• A sample size of 1059 patients (353 patients in each treatment arm) provided 80% power to detect a 43% reduction in the ARR (i.e. an ARR of 0.17 for ozanimod) • To account for an assumed dropout rate of approximately 12%, approximately 1200 patients (400 per treatment group) were to be enrolled in each controlled Phase 3 clinical study		-
Data management, patient withdrawals	• The clinical monitoring, data management and statistical analysis are being performed under contract with PPD, in collaboration with the manufacturer		-

	• Patients could withdraw from the trial • Patients in the ITT population who withdraw from the study after the Baseline visit but prior to the first clinical evaluation scheduled visit were censored at Baseline	

Table 7. Summary of statistical analyses

Trial	RADIANCE Part B	SUNBEAM	Integrated summary of efficacy
Duration	**24 months**	**≥ 12 months**	**12 months**
Hypothesis objective	To assess whether the clinical efficacy of ozanimod is superior to IFN β-1a in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS	To assess whether the clinical efficacy of ozanimod is superior to IFN β-1a in reducing the rate of clinical relapses at the end of Month 12 in patients with RMS	To assess the pre-specified primary and secondary efficacy endpoints from RADIANCE Part B and SUNBEAM studies in a pooled analysis
Statistical analysis	• Statistical testing for the primary efficacy endpoint will be made between each ozanimod group and the IFN β-1a group (2 treatment contrasts). To account for multiple comparisons, each of the 2 treatment comparisons will be tested at the alpha = 0.025 level • To control for type 1 error, the 3 key secondary endpoints will be tested in order in a sequential, closed hierarchical testing procedure that ranks the ozanimod 1 mg dose above the ozanimod 0.5 mg dose and the key secondary endpoints in their rank order • Unless specified otherwise, all statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance • The primary analyses will compare the ARRs in each of the ozanimod groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level. The control ARR is assumed to be equal to 0.3		• The primary analysis of ARR will be performed using a Poisson regression model • The natural log transformation of time on study as an offset term • Adjusted relapse rates and their associated 95% CIs for each treatment group, rate ratios comparing treatment groups and their associated 95% CIs, and p-values will be reported
Sample size, power calculation	• A sample size of 1059 patients (353 patients in each treatment arm) provided 80% power to detect a 43% reduction in the ARR (i.e. an ARR of 0.17 for ozanimod) • To account for an assumed dropout rate of approximately 12%, approximately 1200 patients (400 per treatment group) were to be enrolled in each controlled Phase 3 clinical study		-
Data management,	• The clinical monitoring, data management and statistical analysis are being performed		-

patient withdrawals	under contract with PPD, in collaboration with the manufacturer • Patients could withdraw from the trial • Patients in the ITT population who withdraw from the study after the Baseline visit but prior to the first clinical evaluation scheduled visit were censored at Baseline	

Source: (Celgene 2015d, Celgene 2015e, Celgene 2019c)

Table 8. Efficacy analyses for primary and key secondary endpoints from SUNBEAM and RADIANCE Part B

Endpoint	Studies	Data presented	Statistical method used
• Primary endpoint: confirmed • ARR during the treatment period	• SUNBEAM: ARR during the treatment period (12 months) • RADIANCE Part B: ARR during the treatment period (24 months) • Pooled SUNBEAM and RADIANCE Part B (data up to 12 months)	• Adjusted relapse rates and their associated 95% CIs, rate ratios and their associated 95% CIs, and p-values • Primary treatment comparisons: o ozanimod 1 mg vs. IFN β-1a 30 µg o ozanimod 0.5 mg vs. IFN β-1a 30 µg	• Poisson regression model • Model compared treatment groups after adjusting for region, age at baseline, and the baseline number of Gd-E lesions • The natural log transformation of study days/365.25 was used as an offset term • Pooled analysis adjusted for study differences in the model
• Number of new or enlarging T2 lesions (1st ordered key secondary endpoint)	• SUNBEAM: New or enlarging T2 lesions, over 12 months • RADIANCE Part B: New or enlarging T2 lesions, over 24 months • Pooled SUNBEAM and RADIANCE	• Adjusted new or enlarging T2 lesions per scan and their associated 95% CIs, the rate ratios and their associated 95% CIs, and p-values • Primary treatment comparisons: o ozanimod 1 mg vs. IFN β-1a 30 µg	• Negative binomial model • Model compared treatment groups after adjusting for region, age at baseline, and the baseline, number of Gd-E lesions • The natural log transformation of number of MRI scans was

Endpoint	Studies	Data presented	Statistical method used
	Part B, over 12 months	o ozanimod 0.5 mg vs. IFN β-1a 30 µg	used as an offset term • Pooled analysis adjusted for study differences in the model
• Number of Gd-E lesions (2nd ordered key secondary endpoint)	• SUNBEAM: Number of Gd-E lesions, at Month 12 • RADIANCE Part B: Number of Gd-E lesions, at Month 24 • Pooled SUNBEAM and RADIANCE Part B, at month 12	• Adjusted Gd-E lesions and their associated 95% CIs, the rate ratios and their associated 95% CIs, and p-values • Primary treatment comparisons: o ozanimod 1 mg vs. IFN β-1a 30 µg o ozanimod 0.5 mg vs. IFN β-1a 30 µg	• Negative binomial model • Model compared treatment groups after adjusting for region, age at baseline, and the baseline, number of Gd-E lesions as a continuous variable • The natural log transformation of number of MRI scans was used as an offset term • Pooled analysis adjusted for study differences in the model
• CDP (3rd ordered key secondary endpoint)	• SUNBEAM and RADIANCE Part B	• Plot of the Kaplan-Meier estimates by treatment group • Adjusted hazard ratios and their associated 95% CIs, p-values • Primary treatment comparisons: o ozanimod 1 mg vs. IFN β-1a 30 µg o ozanimod 0.5 mg vs. IFN β-1a 30 µg	• Kaplan-Meier product limit estimates • Cox regression model, stratified by study, with region, age at baseline, and EDSS at baseline as covariates • Model compared treatment groups, adjusted for study, region, baseline age, and baseline EDSS scores

Endpoint	Studies	Data presented	Statistical method used
			• Subjects were censored if they did not have a progression event and one of the following: 1) they completed the study, or 2) early termination

Source: (Celgene 2019c)

Abbreviations: ARR: annualised relapse rate; CDP: confirmed disability progression; CI: confidence interval; EDSS: enhanced disability status scale; Gd-E: gadolinium-enhanced; IFN: interferon; MRI: magnetic resonance imaging

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trials (RCTs) was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D 1.2.3.

B.2.6 Clinical effectiveness results of the relevant trials

The data discussed in this section has been sourced from the primary analysis of RADIANCE Part A and B, and SUNBEAM. Clinical effectiveness results for RADIANCE Part B and SUNBEAM together with the integrated (pooled) efficacy analyses will be presented first followed by clinical effectiveness results for RADIANCE Part A.

Pre-specified and post-hoc subgroup analyses are presented in Section B.2.7.1 and B.2.7.3.

Please note that in this section, only ozanimod 1 mg data is presented to be aligned with the expected marketing authorisation of ozanimod (1 mg) in active RRMS.

B.2.6.1. RADIANCE Part B and SUNBEAM

Ozanimod 1 mg demonstrated superior (pooled across RADIANCE Part B and SUNBEAM), dose dependent efficacy compared to IFN β-1a in reducing ARR, reducing the number of new or enlarging hyperintense T2-weighted brain MRI lesions, and reducing the number of Gd-E T1 lesions in patients with RMS.

Patients had a wide range of disease activity and approximately 70% had received no prior DMT treatment for MS. Ozanimod treatment also resulted in reductions in brain volume loss (BVL) compared with IFN β-1a treatment. There were significantly greater increases in SDMT score in ozanimod-treated patients versus those receiving IFN β-1a at month 12 and significantly more ozanimod-treated patients had clinically meaningful improvements in processing speed versus those receiving IFN β-1a. Numerically favourable outcomes with ozanimod were also observed for cognition as assessed by multiple sclerosis functional composite (MSFC). In SUNBEAM, the physical health composite summary score, as reported by patients using Multiple Sclerosis Quality of Life (MSQOL-54), showed statistically significant increase in mean value from baseline to month 12 (corresponding to an improvement in score) in the ozanimod 1 mg group compared with the IFN β-1a group (1.642 [CI: 0.104, 3.180]) ($p = 0.0364$).

A full description of the results from RADIANCE Part B and SUNBEAM is provided below. Results from the integrated (pooled) efficacy analyses conducted are also presented alongside the results from the individual trials to further strengthen the evidence package.

B.2.6.2. Endpoints associated with relapses

In both RADIANCE Part B and SUNBEAM as well as in the pooled analysis, ozanimod significantly reduced ARR compared with IFN β-1a. The primary endpoint, ARR was statistically significantly lower for ozanimod compared to IFN- β-1a across both trials (Celgene 2017a, Celgene 2017b, Celgene 2019c).

In the RADIANCE Part B trial, treatment with ozanimod 1 mg resulted in significantly lower ARR compared with IFN β-1a (adjusted ARR 0.172 vs 0.276, respectively). The adjusted ARR was [redacted] lower with ozanimod 1 mg ($p < 0.0001$) than with IFN β-1a (Table 9.) (Celgene 2017a).

In the SUNBEAM trial, treatment with ozanimod 1 mg resulted in statistically significantly lower ARR compared with IFN β-1a (adjusted ARR 0.181 vs. 0.350, respectively). The adjusted ARR was [redacted] lower with ozanimod 1 mg ($p < 0.0001$) than with IFN β-1a (Table 9.) (Celgene 2017b).

In the pooled analysis, the percent reductions in the ARR for ozanimod 1 mg compared to IFN β-1a was [redacted]

Table 9. ARR in RADIANCE Part B, SUNBEAM and the pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled analysis [a]	
Duration	**24 months**		**≥ 12 months**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
Subjects with relapses, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ARR (95% CI)	0.276 (0.234, 0.324)	0.172 (0.142, 0.208)	0.350 (0.279, 0.440)	0.181 (0.140, 0.236)	[redacted]	[redacted]
Unadjusted ARR [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percent reduction (ozanimod/IFN β-1a 30 µg) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (ozanimod/I	-	0.623 (0.506, 0.768)	-	0.518 (0.405, 0.663)	[redacted]	[redacted]

FN β-1a) (95% CI)						
p-value[c]	-	<0.0001	-	<0.0001	[redacted]	[redacted]
Subject relapse rate[d]						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse-free rate[e]						
Kaplan-Meier estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017a, Celgene 2017b, Celgene 2019a)

[a] Includes only pooled data up to 12 months except for CDP
[b] The unadjusted relapse rate for each treatment group was calculated as the total number of relapses experienced in the group divided by the total number of days in the study for the group, and multiplied by 365.25
[c] Based on the Poisson regression model, adjusted for region (Eastern Europe versus Rest of the World), age at baseline, and the baseline number of Gd-E lesions, and included the natural log transformation of time on study as an offset term. Pooled analysis was adjusted for study effect differences
[d] The number of relapses for each subject divided by the number of days the subject participated in the study, and then multiplied by 365.25.
[e] Relapse-free rate is 1 minus the Kaplan-Meier estimate for time-to-first relapse
[f] Based on the Cox proportional hazard model adjusted for study, region (Eastern Europe vs rest of the world), age at baseline, and baseline EDSS score.

B.2.6.3. Endpoints associated with MRI lesions and brain volume

New or enlarging hyperintense T2-weighted brain MRI lesions

Ozanimod demonstrated superiority to IFN β-1a in the number new or enlarging T2 and Gd-E lesions in patients with RMS. The mean number of new or enlarging T2 and Gd-E lesions was the 1st ranked key secondary endpoint in RADIANCE Part B and SUNBEAM, and it was met compared to IFN β-1a (Celgene 2019c).

In the RADIANCE Part B trial, a statistically significant reduction in the total adjusted mean number of new of enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg ($p < 0.0001$) compared to IFN β-1a (1.848 and 3.183 lesions, respectively), corresponding to a [redacted] reduction over 24 months (Table 10.) (Celgene 2017a).

In the SUNBEAM trial, there was also a statistically significant reduction in the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan with ozanimod 1 mg ($p < 0.0001$) compared to IFN β-1a (1.465 and 2.836 lesions, respectively), corresponding to a [redacted] reduction over 12 months (Table 10.) (Celgene 2017b).

In the pooled analysis over 12 months, the adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg ($p < 0.0001$) compared to IFN β-1a ([redacted] and [redacted] lesions, respectively), corresponding to a [redacted] reduction (Table 10.) (Celgene 2019c).

Table 10. Number of new or enlarging T2-weighted brain MRI lesions in RADIANCE Part B, SUNBEAM and the pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled Analysis	
Duration	**24 months**		**> 12 months+**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of lesions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of available MRI scans	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (95% CI) per scan	3.183 (2.640, 3.838)	1.848 (1.533, 2.227)	2.836 (2.331, 3.451)	1.465 (1.203, 1.784)	[redacted]	[redacted]
Adjusted mean (95% CI) over 24 months	[redacted]	[redacted]	[redacted]	[redacted]		
Rate ratio (Ozanimod/ IFN β-1a 30µg) (95% CI)	-	0.581 (0.469, 0.719)	-	0.517 (0.427, 0.625)	[redacted]	[redacted]
Percent reduction ozanimod vs. IFN β-1a 30 µg (95% CI)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	-	<0.0001	[redacted]	<0.0001*	[redacted]	[redacted]

Source: (Celgene 2017a, Celgene 2017b, Celgene 2019c)

* Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at Baseline, and Baseline number of Gd-E lesions. The natural log transformation of the number of available MRI scans over 24 months is used as an offset term.

Gd-E brain MRI lesions

The second rank-ordered key secondary efficacy endpoint, the number of Gd-E T1 brain MRI lesions, was met for ozanimod 1 mg compared to IFN β-1a, in both controlled Phase III clinical studies and in the pooled analysis.

In RADIANCE Part B, a statistically significant reduction in the adjusted mean number of Gd-E brain MRI lesions was demonstrated with ozanimod 1 mg (p = 0.0006) compared to IFN β-1a (0.176 and 0.373 lesions, respectively), corresponding to a [redacted] reduction at Month 24 (Table 11.) (Celgene 2017a).

In SUNBEAM, a statistically significant reduction in the adjusted mean number of Gd-E brain MRI lesions was demonstrated with ozanimod 1 mg (p < 0.0001), compared to IFN β-1a (0.160 and 0.433 lesions, respectively), corresponding to a [redacted] reduction at Month 12 (Table 11.) (Celgene 2017b).

In the pooled analysis at Month 12, the adjusted mean number of Gd-E T1 brain MRI lesions was demonstrated with ozanimod 1 mg (p<0.0001) compared to IFN β-1a ([redacted] and [redacted] lesions, respectively), corresponding to a [redacted] reduction (Table 11.) (Celgene 2019c).

Table 11. Number of Gd-E Brain MRI Lesions in RADIANCE Part B, SUNBEAM and the pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	**24 months**		**> 12 months**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted Mean (95% CI)	0.373 (0.256, 0.543)	0.176 (0.116, 0.266)	0.433 (0.295, 0.635)	0.160 (0.106, 0.242)	[redacted]	[redacted]
Rate Ratio (Ozanimod/IFN β-1a 30 µg) (95% CI)	-	0.470 (0.305, 0.724)	-	0.370 (0.256, 0.536)		
Percent Reduction Ozanimod vs. IFN β-1a 30 µg (95% CI)*	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
p-value*	-	0.0006	-	<0.0001		[redacted]

Source: (Celgene 2017a, Celgene 2017b, Celgene 2019c)

* Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at Baseline, and Baseline number of Gd-E lesions. The natural log transformation of the number of available MRI scans over 24 months is used as an offset term.

MRI measures of disease activity

Measures of brain atrophy included MRI assessment of total brain volume, cortical grey volume and thalamic volume. These were exploratory endpoints in RADIANCE Part B and SUNBEAM.

Treatment with ozanimod 1 mg resulted in nominally significant reductions in mean percentage whole brain volume loss compared to IFN β-1a in the two controlled Phase III clinical studies, and in the pooled analysis (Table 12.) (Celgene 2017a, Celgene 2017b, Celgene 2019c).

The difference in mean percent change from baseline in whole brain volume loss for ozanimod 1 mg vs IFN β-1a 30 µg was 0.24, 0.19 and [redacted] in RADIANCE Part B, SUNBEAM and in the pooled analysis, respectively.

Treatment with ozanimod 1 mg nominally significantly reduced mean percentage in cortical gray matter volume loss compared with IFN β-1a in the two controlled Phase III clinical studies and in the pooled analysis. The difference in mean percent change from baseline in cortical grey matter volume loss was 0.67, 0.84 and [redacted] in RADIANCE Part B, SUNBEAM and the pooled analysis, respectively (Table 13.) (Celgene 2017a, Celgene 2017b, Celgene 2019c).

Treatment with ozanimod 1 mg nominally significantly reduced mean percentage thalamic volume loss compared to IFN β-1a in the two controlled Phase III clinical studies and in the pooled analysis. The difference in mean percent change from baseline in thalamic volume loss was 0.49, 0.55 and [redacted] in RADIANCE Part B, SUNBEAM and the pooled results respectively (Table 14.) (Celgene 2017a, Celgene 2017b, Celgene 2019c).

Table 12. Normalised brain volume (cm^3) percent change from baseline to month 12 and month 24 in Phase III studies and pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	**24 months**		**> 12 months**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
N	397	390	406	397	[redacted]	[redacted]
Mean (SD)	-0.94 (0.944)	-0.71 (0.878)	-0.61 (0.686)	-0.41 (0.640)	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in mean percent change from baseline (Ozanimod vs IFN β-1a 30 µg) [95% CI]	-	0.24 (0.12, 0.36)	-	0.19 [0.10, 0.28]	[redacted]	[redacted]
p-value (Ozanimod vs IFN β-1a 30 µg)[a]	-	*< 0.0001*	-	*< 0.0001*	[redacted]	[redacted]
p-value (Ozanimod vs IFN β-1a 30 µg)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017a, Celgene 2017b, Celgene 2019c)

ANCOVA = analysis of covariance; CSR = clinical study report; EDSS = Expanded Disability Status Scale; IFN = interferon; ISE = integrated summary of efficacy; ITT = intent-to-treat, IVRS = Interactive Voice Response System; LOCF = last observation carried forward; SD = standard deviation.

[a] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study is based on the ANCOVA model adjusted for region and EDSS category per IVRS.

[b] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study and studies pooled based on the ranked based ANCOVA model (Quade, 1967) adjusted for region and EDSS category per IVRS.

Note: P-values in italics are considered nominally significant.

Table 13. Cortical grey matter volume (cm^3) percent change from baseline to month 12 and month 24 in Phase III studies and pooled analysis

	RADIANCE Part B	SUNBEAM	Pooled analysis
Duration	**24 months**	**> 12 months**	**12 months**

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
N	390	382	407	398	[redacted]	[redacted]
Mean (SD)	-0.50 (0.798)	-0.44 (0.859)	-1.00 (0.969)	-0.16 (0.872)	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in mean percent change from baseline (Ozanimod vs IFN β-1a 30 µg) [95% CI]	-	0.67 [0.55, 0.79]	-	0.84 [0.72, 0.96]	[redacted]	[redacted]
p-value (Ozanimod vs IFN β-1a 30 µg) [a]	-	*<0.0001*	-	*<0.0001*	[redacted]	[redacted]
p-value (Ozanimod vs IFN β-1a 30 µg) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017a, Celgene 2017b, Celgene 2019c)

ANCOVA = analysis of covariance; CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ISE = integrated summary of efficacy; ITT = intent-to-treat, IVRS = Interactive Voice Response System; LOCF = last observation carried forward; SD = standard deviation.

[a] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study is based on the ANCOVA model adjusted for region and EDSS category per IVRS.

[b] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study and studies pooled based on the ranked based ANCOVA model adjusted for region and EDSS category per IVRS.

Note: P-values in italics are considered nominally significant.

Table 14. Thalamic volume (cm^3) percent change from baseline to month 12 and month 24 in Phase III studies and pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	**24 months**		**> 12 months**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
N	391	385	406	393	[redacted]	[redacted]
Mean (SD)	-1.85 (1.966)	-1.40 (2.055)	-1.72 (1.936)	-1.12 (1.633)	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in mean percent change from baseline (Ozanimod vs IFN β-1a 30 µg) [95% CI]	-	0.49 [0.22, 0.75]	-	0.55 [0.31, 0.78]	[redacted]	[redacted]
p-value (Ozanimod vs IFN β-1a 30 µg) [a]	-	*0.0004*	-	*< 0.0001*	[redacted]	[redacted]
p-value (Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	RADIANCE Part B		SUNBEAM		Pooled analysis	
vs IFN β-1a 30 µg) [b]						

Source: (Celgene 2017a, Celgene 2017b, Celgene 2019c)

ANCOVA = analysis of covariance; CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ISE = integrated summary of efficacy; ITT = intent-to-treat, IVRS = Interactive Voice Response System; LOCF = last observation carried forward; SD = standard deviation.

[a] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study is based on the ANCOVA model adjusted for region and EDSS category per IVRS.

[b] p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups in each study and studies pooled based on the ranked based ANCOVA model adjusted for region and EDSS category per IVRS. P-values in italics are considered nominally significant.

Note: P-values in italics are considered nominally significant.

Endpoints associated with disability

Confirmed Disability Progression at 3 months

As the number of disability progression events was low, the data on patients with a confirmed disability progression at 3 months (CDP-3M) exhibited high variability and wide statistical range, with no evidence of statistical difference between the two treatment groups. The observed Kaplan-Meier estimates for CDP-3M in the IFN β-1a group was lower than anticipated, which reduced the ability to detect a difference between ozanimod and IFN β-1a (Celgene 2019c).

In RADIANCE Part B, the number of patients with a confirmed disability progression after 3 months was 54 (12.5%) in the ozanimod 1 mg group compared with 50 (11.3%) in the IFN β-1a group (p=0.8224) (Celgene 2017a).

In SUNBEAM, the number of patients with a confirmed disability progression after 3 months was [redacted] in the ozanimod 1 mg group compared with [redacted] in the IFN β-1a group [redacted] (Celgene 2017b).

The confirmed disability progression at 3 months for RADIANCE Part B, SUNBEAM, and the pooled analysis is presented in Table 15.

Table 15. Confirmed Disability Progression at 3 months in RADIANCE Part B, SUNBEAM and pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	**24 months**		**> 12 months**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
Number of patients with a confirmed progression n (%)	50 (11.3)	54 (12.5)	[redacted]	[redacted]	69 (7.8)	67 (7.6)
Number of patients censored n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR for Ozanimod vs. IFN β-1a 30 µg (95% CI)	-	1.045 (0.711, 1.537)*	[redacted]	[redacted]	-	0.950 (0.679, 1.330)**

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Percentage reduction of disability progression risk (Ozanimod/IFN β-1a 30 µg) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	-	0.8224*	[redacted]	[redacted]	-	0.7651**

Source: (Celgene 2015a, Celgene 2017a, Celgene 2017b, Comi 2018b)

*Based on the Cox proportional hazard model with factors for treatment group, adjusted for region (Eastern Europe vs Rest of the World), age at Baseline, and Baseline EDSS score

** Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at baseline, and baseline number of Gd-E lesions. The natural log transformation of the number of available MRI scans was used as an offset term. Pooled analysis was adjusted for study effect differences.

Confirmed Disability Progression at 6 months

As the number of disability progression events was low, the data on patients with a confirmed disability progression after 6 months (CDP-6M) exhibited high variability and wide statistical range, with no evidence of statistical difference between the two treatment groups. The observed Kaplan-Meier estimates for CDP-6M in the IFN β-1a group was lower than anticipated, which reduced the ability to detect a difference between ozanimod and IFN β-1a (Celgene 2019c).

In RADIANCE Part B, the number of patients with a confirmed disability progression after 6 months was 42 (9.7%) in the ozanimod 1 mg group compared with 29 (6.6%) in the IFN β-1a group p=0.1353 (Celgene 2017a).

In SUNBEAM, the number of patients with a confirmed disability progression after 6 months was [redacted] in the ozanimod 1 mg group compared with [redacted] in the IFN β-1a group [redacted] (Celgene 2017b).

The confirmed disability progression at 6 months for RADIANCE Part B, SUNBEAM, and the pooled analysis is presented in Table 16.

Table 16. Confirmed Disability Progression at 6 months in RADIANCE Part B, SUNBEAM and pooled analysis

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	24 months		> 12 months		12 months	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
Number of patients with a confirmed progression n (%)	29 (6.6)	42 (9.7)	[redacted]	[redacted]	36 (4.0)	51 (5.8)
Number of patients censored n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR for Ozanimod vs. IFN β-1a 30 µg (95% CI)	-	1.435 (0.893, 2305)*	[redacted]	[redacted]	-	1.413 (0.922, 2.165)**

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Percentage reduction of disability progression risk (Ozanimod/IFN β-1a 30 µg) (95% CI)	[redacted]		[redacted]		[redacted]	
p-value	-	0.1353*	[redacted]		-	0.1126**

Source: (Celgene 2015b, Celgene 2017a, Celgene 2017b, Comi 2018a)

*Based on the Cox proportional hazard model with factors for treatment group, adjusted for region (Eastern Europe vs Rest of the World), age at Baseline, and Baseline EDSS score

** Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at baseline, and baseline number of Gd-E lesions. The natural log transformation of the number of available MRI scans was used as an offset term. Pooled analysis was adjusted for study effect differences.

Other endpoints

Multiple Sclerosis Functional Composite Score

Across the RADIANCE Part B and SUNBEAM trials, numerically favourable treatment effects in MSFC and MSFC (LCLA) z-scores were seen although no significant difference in the MSFC was observed in the ozanimod group versus the IFN β-1a group (Table 17.).

Notably, in both the SUNBEAM trial and the pooled analysis, there were significantly greater increases in cognitive processing speed as measured by the SDMT/PASAT score in ozanimod-treated patients versus those receiving IFN β-1a at month 12. To note that PASAT-3 was used in RADIANCE Part B and SDMT was used in SUNBEAM; SDMT/PASAT-3 were combined in the pooled analysis. In addition, significantly more ozanimod-treated patients had clinically meaningful improvements in processing speed versus those receiving IFN β-1a (Table 17.). These results are consistent with BVL findings from SUNBEAM and pooled analyses which showed preservation of thalamic volume as well as cortical grey matter volume in ozanimod-treated patients at 12 and 24 months. BVL is thought to play an important role in the loss of cognition and increase in disability progression in MS.

Table 17. MSFC composite and component scores at month 12

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	24 months		> 12 months		12 months	
Treatment	IFN β-1a 30 µg (N = 441)	Ozanimod 1 mg (N = 433)	IFN β-1a 30 µg (N = 448)	Ozanimod 1 mg (N = 447)	IFN β-1a 30 µg (N = 889)	Ozanimod 1 mg (N = 880)
MSFC z-score						
n[a]	441	432	448	447	[redacted]	
Mean (SD) change from baseline	-0.067 (0.745)	-0.006 (0.779)	-0.024 (0.366)	0.006 (0.382)	[redacted]	
Difference in means[b] (95% CI)	-	0.060 (-0.029, 0.148)	-	0.040 (-0.009, 0.090)	[redacted]	
p-value[b]	-	0.1874	-	0.1091	[redacted]	
MSFC (LCLA) z-score						

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	RADIANCE Part B		SUNBEAM		Pooled analysis	
n[a]	437	428	447	447	[redacted]	[redacted]
Mean (SD) change from baseline	0.052 (0.601)	-0.010 (0.622)	-0.022 (0.334)	0.003 (0.328)	[redacted]	[redacted]
Difference in means[b] (95% CI)	-	0.043 (-0.030, 0.116)	-	0.034 (-0.010, 0.077)	[redacted]	[redacted]
p-value[b]	-	0.2480	-	0.1290	[redacted]	[redacted]
MSFC Component: Timed 25-foot Walk Score - Actual Time (seconds)						
Mean baseline value[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean actual value (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in means[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSFC Component: Timed 25-foot Walk Score - z-score						
n[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in meansb (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSFC Component: 9-hole Peg Test – Actual Time (Seconds)						
Mean baseline value[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean actual value (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in means[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSFC Component: 9-hole Peg Test - z-score						
n[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in means[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	RADIANCE Part B		SUNBEAM		Pooled analysis	
p-value[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSFC Component: SDMT/PASAT Score – Total Correct Responses[d]						
Mean baseline value[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean actual value (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in means[b] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSFC Component: SDMT/PASAT Score - z-score[d]						
n[a]	[redacted]	[redacted]	448	447	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	-0.029 (0.508)	0.073 (0.653)	[redacted]	[redacted]
Difference in means[b] (95% CI)	[redacted]	[redacted]	-	0.111 (0.039, 0.182)	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]	-	*0.0024*	[redacted]	[redacted]

Source: (Celgene 2019c)

ANCOVA = analysis of covariance; CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ISE = integrated summary of efficacy; ITT = intent-to-treat; LCLA = Low-Contrast Letter Acuity; LOCF = last observation carried forward; MSFC = Multiple Sclerosis Functional Component; PASAT = Paced Auditory Serial Addition Test; SD = standard deviation; SDMT = Symbol Digit Modalities Test.

[a] Number of subjects at time of assessment (Pooled Phase III Studies at Month 12, Study RPC01-301 at Month 12, and Study RPC01-201B at Month 24).

[b] Difference in means and p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups are based on the ANCOVA model, adjusted for region, EDSS category at baseline, and the baseline value of the parameter of interest.

[c] Baseline mean for the total population.

[d] PASAT-3 was used in Study RPC01-201B and SDMT was used in Study RPC01-301; SDMT/PASAT-3 were combined in the pooled analysis.

Multiple Sclerosis Quality of Life-54 Summary Scores

The results of the MSQOL-54 physical health composite summary in SUNBEAM showed a statistically significant improvement for the ozanimod 1 mg group at 12 months (p = 0.0364) (Table 18). RADIANCE Part B showed a numerical improvement; however, it did not reach significance (Celgene 2017a, Celgene 2017b, Celgene 2019c).

For the mental health composite summary score, no differences were observed between the ozanimod and IFN β-1a dose groups in the active-controlled Phase III clinical studies and in the pooled month 12 analysis (Table 18).

Table 18. Multiple Sclerosis Quality of Life-54 Summary Scores: change from baseline at month 12 (SUNBEAM) and at month 24 (RADIANCE Part B)

	RADIANCE Part B		SUNBEAM		Pooled analysis	
Duration	**24 months**		**≥ 12 months**		**12 months**	
Treatment	**IFN β-1a 30 µg (N = 441)**	**Ozanimod 1 mg (N = 433)**	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
Physical health composite summary						
N	441	433	445	443	[redacted]	[redacted]
Mean (SD)	-1.526 (12.319)	0.209 (12.321)	0.046 (12.578)	1.925 (11.870)	[redacted]	[redacted]
Difference in mean[a] (95% CI)	-	1.345 (-0.252, 2.943)	-	1.642 (0.104, 3.180)	[redacted]	[redacted]
p-value[a]	-	0.0988	-	*0.0364*	[redacted]	[redacted]
Mental health composite summary						
N	441	433	448	446	[redacted]	[redacted]
Mean (SD)	-1.831 (16.422)	-1.517 (15.544)	-0.123 (15.240)	0.260 (15.800)	[redacted]	[redacted]
Difference in mean[a] (95% CI)	-	0.380 (-1.553, 2.313)	-	0.356 (-1.523, 2.234)	[redacted]	[redacted]
p-value[a]	-	0.6997	-	0.7104	[redacted]	[redacted]

Source: (Comi 2018b, Comi 2018a, Celgene 2019c, Cohen 2019a, Cohen 2019b)

CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ISE = integrated summary of efficacy; ITT = intent-to-treat; IVRS = Interactive Voice Response System; SD = standard deviation.

[a] Difference in means and p-value for comparison between the ozanimod and IFN β-1a 30 µg treatment groups are based on the analysis of covariance model, adjusted for region (Eastern Europe vs Rest of World), EDSS category per IVRS, and the Baseline summary score of interest.

Note: Missing data were imputed using a mixed-effects regression model (random slope and intercept).

No evidence of disease activity (NEDA)

No evidence of disease activity (NEDA) is a comprehensive measure of treatment response in patients with RRMS.

NEDA-3

NEDA-3 is a composite endpoint comprised of three outcomes: ARR, CDP and MRI.

There was a statistically significant increase in the proportion of patients in RADIANCE Part B with NEDA-3 at month 24 in the ozanimod 1 mg group compared with the IFN β-1a group (p=0.0309) (Table 19.)(Celgene 2017a).

In SUNBEAM, there was no statistically significant difference in the proportion of patients with NEDA-3 at month 12 for the ozanimod 1 mg group compared with the IFN β-1a group ([redacted] vs [redacted] respectively; p=0.1732)(Table 19.)(Celgene 2017b).

Table 19. Proportion of patients with NEDA-3 through month 12 in SUNBEAM and month 24 in RADIANCE Part B

	RADIANCE Part B		SUNBEAM	
Duration	24 months		≥ 12 months	
Treatment	IFN β-1a 30 µg (N = 440)	Ozanimod 1 mg (N = 434)	IFN β-1a 30 µg (N = 448)	Ozanimod 1 mg (N = 447)
Proportion No Evidence of Disease Activity (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017a, Celgene 2017b)

Abbreviations: CI = confidence interval; IFN = interferon; ITT: intent-to-treat

[a] Based on Wald 95% CI.

[b] Based on the Cochran-Mantel-Haenszel test stratified by region (Eastern Europe vs Rest of the World) and EDSS category per IVRS.

Note: No evidence of disease activity is defined as no relapses, no disability progression, no new or enlarging T2 lesions, and no new Gd-E lesions.

NEDA-4

NEDA-4 is a composite endpoint comprised of the three outcomes of NEDA-3: ARR, CDP, and MRI, plus BVL (annualized BVL <0.4%).

A *post-hoc* pooled analysis of RADIANCE Part B and SUNBEAM revealed that there was a statistically significant increase in the proportion of patients with NEDA-4 at 24 months in patients receiving ozanimod 1 mg compared to the IFN β-1a group (Table 20) (Celgene 2019e).

Table 20. Proportion of patients with NEDA-4 through months 12 and 24 in the pooled analysis of RADIANCE Part B and SUNBEAM

	RADIANCE Part B and SUNBEAM pooled analysis	
Duration	24 months	
Treatment	IFN β-1a 30 µg (N = 889)	Ozanimod 1 mg (N = 880)
Proportion No Evidence of Disease Activity at month 12 (95% CI)	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)[a]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]
Odds ratio ozanimod vs IFN β-1a (95% CI)[b]	[redacted]	[redacted]
Proportion No Evidence of Disease Activity at month 24 (95% CI)	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)[a]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]
Odds ratio ozanimod vs IFN β-1a (95% CI)[b]	[redacted]	[redacted]

Source: (Celgene 2019e)

a Based on Wald 95% CI.

b Based on the Cochran-Mantel-Haenszel test stratified by region and EDSS category per IVRS.

Note: No evidence of disease activity is defined as no protocol-defined relapses, no disability progression, no new or enlarging T2 lesions, and no new GdE lesions, and annualized brain volume loss (AR-BVL) <= 0.4%.

B.2.6.4. RADIANCE Part A

In the ozanimod Phase II trial RADIANCE Part A, all of the primary and secondary MRI efficacy endpoints (GdE lesions from Week 12 to Week 24, GdE lesions at Week 24, proportion of patients who were GdE lesion-free at Week 24, and number of new or enlarging T2 lesions from Week 12 to Week 24) were met, with ozanimod demonstrating a highly statistically significant effect compared with placebo. While this study was not adequately powered to detect a difference in ARR, an encouraging, dose-dependent trend for ARR reduction, as compared to placebo, was observed. Therefore, ozanimod demonstrated significant therapeutic benefit in the treatment of patients with RMS that supports the continuation of the Phase III RADIANCE Part B trial (Celgene 2015c).

In the blinded extension of RADIANCE Part A, ozanimod sustained efficacy in patients continuing treatment up to 2 years and reached similar efficacy in patients who switched from placebo; no unexpected safety signals were detected. Patients switching to ozanimod during the extension period entered the blinded extension period with a higher rate of GdE lesions, new or enlarging T2 lesions, and unadjusted ARR compared with patients who continued on ozanimod (Celgene 2017a).

A description of the key results from the RADIANCE Part A trial, including the blinded extension, is provided below.

Primary endpoint

Ozanimod demonstrated superiority to placebo in the total number of GdE lesions from Week 12 to Week 24, the primary endpoint in RADIANCE Part A. The total number of GdE lesions from Week 12 to Week 24 was statistically significantly lower in the ozanimod treatment group (P<0.0001) than in the placebo group (mean [SD] = [redacted] in the placebo group and [redacted] in the ozanimod 1 mg treatment group, a [redacted] reduction in mean for ozanimod vs placebo). Most patients in the ozanimod treatment group had [redacted] GdE lesions from Week 12 to Week 24 ([redacted] patients), while only [redacted] of patients from the placebo group were GdE lesion-free (Table 21.)(Celgene 2015c).

Table 21. Total number of GdE lesions in RADIANCE Part A at week 24

	RADIANCE Part A	
Treatment	**Placebo (N = 88)**	**Ozanimod 1 mg (N = 83)**
Number of GdE lesions		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Category, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3-4	[redacted]	[redacted]

	RADIANCE Part A	
≥5	[redacted]	[redacted]
P value[a]	[redacted]	[redacted]

Source: (Celgene 2015c)

GdE = gadolinium-enhancing; Max = maximum; Min = minimum

[a] P value for comparison between the active and placebo groups was based on the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.

In the RADIANCE Part A blinded extension, the mean number of GdE lesions decreased for patients in the placebo – ozanimod 1mg group ([redacted] to [redacted]) by Week 48 (24 weeks after entry into the blinded extension period) and remained low at Year 1 (Week 72) and Year 2 (Week 120) of the blinded extension period (Celgene 2017a).

The mean total number of GdE lesions was low and stable throughout Year 1 (Week 72) and Year 2 (Week 120) of the blinded extension period for subjects in the ozanimod 1 mg (mean [redacted]) group (Table 22.)(Celgene 2017a).

Table 22. Summary of GdE lesion counts by visit in RADIANCE Part A extension (ozanimod population)

	Ozanimod treatment groups	
Treatment	**Placebo – ozanimod 1mg[a]**	**Ozanimod 1 mg[b]**
Entry into blinded extension		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Week 48		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Week 72 (Year 1 in blinded extension)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Week 120 (Year 2 in blinded extension)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Source: (Celgene 2017a)

[a] Subjects who were randomized to receive placebo in the placebo-controlled period were re-randomized to receive ozanimod treatment (0.5 mg or 1 mg) in the blinded extension period. Only 1 mg data is presented in this submission

[b] Subjects who were randomized to receive ozanimod treatment (0.5 mg or 1 mg) in the placebo-controlled period continued to receive the same ozanimod treatment in the blinded extension period. Only 1 mg data is presented in this submission

Endpoints associated with relapses

Annualized relapse rate

In RADIANCE Part A, the adjusted ARR at the end of week 24 was numerically higher in the ozanimod group (adjusted ARR [95%CI] = [redacted]) vs placebo ([redacted]). This trend however did not achieve statistical significance (P = 0.0531) (Table 23)(Celgene 2015c).

The ARR results at week 24 were similar when analysing the ITT population by demographic subgroups of sex, baseline age and weight, or region. The one exception to this general trend was for patients in the subgroup of baseline EDSS score ≤3.5. In this subgroup, the ozanimod 1 mg treatment group had a statistically significantly lower ARR than the placebo group (rate ratio [active/placebo] = [redacted] [95% CI = 0.086, 0.786])(Celgene 2015c).

Table 23. Summary of ARR at the end of week 24 in RADIANCE Part A

	RADIANCE Part A	
	Placebo (N = 88)	Ozanimod 1 mg (N = 83)
Number of patients with relapses: n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥4	[redacted]	[redacted]
Unadjusted ARR	[redacted]	[redacted]
Adjusted ARR (95% CI)[a]	[redacted]	[redacted]
Rate ratio (active/placebo) (95% CI)[a]	[redacted]	[redacted]
P value[a]	[redacted]	[redacted]
Patient relapse rate[b]		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]

Source: (Celgene 2015c)

ARR = annualized relapse rate; Max = maximum; Min = minimum

[a] Based on the Poisson regression model, adjusted for region, the number of relapses within 24 months prior to the study, and presence of gadolinium-enhancing lesions at baseline.

b The number of relapses for each patient divided by the number of days the patient participated in the study, and then multiplied by 365.

In the RADIANCE Part A blinded extension, the unadjusted ARR observed during the placebo-controlled period were maintained during the blinded extension period. Unadjusted ARR remained stable over Year 1 (Week 72) and Year 2 (Week 120) in all the treatment groups. Unadjusted ARR for the placebo-controlled baseline period to end of placebo-controlled

period, entry into the blinded extension period to Week 72 (Year 1) of the blinded extension period, and Week 72 to Week 120 (Year 2) of the blinded extension period is summarised in Table 24 (Celgene 2017a).

Table 24. Summary of ARR in patients entering the blinded extension period of RADIANCE Part A

	Ozanimod treatment groups	
	Placebo - ozanimod 1 mg (N = 42)	Ozanimod 1 mg (N = 81)
Placebo-controlled period baseline to end of placebo-controlled period		
n	[redacted]	[redacted]
Unadjusted ARR	[redacted]	[redacted]
Year 1 of the blinded extension period[a]		
n	[redacted]	[redacted]
Unadjusted ARR	[redacted]	[redacted]
Year 2 of the blinded extension period[b]		
n	[redacted]	[redacted]
Unadjusted ARR	[redacted]	[redacted]

Source:(Celgene 2017a)

ARR = annualized relapse rate

[a] Year 1 of the blinded extension period is the 1-337 days after the first dose date of blinded extension period.

[b] Year 2 of the blinded extension period is the 338-674 days after first dose date of blinded extension period.

Endpoints associated with MRI lesions and brain volume

In RADIANCE Part A, the number of GdE lesions at Week 24 was statistically significantly lower in the ozanimod group than in the placebo group (mean [SD] = [redacted] in the placebo group, vs [redacted] in the ozanimod group) (Table 25). In the RADIANCE Part A blinded extension, the reference point for evaluation of new or enlarging T2 lesions was based on the cumulative number of T2 lesions present from Week 12 to Week 24 of the placebo-controlled period for all patients. The mean number of new or enlarging T2 lesions decreased from this reference point for the placebo-ozanimod 1 mg groups with a continued reduction in T2 lesions from entry into the blinded extension period through Year 1 (Week 72) and from Year 1 (Week 72) to Year 2 (Week 120).

The number of new or enlarging T2 lesions from Week 12 to Week 24 was statistically significantly lower in the ozanimod treatment group (mean [SD] = [redacted] in the placebo group, vs [redacted] in the ozanimod group)(Table 25)(Celgene 2015c).

In the RADIANCE Part A blinded extension, the reference point for evaluation of the new or enlarging T2 lesions was based on the cumulative number of T2 lesions present from Week 12 to Week 24 of the placebo-controlled period for all patients. The mean number of new or enlarging T2 lesions decreased from this reference point for the placebo-ozanimod 1 mg groups with a continued reduction in T2 lesions from entry into the blinded extension period through Year 1 (Week 72) (Table 26)(Celgene 2017a).

Table 25. Summary of GdE lesions and new or enlarging T2 lesions in RADIANCE Part A

	RADIANCE Part A	
Treatment	**Placebo (N = 88)**	**Ozanimod 1 mg (N = 83)**
Number of GdE lesions at week 24		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
P value[a]	[redacted]	[redacted]
Number of new or enlarging T2 lesions from Week 12 to Week 24		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
P value[a]	[redacted]	[redacted]

Source:(Celgene 2015c)

GdE = gadolinium-enhancing; Max = maximum; Min = minimum

[a] P value for comparison between the active and placebo groups was based on the stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.

Table 26. Total number of new or enlarging T2 lesions in RADIANCE Part A blinded extension

	RADIANCE Part A blinded extension	
Treatment	**Placebo – ozanimod 1mg[a] (N = 42) N (%)**	**Ozanimod 1 mg[b] (N = 81) N (%)**
Week 12 - Week 24 of placebo-controlled period		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Entry into Blinded Extension-Week 72 (Year 1 of the blinded extension period)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Week 72-Week 120 (Year 2 of the blinded extension period)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]

Source: (Celgene 2017a)

a Subjects who were randomized to receive placebo in the placebo-controlled period were re-randomized to receive ozanimod treatment (0.5 mg or 1 mg) in the blinded extension period. Only 1mg data is presented in this submission

b Subjects who were randomized to receive ozanimod treatment (0.5 mg or 1 mg) in the placebo-controlled period continued to receive the same ozanimod treatment in the blinded extension period. Only 1mg data is presented in this submission

B.2.7 Subgroup analysis

B.2.7.1. Pre-planned subgroup analyses

Across all Phase III and pooled analyses, ozanimod demonstrated a consistent reduction in relapses across various subgroups.

B.2.7.2. ARR (primary endpoint) subgroup analysis

The ARR during the treatment period is summarised by subgroups for the ITT population in Figure 4 for RADIANCE Part B and in Figure 5 for SUNBEAM. The rate ratios and 95% CIs were consistent across the subgroups (age, sex, baseline weight, race, relapses in prior 12 months, baseline Gd-E lesions, and prior DMT).

A treatment effect in favour of ozanimod 1 mg versus IFN β-1a was observed for ARR across all subgroups analysed in the pooled analysis, including those with high disease activity (Figure 6 and Figure 7). A treatment effect was also observed for ARR regardless of prior DMT use.

Figure 4. Forest Plot: ARR during the treatment period in RADIANCE Part B

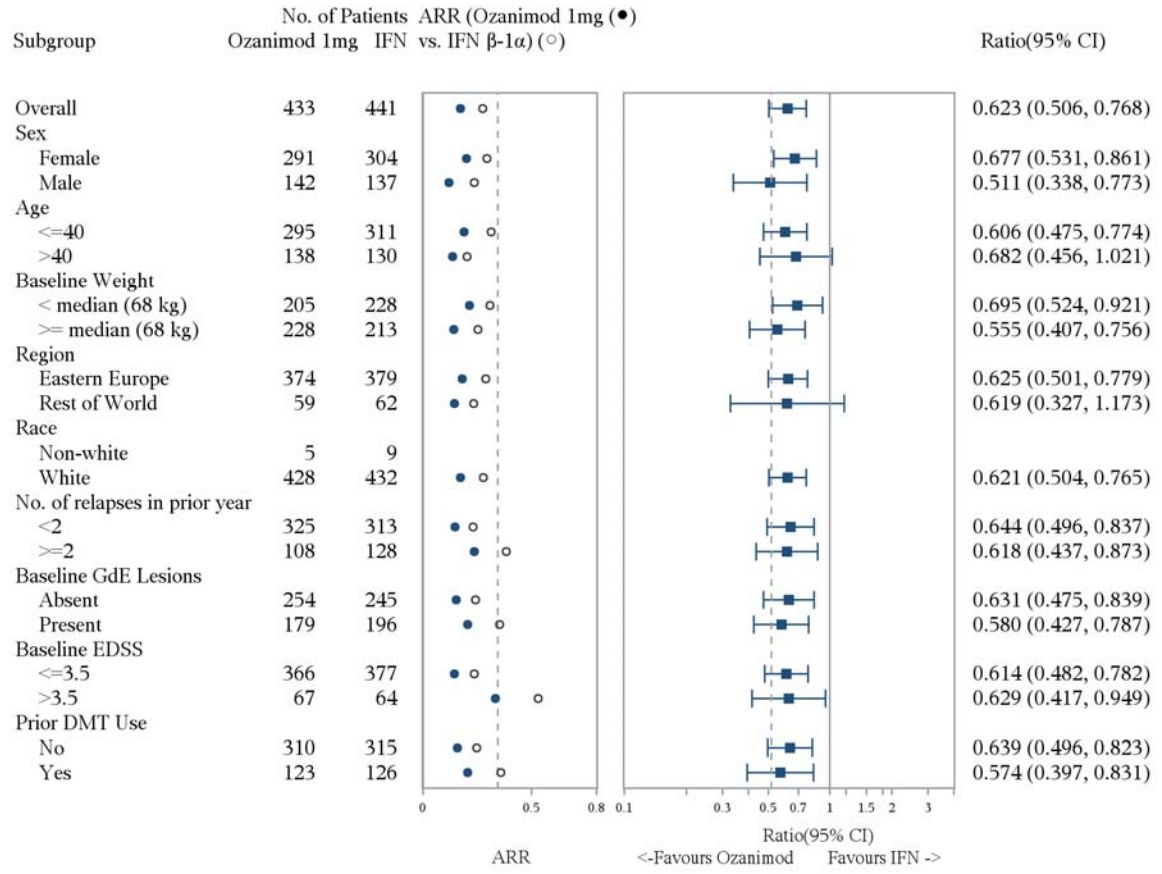
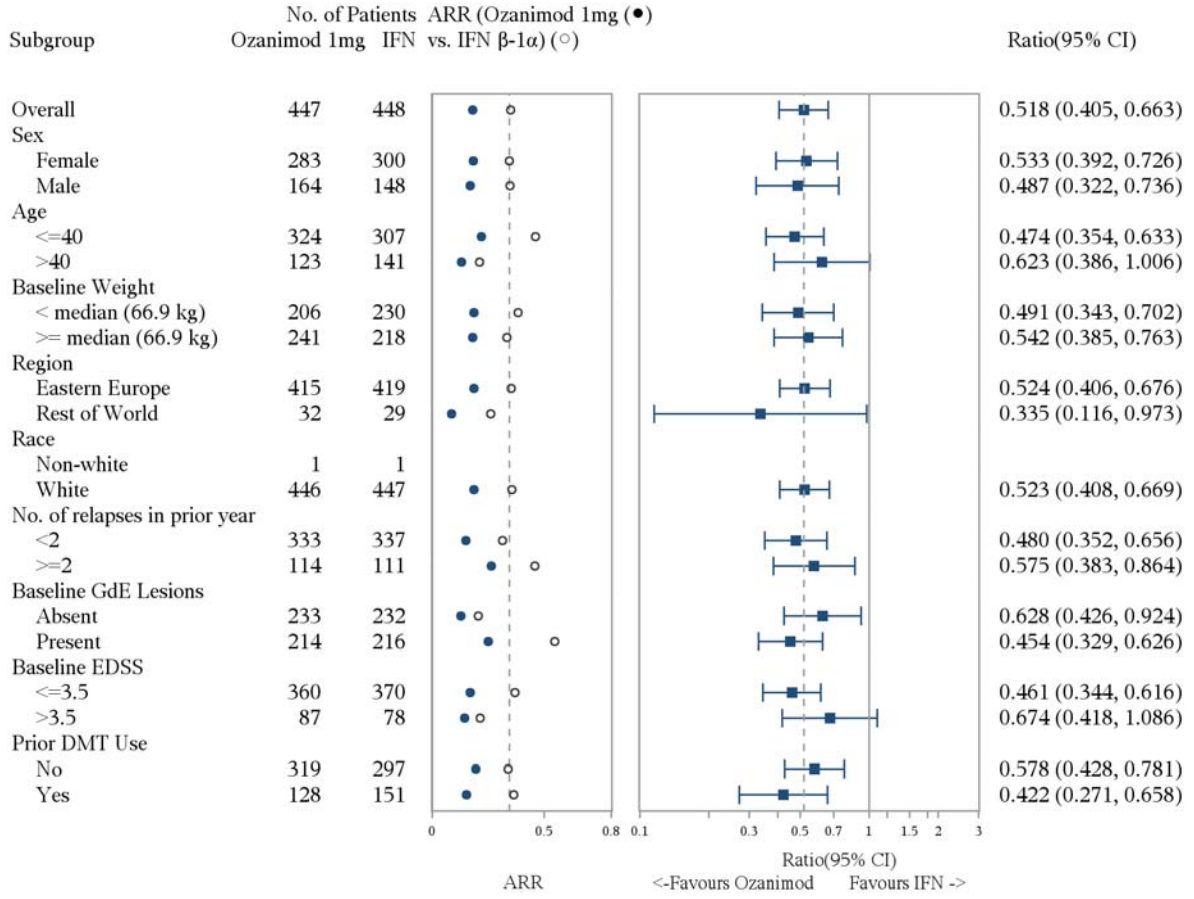
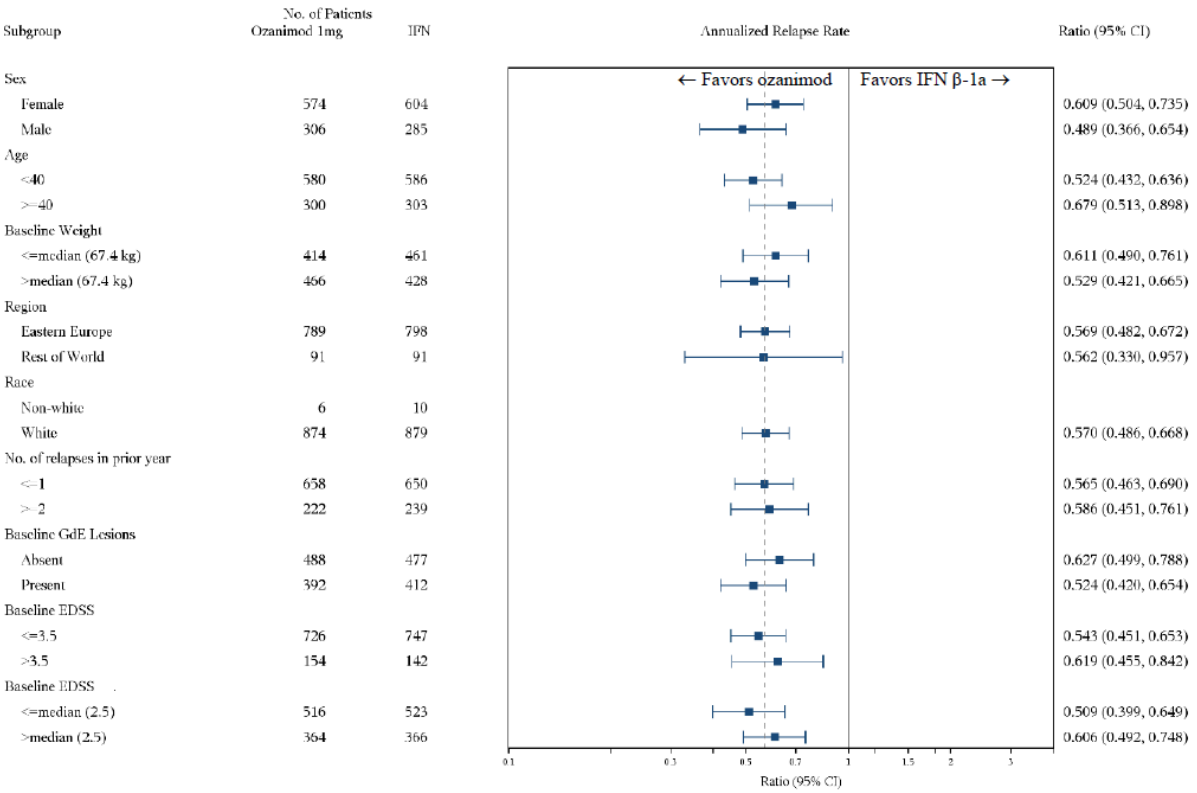


Figure 5. Forest Plot: ARR during the treatment period in SUNBEAM



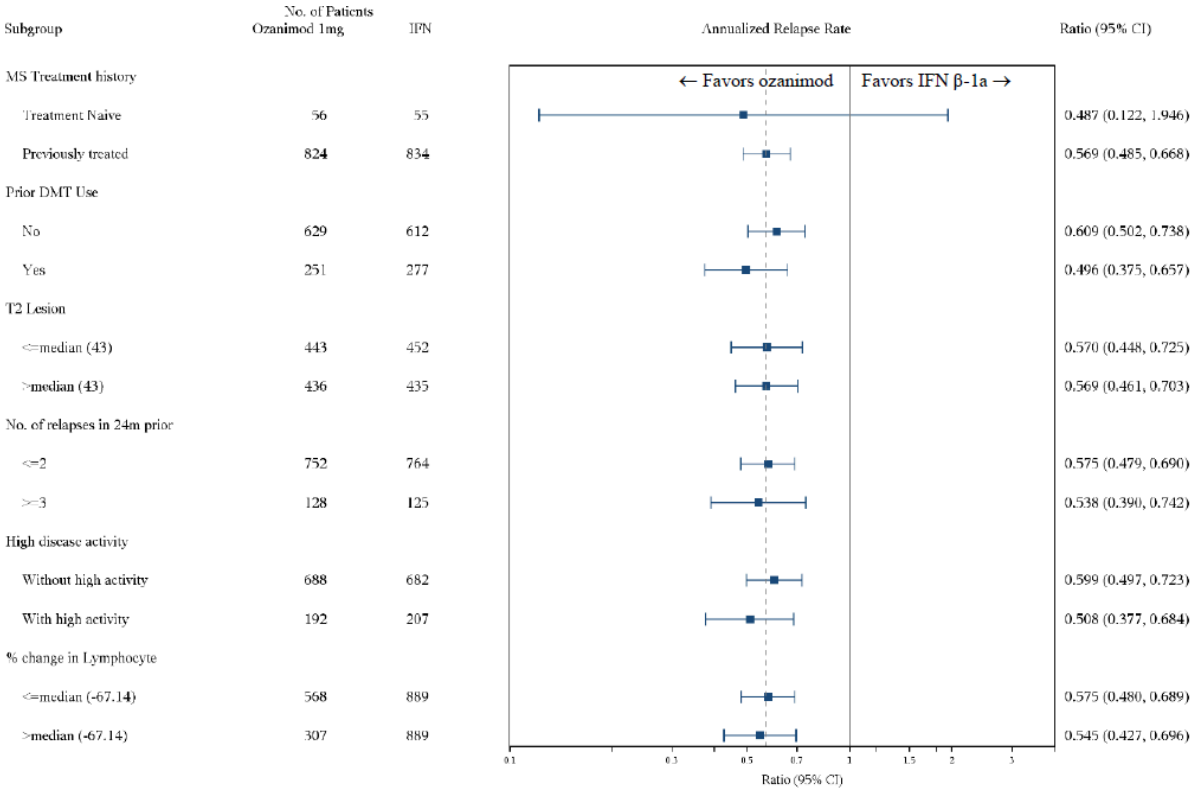
Source: (Celgene 2017b)

Figure 6. Forest Plot: ARR ratio during the treatment period by subgroups (ozanimod 1 mg vs IFN β-1a) - Pooled Phase III Clinical Studies – Panel A



Source: (Celgene 2019c)

Figure 7. Forest Plot: ARR ratio during the treatment period by subgroups (ozanimod 1 mg vs IFN β-1a) - Pooled Phase III Clinical Studies – Panel B



Source: (Celgene 2019c)

B.2.7.3. Post-hoc subgroup analyses

In a pooled analysis, ozanimod reduced the risk of relapse by [redacted] (HR [redacted]; 95% CI [redacted]) in patients with RMS who had no prior exposure to DMTs, and by [redacted] (HR [redacted]; 95% CI [redacted]) in patients who had previously received a prior DMT compared with IFN β-1a 30 µg (Table 25 and Table 26 in Appendix E1.2). Similar and consistent reductions in the risk of relapse have been seen across all pre-specified subgroups (Celgene 2019c).

B.2.8 Meta-analysis

A meta-analysis for the two pivotal Phase III studies (SUNBEAM [RPC01-301] and RADIANCE Part B [RPC01-201 Part B]) was not conducted, however, the results of these two studies were pooled for integrated efficacy analysis of ozanimod relative to IFN β-1a 30 µg due to similarities in study design, randomization ratio, patient population, and other design aspects (Celgene 2017b):

- Both studies are multicentre, double-blind, double-dummy, parallel group trials with an equal randomization ratio to each treatment group, with randomization stratified by baseline EDSS category (≤ 3.5, > 3.5) and country;
- Both studies evaluate the same daily dose regimens of ozanimod (0.5 mg and 1.0 mg, including an initial 7-day dose escalation regimen) and utilize IFN β-1a 30 µg as the active control group;
- Both studies include similar patient populations as reflected by study eligibility criteria. In addition, regional enrolment in the two trials is similar.

- Both studies include similar sets of primary and key secondary efficacy endpoints relating to annualized relapse rate, MRI lesion activity (new/enlarging T2 lesions and gadolinium-enhancing [Gd-E] lesions), and time to disability progression.
- Both studies utilised the same central MRI reading centre for evaluation of MRI parameters.

The primary objective of the integrated efficacy analysis was treatment effect estimation and not statistical hypothesis testing, with the notable exception of the pooled evaluation of CDP that was utilised for statistical hypothesis testing for disability progression. The primary analysis for time to first CDP was based on the Cox proportional hazards model with treatment, study, region, age at baseline, and baseline EDSS in which the handling of tied progression events was accounted for using Efron's method. The hazard ratio, 95% CI, and corresponding p-value for testing a treatment effect (i.e. hazard ratio = 1 under the null hypothesis) were reported.

The results of the integrated analyses for studies RPC01-301 and RPC01-201 Part B are presented in Section B.2.

In the absence of head-to-head RCTs conducted between comparator treatments listed in the NICE scope, a comprehensive systematic literature review and network meta-analyses (NMA) were conducted to estimate the comparative efficacy of these treatments.

Indirect comparisons can provide relative measures of effect for all relevant comparators in the absence of direct evidence and is most suitable when there are multiple-arm trials included within networks. The use of an indirect comparison, in preference to pairwise meta-analysis, allows the evidence of all available and relevant comparators listed in the scope to be included, enabling more precise relative treatment effects to be calculated using direct and indirect evidence. In addition, the indirect comparison feeds into the economic model to provide cost-effectiveness results for ozanimod against relevant comparators.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1. Summary of results

A standard Bayesian NMA was undertaken to establish the comparative effectiveness of ozanimod 1 mg versus its relevant comparator treatments.

For completeness, the NMA findings for the RRMS population are summarised briefly below (Table 27), with full methods and results available in Appendix D.

Table 27. Summary of key efficacy and safety outcomes of ozanimod 1 mg vs comparator

Comparator	ARR, Rate ratio (95% CrI)	CDP-3M, Annualized HR (95% CrI)	CDP-6M, Annualized HR (95% CrI)	CDP-3M and CDP-6M combined Annualized HR (95% CrI)	Discontinuation, Annualized HR (95% CrI)	AE, Odds ratio (95% CrI)	Serious AE Odds ratio (95% CrI)
Placebo	0.48 (0.4, 0.57)	[redacted]	[redacted]	[redacted]	[redacted]	0.98 (0.74, 1.32)	0.84 (0.49, 1.44)
Interferon beta-1a, 30µg	0.57 (0.48, 0.66)	[redacted]	[redacted]	[redacted]	[redacted]	0.53 (0.43, 0.65)	1.07 (0.68, 1.69)
Interferon beta-1a, 22µg	0.68 (0.54, 0.85)	[redacted]	[redacted]	[redacted]	[redacted]	--	--
Interferon beta-1b, 250µg	0.7 (0.58, 0.85)	[redacted]	[redacted]	[redacted]	[redacted]	2.08 (0.89, 4.89)	1.38 (0.72, 2.65)
Teriflunomide, 14mg	0.72 (0.56, 0.93)	[redacted]	[redacted]	[redacted]	[redacted]	0.77 (0.51, 1.16)	0.77 (0.42, 1.42)
Glatiramer acetate, 20mg	0.72 (0.58, 0.89)	[redacted]	[redacted]	[redacted]	[redacted]	1.2 (0.79, 1.83)	1.15 (0.65, 2.02)
Interferon beta-1a, 44 µg	0.72 (0.6, 0.87)	[redacted]	[redacted]	[redacted]	[redacted]	0.66 (0.34, 1.25)	0.95 (0.47, 1.9)
Glatiramer acetate, 40mg	0.72 (0.6, 0.87)	[redacted]	[redacted]	[redacted]	[redacted]	0.61 (0.42, 0.89)	0.75 (0.36, 1.54)
Peg-Interferon beta-1a, 125µg EOW	0.74 (0.55, 1.01)	[redacted]	[redacted]	[redacted]	[redacted]	0.32 (0.19, 0.53)	1.26 (0.66, 2.42)
Dimethyl fumarate, 240mg (bid)	0.88 (0.7, 1.1)	[redacted]	[redacted]	[redacted]	[redacted]	0.58 (0.36, 0.91)	1.07 (0.6, 1.9)

Source: (Pharmerit International 2019, Pharmerit International 2019c)

ARR: Annualised Relapse Rate; bid: twice a day; CDP: Confirmed Disease Progression; CrI: Credible Interval; HR: Hazard ratio; µg: microgram; mg: milligram; OR: Odds ratio

NMA analyses for the RRMS population indicated that ozanimod 1 mg was associated with a statistically significantly better efficacy profile in reducing ARR compared to Interferon beta-1a 30 µg (HR: 0.57, [95% CrI:0.48, 0.66]), Interferon beta-1a 22 µg (HR: 0.68, [95% CrI:0.54, 0.85]), Interferon beta-1a 44 µg (HR: 0.72, [95% CrI:0.60, 0.87]), Glatiramer acetate 20mg (HR: 0.72, [95% CrI:0.58, 0.89]), Glatiramer acetate 40mg (HR: 0.72, [95% CrI:0.60, 0.87]) and Teriflunomide 14mg (HR: 0.72, [95% CrI:0.56, 0.93]) (Pharmerit International 2019).

[redacted] (Pharmerit International 2019). Alternative methodologies to evaluate the comparative effectiveness of ozanimod relative to other RRMS treatments at 3- and 6-months CDP (CDP-3M and CDP-6M) are discussed in Appendix D (Pharmerit International 2019c).

When tolerability and safety were considered, the NMA results indicated that ozanimod 1 mg had significantly lower annualized rate of discontinuation than Glatiramer acetate 40 mg (HR: [redacted] [95% CrI:[redacted]]), Interferon beta-1a 30 µg (HR: [redacted] [95% CrI: [redacted]]), Interferon beta-1a 22 µg (HR: [redacted], [95% CrI: [redacted]]), Interferon beta-1a 44 µg (HR: [redacted] [95% CrI:[redacted]]), and Peg-Interferon beta-1a 125µg (HR: [redacted], [95% CrI: [redacted]]). The odds of experiencing AEs were significantly lower for ozanimod compared to Glatiramer acetate 40 mg (HR: [redacted] [95% CrI:[redacted]]), Interferon beta-1a 30 µg (HR: [redacted] [95% CrI [redacted] Peg-Interferon beta-1a 125µg (HR: [redacted] [95% CrI[redacted]]) and Dimethyl fumarate 240mg (bid) (HR: [redacted] [95% CrI[redacted]]) (Pharmerit International 2019).

For the prevention of new Gd+ lesions, ozanimod scored significantly better than Interferon beta-1a 30 µg with mean (95% CrI) difference of [redacted] (Pharmerit International 2019).

T2 lesions at 12 months were prevented significantly better by ozanimod compared to Glatiramer acetate 20mg, Interferon beta-1a 44 µg and Interferon beta-1a 30 µg, and there was also significantly better prevention of T2 lesions by ozanimod at 24 months compared to Interferon beta-1a 30 µg (mean [95% CrI] difference, [redacted]. (Pharmerit International 2019).

B.2.9.2. Uncertainties in the indirect and mixed treatment comparisons

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

- For ARR, the Poisson NMA model accounts for the length of the observation period. The assumption is that the relapse rate is constant over time.
- The CDP outcomes were analysed as survival outcomes. For these outcomes, the assumption is that the proportional hazards assumption holds.

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

The treatment comparisons have limited power to detect differences between treatments. Where the number of studies is low, relative to the number of treatments, treatment comparisons may lead to uncertain results. The further apart two treatments are in the network, the less precision there will be in their relative treatment effect. Thus, the uncertainty in comparisons between ozanimod and the other treatments will depend on the quality and quantity of the linking trials and the distance between ozanimod and the other treatments in the network.

The association between the CDP-3M and CDP-6M HRs of nearly all trials is a linear one. However, the CDP-3M and CDP-6M HRs of ozanimod versus Interferon beta-1a 30 µg in RADIANCE Part B and SUNBEAM do not follow this same pattern. The reasons for this are

unclear; but it is thought to be an anomaly and not due to the actual effect of ozanimod on CDP-6M.

B.2.10 Adverse reactions

AE study specific safety analyses were conducted in the pivotal RADIANCE Part B and SUNBEAM trials.

Integrated safety analyses were performed on combined data from RADIANCE Part B and SUNBEAM comprising of six safety pools, of which two are presented in this submission (Pool A1 [RADIANCE Part B, and SUNBEAM)] and Pool B [All five RMS studies, RADIANCE Part A and Part B, SUNBEAM, the phase I PK/PD study RPC01-1001, and the DAYBREAK OLE]).

Safety profile

- Ozanimod has demonstrated a consistent safety profile in patients treated across RADIANCE Part B and SUNBEAM
- Ozanimod had lower overall incidence of adverse events (AEs) compared with IFN β-1a
- The most frequently reported AEs were similar across both Phase III studies and pool A1 analysis
- Incidence of serious treatment-emergent adverse events (TEAEs) were infrequent with ozanimod and similar to IFN β-1a
- In both Phase III studies and the pool A1 analysis, the incidence of TEAEs and adverse events of special interest (AESIs) were similar across treatment groups
- Low incidence of pulmonary AEs was observed across treatment groups without association to pulmonary function test (PFT) findings
- No clinically meaningful cardiac AEs or findings considered related to ozanimod were reported during dose escalation

Discontinuations and withdrawals

- Ozanimod had a lower rate of AEs leading to discontinuation compared with IFN β-1a in both Phase III studies and pooled A1
- Few patients permanently discontinued ozanimod because of AEs of increased ALT
- No patients discontinued study drug due to pulmonary events
- There was no evidence of rebound or withdrawal in the active-controlled Phase III RMS studies

Risks

- The system organ classes with the highest incidence across both Phase III studies and pool A1 analysis included infections and infestations, nervous system disorders, and investigations
- Patients treated with ozanimod did not show any significant occurrence of cardiac AEs in clinical trials

- No serious infections including PML were reported in patients with an ALC in Pool A1< 0.2 x 109
- There was no evidence of increased risk of macular oedema in patients without pre-existing risk-factors
- In both Phase III studies and the pool A1 analysis, the incidence of malignancies were low with both ozanimod and IFN β-1a
- In both Phase III studies and the pool A1 analysis, suicidal ideation or behaviour was low for both ozanimod and IFN β 1a

Deaths

- No deaths related to ozanimod occurred in the Phase III studies
- The safety profile of ozanimod has been examined in a large active-controlled Phase III RMS clinical program in 1774 patients. Ozanimod demonstrated a favourable safety profile as compared to IFN β-1a (Celgene).
- AEs reported in the pivotal RADIANCE Part B and SUNBEAM trials are presented in Section B.2.10.1 and Section B.2.10.2, respectively (Celgene 2017a, Celgene 2017b). In addition, integrated safety analyses on combined data (Pool A1 - RADIANCE Part B, and SUNBEAM) and Pool B (All five RMS studies]) are also presented in this submission (Sections B.2.10.3 and B.2.10.4 respectively) (Celgene).

B.2.10.1. Overview of AEs in RADIANCE Part B

Ozanimod demonstrated lower overall incidence of AEs compared with IFN β-1a. A total of [redacted] patients in RADIANCE Part B experienced at least 1 AE. The proportion of patients who experienced an AE was lower in the ozanimod 1 mg group (74.7% of patients) and the ozanimod 0.5 mg group (74.3% of patients) compared with the IFN β-1a group (83.0% of patients) (Table 28.) (Celgene 2017a).

Adverse events with an incidence increase ≥ 1% for the ozanimod 1 mg and 0.5 mg groups compared with the IFN β-1a group included the following PTs (Table 29.):

- nasopharyngitis
- alanine aminotransferase increased
- hypertension
- gamma-glutamyltransferase increased
- back pain
- fatigue
- arthralgia

A low incidence of pulmonary AEs was observed across treatment groups without association to PFTs findings. No patients discontinued ozanimod due to these events.

No clinically meaningful cardiac AEs or findings considered related to ozanimod were reported during dose escalation. Serious cardiac AEs were infrequent and similar across treatment groups, with none reported in the ozanimod 1 mg group (Celgene 2017a).

- The maximum mean reduction in supine heart rate on day 1 over hours 1–6 following administration of ozanimod 0.25 mg was 0.6 beats per minute (bpm) (mean heart rate, 68 bpm), occurring at hour 5. Four ozanimod-treated patients

had a minimum supine heart rate <45 bpm over hours 1–6 on day 1; all resolved spontaneously by hour 7 or 8. All cases had low pre-dose heart rate (55–64 bpm) and remained asymptomatic.

- Symptomatic bradycardia was reported as an AE after the initial ozanimod 0.25 mg dose in one patient with a history of dysautonomia and low pre-dose blood pressure (90/60 mm Hg) and heart rate (60 bpm by pulse, 48 bpm by electrocardiogram [ECG]).
- No ECG findings or AEs of second- or third-degree atrioventricular (AV) block were reported. At month 24, the mean (SD) change in supine corrected QT interval using Bazett's formula (QTcB) interval from baseline was comparable across treatment groups ([redacted] ms in the ozanimod 1 mg group compared with [redacted]) ms in the IFN β-1a group.

Table 28. Summary of adverse events in RADIANCE Part B (Safety population)

AE	IFN β-1a 30 µg (N = 440) N (%)	Ozanimod 0.5 mg (N = 439) N (%)	Ozanimod 1mg (N = 434) N (%)	Total Ozanimod (N = 873) N (%)
At least one TEAE	365 (83.0)	326 (74.3)	324 (74.7)	[redacted]
At least one moderate or severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one severe TEAE	19 (4.3)	19 (4.3)	15 (3.5)	[redacted]
At least one suspected TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one serious TEAE	28 (6.4)	31 (7.1)	28 (6.5)	[redacted]
At least one suspected serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one TEAE leading to permanent discontinuation of study drug	18 (4.1)	14 (3.2)	13 (3.0)	[redacted]
At least one TEAE leading to study withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Death on study	0	1 (0.2)	0	[redacted]
Death related to study drug	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017a, Cohen 2019b)

Abbreviations: TEAE: Treatment-emergent adverse event

Note: Denominators for percentages are N, the total number of subjects. The suspected relationships are “Possible”, “Probable”, “Related” or missing relationship. A TEAE is defined as an adverse event with a start date on or after the date of first dose of study drug, up through the first dose of study drug in the open-label extension (Study RPC01-3001) for subjects who continued into the open-label extension. At each level of subject summarization, a subject is counted only once if the subject reported one or more events.

Table 29. Incidence of most frequent adverse events (incidence ≥2% in the total ozanimod group) by preferred term in RADIANCE Part B (Safety population)

Preferred Term[a] n (%)	IFN β-1a 30 µg (N = 440) N (%)	Ozanimod 0.5 mg (N = 439) N (%)	Ozanimod 1mg (N = 434) N (%)	Total Ozanimod (N = 873) N (%)
Subjects With at least one TEAE[b]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	48 (10.9)	59 (13.4)	68 (15.7)	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	20 (4.5)	29 (6.6)	26 (6.0)	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	14 (3.2)	20 (4.6)	24 (5.5)	[redacted]
Gamma-glutamyltransferase increased	9 (2.0)	16 (3.6)	25 (5.8)	[redacted]
Pharyngitis	15 (3.4)	24 (5.5)	17 (3.9)	[redacted]
Urinary tract infection	17 (3.9)	22 (5.0)	19 (4.4)	[redacted]
Back pain	14 (3.2)	21 (4.8)	18 (4.1)	[redacted]
Fatigue	12 (2.7)	17 (3.9)	16 (3.7)	[redacted]
Arthralgia	6 (1.4)	17 (3.9)	15 (3.5)	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	6 (1.4)	8 (1.8)	14 (3.2)	[redacted]

Preferred Term[a] n (%)	IFN β-1a 30 µg (N = 440) N (%)	Ozanimod 0.5 mg (N = 439) N (%)	Ozanimod 1mg (N = 434) N (%)	Total Ozanimod (N = 873) N (%)
Diarrhoea	8 (1.8)	14 (3.2)	8 (1.8)	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	5 (1.1)	10 (2.3)	8 (1.8)	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017a, Cohen 2019b)

a Coded using MedDRA, version 18.1

b A subject that reports an event more than once is counted only once within each system organ class/preferred term for that event.

Note: Denominators for percentages are N, the total number of subjects. Treatment-Emergent Adverse Events are sorted by descending incidence in the Total Ozanimod column and then alphabetically by Preferred Term. A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date on or after the date of first dose of study drug, up through the first dose of study drug in the open-label extension (Study RPC01-3001) for subjects who continued into the open-label extension.

B.2.10.2. Overview of AEs in SUNBEAM

In the SUNBEAM trial, the safety profile of ozanimod showed lower rates of AEs compared with IFN β-1a. The proportion of patients who experienced an AE was greater in the IFN β-1a group (75.5% of patients) compared to both ozanimod groups, with the ozanimod 1 mg group (59.8% of patients) experiencing more AEs than the ozanimod 0.5 mg group (57.2% of patients) (Table 30.) (Celgene 2017b).

The most frequently occurring AEs (≥ 2% in the total ozanimod group) by PT were nasopharyngitis (8.2%), headache (6.8%), upper respiratory tract infection (5.4%), influenza like illness ([redacted]), alanine aminotransferase increased (3.7%), back pain (3.0%), gamma-glutamyltransferase increased (2.8%), respiratory tract infection viral (2.8%), and urinary tract infection (2.8%) (Table 31.) (Celgene 2017b).

A low incidence of pulmonary-specific AEs was observed across treatment groups without association to pulmonary findings. No patients discontinued study drug due to these events.

The overall incidence of cardiac AEs was similar in ozanimod 1 mg compared with the IFN β-1a group. The majority of the cardiac AEs were mild to moderate in intensity and recovered or resolved (Celgene 2017b).

- The mean (SD) change in supine heart rate from pre-dose value to Hour 6 was [redacted]) bpm for patients in the total ozanimod group (0.25 mg) compared with [redacted]) bpm for patients in the IFN β-1a group. For the total ozanimod group (0.25 mg), the maximum mean change in the first 6 hours was -1.8 bpm and was observed at Hour 5. The majority ([redacted]) of patients who received 0.25 mg of ozanimod maintained supine heart rate ≥60 bpm. No patient had a heart rate <45 bpm.

- One patient with a pre-dose supine heart rate of 76 bpm was reported as having symptomatic bradycardia (headache) after the initial dose of ozanimod 0.25 mg, but there was no evidence of bradycardia on heart rate monitoring. One patient with a baseline heart rate (HR) of 60 bpm and lowest HR of 50 bpm at hour 6 underwent extended monitoring, during which a serious AE of asymptomatic sinus bradycardia was reported; the event resolved.
- There were no AEs of second- or third-degree AV block during the study. At month 12, the mean (SD) change in supine QTcB interval from baseline was comparable across treatment groups ([redacted] [redacted] ms in the ozanimod 1 mg group compared with [redacted] [redacted] ms in the IFN β-1a group).

Table 30. Summary of adverse events in SUNBEAM (Safety population)

	IFN β-1a 30 µg (N=445) n (%)	Ozanimod 0.5 mg (N=453) n (%)	Ozanimod 1 mg (N=448) n (%)	Total Ozanimod (N=901) n (%)
At least one TEAE	336 (75.5)	259 (57.2)	268 (59.8)	[redacted]
At least one moderate or severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one severe TEAE	10 (2.2)	10 (2.2)	7 (1.6)	[redacted]
At least one suspected[a] TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one serious TEAE	11 (2.5)	16 (3.5)	13 (2.9)	[redacted]
At least one suspected[a] serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
At least one TEAE leading to permanent discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]
At least one TEAE leading to study withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
Death	0	0	0	[redacted]
Death related to study drug	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene 2017b, Cohen 2019a)

Abbreviations: IFN = interferon; TEAE = treatment-emergent adverse event.

[a] The suspected relationships were "Possible", "Probable", "Related" or missing relationship.

Note: Denominators for percentages are N, the total number of subjects. A treatment-emergent adverse event (TEAE or AE) was defined as an adverse event with a start date on or after the date of first dose of study drug, up through the first dose of study drug in the open-label extension (Study RPC01-3001) for subjects who continued into the open-label extension.

Table 31. Incidence of most frequent adverse events (incidence ≥ 2% in the total ozanimod group) by preferred term in SUNBEAM (safety population)

Preferred Term[a] n (%)	IFN β-1a 30 µg (N = 445) N (%)	Ozanimod 0.5 mg (N = 453) N (%)	Ozanimod 1 mg (N = 448) N (%)	Total Ozanimod (N = 901) N (%)
Number of subjects with at least 1 TEAE[b]	336 (75.5)	259 (57.2)	268 (59.8)	[redacted]
Nasopharyngitis	36 (8.1)	44 (9.7)	30 (6.7)	[redacted]
Headache	25 (5.6)	27 (6.0)	34 (7.6)	[redacted]
Upper respiratory tract Infection	24 (5.4)	31 (6.8)	18 (4.0)	[redacted]
Influenza like Illness	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	8 (1.8)	12 (2.6)	21 (4.7)	[redacted]
Back pain	9 (2.0)	10 (2.2)	17 (3.8)	[redacted]
Gamma-glutamyltransferase increased	2 (0.4)	10 (2.2)	15 (3.3)	[redacted]
Respiratory tract infection viral	3 (0.7)	10 (2.2)	15 (3.3)	[redacted]
Urinary tract infection	10 (2.2)	8 (1.8)	17 (3.8)	[redacted]

Source: (Celgene 2017b, Cohen 2019a)

Abbreviations: IFN = interferon; TEAE = treatment-emergent adverse event.

[a] Coded using MedDRA, version 18.1.

[b] A subject that reported an event more than once was counted only once within each system organ class/preferred term for that event.

Note: Denominators for percentages are N, the total number of subjects. A treatment-emergent adverse event (TEAE or AE) was defined as an adverse event with a start date on or after the date of first dose of study drug, up through the first dose of study drug in the open-label extension (Study RPC01-3001) for subjects who continued into the open-label extension.

B.2.10.3. Overview of AEs in Pool A1 from the summary of clinical safety

Pooled safety analyses were conducted, analysing the safety population including patients who received at least 1 dose of the study drug. The 1774 patients in the A1 pool included the safety populations from the pivotal trials RADIANCE Part B and SUNBEAM. Exposure to ozanimod was well balanced, with over [redacted] of patients exposed to ozanimod for at least 12 months (Table 32.) (Celgene).

The overall incidence of AEs was lower in the ozanimod treatment groups compared with IFN β-1a (Table 32.). The incidence of severe and serious TEAEs were low and similar across the three treatment groups. Adverse events leading to permanent discontinuation of study drug or to withdrawal from the study were infrequent in all treatment groups and reported at a slightly lower incidence in the ozanimod treatment groups compared with the IFN β-1a group (Celgene).

The incidence of AEs in the Respiratory, Thoracic and Mediastinal Disorders system organ class were similar across the two treatment groups in Phase III studies: [redacted] for ozanimod

1mg, and [redacted] for IFN β-1a. PFT values for forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), were generally similar across all treatment groups. For diffusing capacity of the lungs for carbon monoxide (DLCO), all 3 treatment groups showed small decreases from baseline, with the largest median decrease observed in the ozanimod 1 mg group (Celgene).

The overall incidence of cardiac AEs was low and similar across the ozanimod and IFN β-1a treatment groups ([redacted] and [redacted] respectively). The frequency of cardiac-related SAEs was low and similar across the treatment groups: [redacted] in ozanimod 1 mg, and [redacted] in IFN β-1a group (Celgene).

- Slight reductions in supine heart rate were observed in ozanimod-treated patients on day 1, with the nadir observed at hour 5; mean heart rate generally returned to baseline by hour 6. Within 6 hours, the greatest reduction from baseline in mean supine heart rate was [redacted] bpm at hour 5 in the ozanimod group, which had a mean heart rate of [redacted] bpm. Asymptomatic, transient supine heart rate reduction <45 bpm on day 1 during hours 1 to 6 was observed in [redacted] ozanimod-treated patients and resolved spontaneously by Hour 7 or 8. No heart rate < 40 bpm was observed. No decrease in mean heart rate was observed with chronic dosing.
- Bradycardia or sinus bradycardia was reported in [redacted] patients ([redacted] randomised to ozanimod 1 mg, and [redacted] patients treated with IFN β-1a on the day of treatment initiation. After day 1, bradycardia or sinus bradycardia was reported in [redacted] patients ([redacted]) treated with ozanimod 1 mg, and [redacted] patients ([redacted] treated with IFN β-1a.
- No ECG findings or AEs of new-onset, second-degree or higher AV block were reported. ECG performed at Months 12 and 24 showed no clinically significant changes in QTcF, and no second- or third-degree AV block with continuous ozanimod treatment. At Month 12, the mean (SD) change in supine QTcB interval from baseline was comparable across treatment groups ([redacted] [[redacted]] ms in the ozanimod 1 mg group compared with [redacted] ([redacted]) ms in the IFN β-1a group).

Table 32. Summary of treatment-emergent adverse events by subject – Pool A1 (safety population)

	IFN β-1a 30 µg (N=885) n (%)	Ozanimod 0.5 mg (N=892) n (%)	Ozanimod 1 mg (N=882) n (%)	Total Ozanimod (N=1774) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to temporary discontinuation or delay of study drug	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to permanent discontinuation of study drug[a]	[redacted]	[redacted]	[redacted]	[redacted]

	IFN β-1a 30 µg (N=885) n (%)	Ozanimod 0.5 mg (N=892) n (%)	Ozanimod 1 mg (N=882) n (%)	Total Ozanimod (N=1774) n (%)
Any TEAE leading to study withdrawal[a]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Celgene)

Abbreviations: TEAE = treatment-emergent adverse event.

[a] Patients who permanently discontinued study drug were permitted to remain in the study; data capture allowed for either or both of these outcomes as the result of an AE.

[b] Two patients in the IFN β-1a treatment group were incorrectly captured as having been terminated from study

[c] One patient in the ozanimod 0.5 mg treatment group should have been captured as having been terminated from the study

[d] One subject died approximately 10 months after the last dose of ozanimod

Note: At each level of subject summarization, a subject is counted only once if the subject reported multiple events. A TEAE is defined as any event with an onset date on or after the first dose date of study drug up through the first dose date of the uncontrolled study.

The most frequently reported AEs with ozanimod were reported in ≥ 2% of subjects in any treatment group and at a ≥ 1% higher incidence in either ozanimod treatment group compared with IFN β-1a. Nasopharyngitis was the most frequently reported AE with ozanimod; the incidence was slightly higher in the ozanimod treatment groups compared with the IFN β-1a treatment group, but no dose effect was observed. Other infections more frequently reported with ozanimod involved primarily the upper respiratory tract or urinary tract (Table 33.).

Table 33. Incidence of the most frequently reported treatment-emergent adverse events with ozanimod (≥ 2% of patients in any treatment group and ≥ 1% higher in either ozanimod treatment group versus IFN β-1a) – Pool A1 (safety population)

Preferred term	IFN β-1a 30 µg (N=885) n (%)	Ozanimod 0.5 mg (N=892) n (%)	Ozanimod 1 mg (N=882) n (%)
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Respiratory tract infection viral	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]

Source: (Celgene)

IFN = interferon.

Note: Preferred terms are listed in order of decreasing frequency in the ozanimod 1 mg treatment group followed by the ozanimod 0.5 mg treatment group.

B.2.10.4. Overview of AEs in Pool B from the summary of clinical safety

Pool B summarised safety data from patients from all ozanimod RMS studies: (RADIANCE Part A and Part B, SUNBEAM, the Phase I PK/PD study RPC01-1001, and the DAYBREAK OLE) Approximately [redacted] of patients in pool B were exposed to ozanimod for at least 12 months. The pool B safety data provides a comprehensive view of the long-term safety of ozanimod in patients with RMS (mean [SD] duration exposure of ozanimod 0.5 mg (months): [redacted]; ozanimod 1 mg: [redacted]), as it includes data from the extension of RADIANCE Part A, as well as the DAYBREAK OLE (Celgene 2019f).

The long-term adverse effects seen with ozanimod in subjects with RMS were analysed by comparing the incidence and incidence rate (per 1000 SY) of the AEs reported in ≥ 5% of subjects in any ozanimod treatment group between Pool A1 and Pool B, which showed no increased incidence of AEs with longer-term exposure to ozanimod 1 mg (Table 34.).

Table 34. Comparison of the incidence and incidence rate of treatment-emergent adverse events reported for ≥ 5% of patients in either ozanimod treatment group in the active-controlled Phase III RMS studies (Pool A1) and all RMS studies (Pool B)

System Organ Class Preferred Term	Pool A1				Pool B			
	Ozanimod 0.5 mg N = 892 SY = 1341.5[a]		Ozanimod 1 mg N = 882 SY = 1345.4[a]		Ozanimod 0.5 mg N = 1033 SY = 1621.7[a]		Ozanimod 1 mg N = 2631 SY = 5703.4[a]	
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Any TEAE	[redacted]							
Nasopharyngitis	[redacted]							
Headache	[redacted]							
Upper respiratory tract infection	[redacted]							
Alanine aminotransferase increased	[redacted]							
Influenza like illness	[redacted]							
Lymphopenia[c]	[redacted]							
Gamma-glutamyltransferase increased	[redacted]							
Lymphocyte count decreased[c]	[redacted]							

Source: (Celgene)

AE = adverse event; IR = incidence rate; RMS = relapsing multiple sclerosis; TEAE = treatment-emergent adverse event; SY = subject-years.

a Total subject-years equals the sum of the number of years on study contributed by each subject from time of first dose to last date on study. The algorithm for the last date on study is dependent on subject disposition and whether subject enrolled into an extension study. If there is a duration gap between parent and extension study, the duration gap is counted.

b Incidence rate per 1000 subject-years is calculated as number of subjects / SY x 1000 for specific SOC category or PT subcategory. Subject-years for each category/subcategory: for a subject in a particular category/subcategory, the time on study is calculated based on the date the subject first has a TEAE within the category/subcategory (date of first TEAE - first dose date of study drug + 1)/365.25; for subjects who don't have a TEAE in the category/subcategory, the time on study is the study duration (last date on study - first dose date of study drug +1)/365.25.

c Investigators in the Phase III RMS studies comprising Pool A1 were blinded to lymphocyte count data (a key pharmacodynamic effect of ozanimod), therefore AEs related to lymphocyte counts were not reported.

B.2.10.5. Overview of AEs in RADIANCE Part A

In the RADIANCE Part A trial, safety results including nature and incidence of TEAEs and SAEs, laboratory parameters, vital signs, cardiac monitoring and other physical examinations were consistent with the patient population studied. No patients discontinued the study due to a TEAE and approximately [redacted] of enrolled patients completed the study. No significant cardiac TEAEs or protocol-defined cardiac TEAEs of special interest were reported in ozanimod-treated patients. The titration regimen using 0.25 mg ozanimod on Day 1 produced modest effects on HR, with no ozanimod-treated patient's HR dropping below 45 bpm on hourly vital signs, no ozanimod-treated patient with a minimum hourly heart rate on Holter monitoring of less than 50 bpm during the first six hours post-dose, and no TEAEs of symptomatic bradycardia or conduction abnormalities in any ozanimod-treated patient. No clinically significant safety findings, as compared with placebo, were observed for ECGs, ophthalmologic or dermatologic examinations, pulmonary function tests, incidence of infections, suicidality ratings, or incidence of malignancies.

Overall, the safety profiles of both doses of ozanimod were generally similar to placebo. These safety data suggest that ozanimod was well tolerated in the studied population and supported the continuation of the Phase III RADIANCE Part B trial.

In the RADIANCE Part A blinded extension, ozanimod was generally well tolerated, with no new or significant AE during continued dosing with ozanimod over 120 weeks. No second-degree AV block Type 1 or higher was observed, and there were no clinically meaningful or unexpected changes in laboratory parameters over time. Overall, the ozanimod safety profile was consistent with previous Phase II data and suggests a favourable benefit-risk profile for ozanimod.

B.2.11 Ongoing studies

There is an ongoing open-label extension trial (DAYBREAK; RPC01-3001), in which patients who completed five parent studies (RADIANCE Part A, RADIANCE Part B, SUNBEAM, or the Phase 1 trial RPC01-1001) were eligible to enrol in the ongoing DAYBREAK OLE. DAYBREAK is designed to further characterise the long-term safety and efficacy of ozanimod 1 mg tablets beyond the RADIANCE B and SUNBEAM registration studies (Celgene 2019d).

Interim results from the DAYBREAK OLE trial are presented in Appendix D1.5.2.

In addition, ozanimod is also currently under clinical investigation in autoimmune indications: Phase III trials of ozanimod are ongoing in Ulcerative Colitis and in Crohn's Disease.

B.2.12 Innovation

Ozanimod is an efficacious DMT with a convenient posology which provides multiple benefits for the patient, clinician, and healthcare providers.

The key innovations for patients relate to the ozanimod mechanism of action and safety:

- Mode of action: ozanimod is a modulator of the S1P1R pathway. It is an immunomodulator that selectively targets sphingosine-1-phosphate receptor-1 (S1P1R) and receptor-5 (S1P5R) to mitigate autoimmune responses and promote neuronal protection.
- In comparison to existing S1P modulators (e.g. fingolimod), ozanimod (following the up-titration scheme reported above) did not demonstrate cardiac conduction abnormalities (primarily QT interval prolongation), nor did ozanimod show to induce hypertension through engagement of S1P3 receptors on vascular smooth muscle cells.
- Ozanimod demonstrated a consistent safety profile in patients treated across all ozanimod MS trials, demonstrating lower rates of AEs compared with IFN β-1a.
- Patient preference: ozanimod is a once daily oral tablet, allowing self-administration at home and minimal disturbance to daily life compared to injectable therapies.

Celgene believes that ozanimod addresses an unmet need for more options in the RRMS treatment landscape and therefore can represent a meaningful addition to the NHS's treatment algorithm for RRMS.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Despite the range of DMT options currently available in the UK to patients with RRMS, there is still an unmet need for effective and well-tolerated treatments for patients who suffer from a chronic and disabling disease, like RRMS. The choice of DMT is largely driven by informed discussion and consensus between the prescribing clinician and the patient, based on the level of disease activity, patient risk tolerance, patient preference, and patient lifestyle considerations. Therefore, availability of a wider range of treatment options is vital to providing the most suitable treatment for all RRMS patients.

In Section B.2 of this submission, Celgene has summarised the relevant evidence from the clinical development programme of ozanimod. The RADIANCE Part B and SUNBEAM trials along with pooled analyses of efficacy and safety from these two pivotal Phase III trials provide

a strong evidence base to support the safety and efficacy of ozanimod in adult patients with RRMS.

In the pivotal Phase III trials, ozanimod 1 mg tablets demonstrated superior efficacy compared to IFN β-1a in a range of traditional and novel endpoints associated with RMS progression.

ARR was a primary endpoint in both RADIANCE Part B and SUNBEAM. In both trials as well as the integrated pooled analysis, ozanimod 1 mg significantly reduced ARR compared with IFN β-1a (adjusted ARR 0.172 vs 0.276, respectively [RADIANCE Part B], adjusted ARR 0.181 vs. 0.350, respectively [SUNBEAM]). In both Phase III studies, ozanimod demonstrated superiority to IFN β-1a in the rates for time to first relapse. The pooled analysis showed the time to first relapse was delayed in the ozanimod groups compared with the IFN β-1a group.

In addition to relapse-related endpoints, ozanimod also met the following prespecified secondary endpoints related to MRI lesions and brain volume in both Phase III trials, namely reducing the number of new/enlarged hyperintense T2-weighted brain MRI lesions, reducing the number of Gd-E T1 lesions, and reduction in BVL.

- Ozanimod 1 mg was significantly superior to IFN β-1a in reducing the total adjusted mean number of new or enlarging T2 lesions, with [redacted] reduction over 24 months in RADIANCE Part B ([redacted] and [redacted] lesions per scan, respectively, p<0.0001), and [redacted] reduction over 12 months in SUNBEAM ([redacted] and [redacted] lesions per scan, respectively, p<0.0001). The proportion of patients who were free of new or enlarging hyperintense T2-weighted brain MRI lesions was higher in ozanimod 1 mg compared with the IFN β-1a group.
- Ozanimod was significantly superior to IFN β-1a in reducing the number of Gd-E brain lesions, with [redacted] reduction at month 24 in RADIANCE Part B ([redacted] and [redacted] lesions per scan, respectively, p<0.0006), and [redacted] reduction at month 12 in SUNBEAM ([redacted], and [redacted] lesions per scan, respectively, p<0.0001). The proportion of patients who were free of Gd-E T1 brain MRI lesions was higher in the ozanimod 1 mg compared with the IFN β-1a group.
- Ozanimod was significantly superior in limiting BVL (associated with loss of cognition and increase in disability progression in MS) compared to IFN β-1a in RADIANCE and SUNBEAM, showing preservation of brain volume.
- In both Phase III studies, there was a statistically significant difference in brain volume, cortical grey matter volume loss, and thalamic volume with ozanimod compared to IFN β-1a. Pooled results showed nominally significant slowing of whole BVL, cortical grey matter volume loss and reductions in thalamic volume with ozanimod compared to IFN β-1a. In the pooled analysis of RADIANCE Part B and SUNBEAM, the difference in mean percent change of normalised brain volume (cm^3) from baseline at 12 months (ozanimod 1 mg vs IFN β-1a 30 µg) was [redacted] (95% CI: [redacted]; p<0.0001). The difference in mean percent change of cortical grey matter volume (cm^3) in the same analysis was [redacted] (95%CI: [redacted], p<0.0001), and the difference in mean percent change of thalamic volume (cm^3) was [redacted] (95% CI: [redacted], p<0.0001).
- In both the SUNBEAM trial and the pooled analysis, patients treated with ozanimod exhibited significant and clinically meaningful improvements in cognitive processing speed as measured by SDMT and PASAT. The mean change from baseline in the pooled analysis for the SDMT/PASAT Score was [redacted] (SD: [redacted]), with difference in means of [redacted] (95% CI: [redacted], p<0.0329). Improvements in cognitive processing speed are consistent with BVL findings demonstrating preservation of both thalamic and cortical gray matter volume.

- Across both trials, there was no significant deterioration in QoL with ozanimod compared to IFN β-1a. Ozanimod maintained the QoL for patients with RMS for 2 years, with no statistically significant declines from baseline in physical or mental health. A statistically significant improvement in the MSQOL-54 physical health composite summary scores was observed for ozanimod compared with IFN β-1a in the SUNBEAM study.
- A higher proportion of patients showed no evidence of disease activity when treated with ozanimod versus IFN β-1a. In RADIANCE Part B, there was a statistically significant increase in the proportion of patients with NEDA-3 at month 24 in the ozanimod 1 mg group compared with the IFN β-1a group (p=0.0309). After 2 years of treatment, [redacted] out of [redacted] patients with RMS on ozanimod showed no evidence of disease activity compared to [redacted] out of [redacted] on IFN β-1a. In both Phase III studies, there are consistent increases in the numbers of individuals with NEDA-3 when patients are treated with ozanimod versus IFN β-1a. In addition, the pooled analysis of RADIANCE Part B and SUNBEAM revealed that there was a statistically significant increase in the proportion of patients with NEDA-4 at 24 months in patients receiving ozanimod 1 mg.

B.2.13.1. Key clinical issues

Confirmed disability progression results need to be interpreted with caution. For CDP-3M and CDP-6M, it was insufficient to detect a significant treatment difference between ozanimod and IFN β-1a due to the low number of events associated with limited follow-up time. This contributed to unstable estimates of disability progression and uncertainty as to the treatment effect on this parameter.

Multiple pre-specified sensitivity analyses for CDP were performed and confirmed there was no increased risk of disability progression (at 3 or 6 months) with ozanimod compared to IFN β-1a. Included in these sensitivity analyses are subjects with longer-term follow-up time to account for the low event rate. For CDP-6M, the missing status frequency was in the 30% range. In order to assess the impact of missing confirmation status, the methodology of Cook and Kosorok (2004) was applied using propensity score models (Cook 2004). This additional sensitivity analysis suggests no statistical or practical differences between ozanimod 1 mg and IFN- β-1a on CDP-6M (Data on file).

It should be noted that treatment with ozanimod significantly reduced normalized total brain volume, cortical and thalamic volume loss, compared with IFN β-1a in the two controlled Phase III clinical studies, and in the pooled analysis. Brain volume loss in MS has been associated with disability progression over time (Jeffrey 2016). Cortical grey matter volume and thalamic volume are believed to be better predictors of cognitive impairment that whole brain MRI measures (Calabrese 2009). Furthermore, ozanimod has demonstrated a statistically significant improvement in the proportion of patients with RRMS with NEDA 4 at 2 years compared with IFN β-1a 30 µg ([redacted] vs [redacted] respectively; [redacted]) (Celgene 2019e). NEDA has been proposed as a surrogate for disease activity-free status (Parks 2017, Steinman 2019).

Although there was no statistically significant difference for ozanimod 1 mg compared with IFN β-1a in the Phase III pivotal trials on confirmed disability progression (CDP-3M and CDP-6M) ozanimod demonstrated statistically significant favourable results versus IFN β-1a in the broad range of traditional (ARR, T2 lesions, and Gd-E lesions) and novel endpoints (BVL, NEDA-3 and NEDA-4).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) and a targeted search of health technology assessments (HTAs) were undertaken to identify economic evaluations in RRMS. Details of the economic evaluation identified in the SLR are reported in Appendix G. No economic evaluations for ozanimod were identified.

The targeted search of HTAs focused on the following RRMS treatments approved by NICE:

- Natalizumab (Tysabri): TA127 (NICE 2007a)
- Fingolimod (Gilenya): TA254 (NICE 2012a)
- Alemtuzumab (Lemtrada): TA312 (NICE 2014b)
- Teriflunomide (Aubagio): TA303 (NICE 2014f)
- Dimethyl Fumarate (Tecfidera): TA320 (NICE 2014c)
- Beta interferons and glatiramer acetate: TA527 (NICE 2018a)
- Cladribine (Mavenclad): TA493 (NICE 2017a)
- Ocrelizumab (Ocrevus): TA533 (NICE 2018d)

The majority of economic models submitted to NICE since 2005 used the same 21-health state structure (except for TA493 where an 11-health state structure was used) based on the assessment group model developed for TA527 (NICE 2018a), a multiple technology appraisal of beta-interferon and glatiramer acetate in RRMS. The model includes the use of a cohort-based Markov state transition structure based on the discrete stages of the EDSS, with separate EDSS states for the relapse-remitting and secondary progressive forms of MS.

The preferred data inputs and modelling assumptions have changed with each successive NICE appraisal, and key issues highlighted from previous appraisals include:

- “Waning” of drug efficacy beyond the follow up of clinical trials
- Use of EQ-5D data from clinical trials versus published observational studies
- Re-initiation of therapy with alemtuzumab
- CDP-3M vs. CDP-6M
- Modelling of the natural history of RRMS, and its associated subgroups
- Consideration of non-medical costs

In TA127(NICE 2007a), concerns were raised over the use of a published survey of people with MS to estimate health state utilities, due to the potential for selection bias and the generalisability of data from a broad MS population, to smaller MS subgroups. The same survey was used in the manufacturer’s base case analyses presented in TA254 (NICE 2012a), TA303 (NICE 2014f), TA312 (NICE 2014b), and TA320 (NICE 2014c). In TA254 (NICE 2012a), the NICE committee concluded that it was more reasonable to use EQ-5D data collected in the manufacturer’s trials, and to use literature estimates for utilities that was not available in trials (e.g. for EDSS 6.0 or greater). In all subsequent STAs (TA303 (NICE 2014f), TA312 (NICE 2014b), and TA320 (NICE 2014c)), the manufacturer’s base case analyses used utilities derived from clinical trials supplemented by literature estimates.

In TA254 (NICE 2012a), the NICE committee was concerned about the assumption in the manufacturer's model that the treatment effect observed in the 1 to 2-year clinical trials would be maintained at the same level during periods of treatment. The model was sensitive to variation in this assumption and so the NICE committee adopted a cautious approach by assuming a reduced efficacy of 50% after a 5-year period. In TA303 (NICE 2014f), it was assumed that treatment effect reduced to 75% at year 2 and 50% at year 5, and similar assumptions were applied in TA320 (NICE 2014c) and TA312 (NICE 2014b).

In TA312 (NICE 2014b), the NICE committee discussed the potential for re-initiation of alemtuzumab, the first therapy in MS with a recommended dosing in years 1 and 2, followed by observation for disease progression. Clinical specialists consulted for TA312 (NICE 2014b) had highlighted that re-initiation with alemtuzumab after the initial two courses was likely in UK practice, and that this trend was likely time-dependent, with rates declining for each successive cycle. Therefore, the costs of re-initiation were considered in the analysis used to inform the final appraisal determination for TA312 (NICE 2014b).

In TA320 (NICE 2014c), the NICE committee concluded that CDP-6M provided a more robust indication of treatment effect than CDP-3M, as this endpoint may be influenced by relapses. This is in line with guidance issued by the EMA that states that an accurate and reliable definition of confirmed progression should include two sequential examinations at least 6 months apart. Yet, all previous appraisals had used the 3-month endpoint in the model base case analysis, and in TA533, the ERG preferred the mixed treatment network to jointly model the outcomes for CDP-3M and CDP-6M.

In TA254 (NICE 2012a), the NICE committee noted the concerns of clinical specialists that the manufacturer's model did not allow for improvement in EDSS and used data from the London Ontario registry which contained EDSS measures collected in the 1970s and 1980s. It was argued that the model may not reflect the natural history of MS in current UK practice given the use of historical data and because all improvements in EDSS were censored in the original analysis. The implications of using London Ontario data for the natural history model were highlighted in TA312 (NICE 2014b), where the NICE committee raised concerns that the manufacturer model yielded an implausibly low QALY (~4 QALYs) relative to life years (18 years) for a population with MS treated with DMT. The review group concluded that this was probably linked to the use of the London Ontario data and its associated faster rate of progression.

In TA320 (NICE 2014c), the inherent limitations of the London Ontario data were partially addressed by the use of transition probability matrices derived from the placebo arms of clinical trials in place of the London Ontario data for lower EDSS states. These matrices allowed for improvements in EDSS at the rates observed in the clinical studies. For higher EDSS states, London Ontario data were used in the absence of a suitable alternative. In ID809 (NICE 2017c) and TA441 (NICE 2017b), London Ontario data were replaced completely by matrices derived from the British Columbia (BC) registry and published by Palace et al (Palace 2014). In both appraisals, it was concluded that the BC dataset provided a more appropriate set of transitions for the natural history of RRMS than London Ontario and was hence the preferred source of natural history data.

In TA533 (NICE 2018d), concerns were raised regarding the use of the MSBase registry as the registry was not restricted to people with MRI scans showing inflammation and the data were largely from Eastern Europe. Nonetheless, the MSBase registry was considered appropriate to inform baseline transitions between EDSS states supplemented with data from the British Columbia MS database. Additionally, the company was unable to provide the committee with evidence of an association between the presence of antibodies and treatment efficacy, and it was therefore concluded that the treatment effect of ocrelizumab was likely to wane in the long-term.

In TA493 (NICE 2017a), an issue was raised relating to patients with RES-RRMS and SOT-RRMS being likely to progress faster than the population reflected within the registries, that had been used for the submission. The NICE committee's preferred assumption was that the acceleration factor is reliant on the assumption of proportional hazards between RES-RRMS and non-RES-RRMS and SOT-RRMS and non-SOT-RRMS.

It is also important to note that the benefits gained from an oral drug may not be fully captured in the QALY estimates. The NICE committees in TA303 (NICE 2014f) and TA320 (NICE 2014c) acknowledged that the modelled analyses did not capture the potential health benefits of taking an oral drug instead of an injectable or infusion therapy because of the need to assume the same utilities across different formulations. It was therefore recognized that oral drugs provide quality of life benefits other than those captured in the QALY calculations.

B.3.2 Economic analysis

A *de novo* economic analysis was performed to assess the incremental cost effectiveness of ozanimod versus relevant alternative treatments within its expected marketing authorisation for active RRMS. A *de novo* analysis was required because of the absence of published cost effectiveness studies for ozanimod.

The *de novo* cost-effectiveness analysis was performed using a cohort-based Markov state transition model to evaluate ozanimod as treatment for patients with active RRMS.

B.3.2.1 Patient population

The baseline patient characteristics used in the economic model were derived from the pivotal Phase III clinical trials (RADIANCE Part B and SUNBEAM) (Table 35). The mean age of the population, proportion of females, distribution of weight and the baseline EDSS distribution are based on a pooled analysis of the SUNBEAM and RADIANCE Part B clinical trials (see section B.2 Clinical effectiveness).

Table 35. Patient characteristics for the RRMS population

Parameter	Base case
Age, mean (years)	36
Proportion female (%)	66.8%
EDSS distribution, %	
EDSS 0	2.3%
EDSS 1	26.9%
EDSS 2	29.6%
EDSS 3	24.0%
EDSS 4	12.6%
EDSS 5	4.7%
EDSS 6	0%
EDSS 7	0.0%
EDSS 8	0.0%
EDSS 9	0.0%

Source: (Celgene 2017a, Celgene 2017b)
EDSS: Expanded Disability Status Scale

B.3.2.2 Model structure

A cohort-based Markov state transition model was developed in Microsoft Excel® 2010 to evaluate ozanimod as a treatment for patients with RRMS using the NHS and PSS perspective. The model evaluates the discounted costs (3.5%) and discounted health outcomes (3.5%) over a lifetime model horizon (50 years) using annual cycles and applying half-cycle correction.

The cost-effectiveness model uses a cohort-based Markov approach to track patients as they progress through health states defined around the Kurtzke EDSS (Kurtzke 1983); this scale ranges from EDSS 0 (normal neurological examination) to EDSS 10 (MS-related death) (see Table 36). Defining health states by EDSS is appropriate because higher EDSS scores have been shown to correlate with increasing levels of health and socio-economic burden (e.g. productivity), and decreasing levels of quality of life in people with MS (Gani 2008, Gold 2010, Kappos 2010, Ahlgren 2012). Furthermore, the EDSS is the recommended tool by the EMA for measuring disability progression and is the preferred measure of disability progression in the majority of MS clinical trials conducted to date, allowing for indirect comparisons of DMT effects on disability progression. EDSS scores are rounded up when distributed into the model health states, so that a score of 1.5-2 is considered to fall within the EDSS 2 health state, for example. The disability progressions from EDSS 0 through to EDSS 9 are estimated using transition matrices, whilst EDSS 10 is implied through a death state.

Table 36. Kurtzke EDSS (Kurtzke 1983)

Score	Description	EDSS health state
0	Normal neurological exam	0
1.0	No disability, minimal signs in one FS	1
1.5	No disability, minimal signs in more than one FS	2
2.0	Minimal disability in one FS	
2.5	Mild disability in one FS or minimal disability in two FS	3
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking	
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking	4
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m	
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m	5
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m	
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m	6
6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting	
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting	7

Score	Description	EDSS health state
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day	
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair	8
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms	
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions	9
9.0	Confined to bed. Can still communicate and eat	
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow	
10.0	Death due to MS	10

Source: (Kurtzke 1983)

EDSS: Expanded Disability Status Scale; FS: Functional system; MS: Multiple sclerosis

The model also accounts for the frequency and severity of relapses, adverse events, and discontinuation from treatment. Patients can experience relapses within each EDSS state, but relapses do not impact the rate of disability progression. In other words, although the occurrence of relapse does not influence disease progression, relapses are dependent on the EDSS score. The assumption that relapses have no impact on disability progression has been made in previous models ((NICE 2014b), (NICE 2014c), (NICE 2012a), (NICE 2007a), (NICE 2014f)).

Patients can discontinue or stop treatment based on pre-defined rules (see Section B.3.3.6). During discontinuation, patients switch to BSC where no treatment effect is maintained, and patients may experience a higher rate of disability progression.

Treatment sequencing has not been included in this analysis as no clinical data were available to populate the model. Furthermore, a patient's treatment sequence would be a result of complex treatment decision-making that would be difficult to accurately replicate in an economic model. In all previous NICE appraisals treatment sequencing has not been included. This is mainly due to the vast complexity it brings to the development of the economic model along with the number of assumptions that must be made regarding the model inputs in subsequent lines, such as treatment effects. The choice of subsequent DMT may vary considerably from person to person because of personal preferences towards administration method and/or the reasons for discontinuing treatment (e.g. adverse event versus lack of efficacy). The mix of subsequent therapies given after discontinuation would therefore be complex and vary by initial DMT. This additional step would require also available evidence, however, there is a lack of data on the efficacy and safety of sequential treatments in MS.

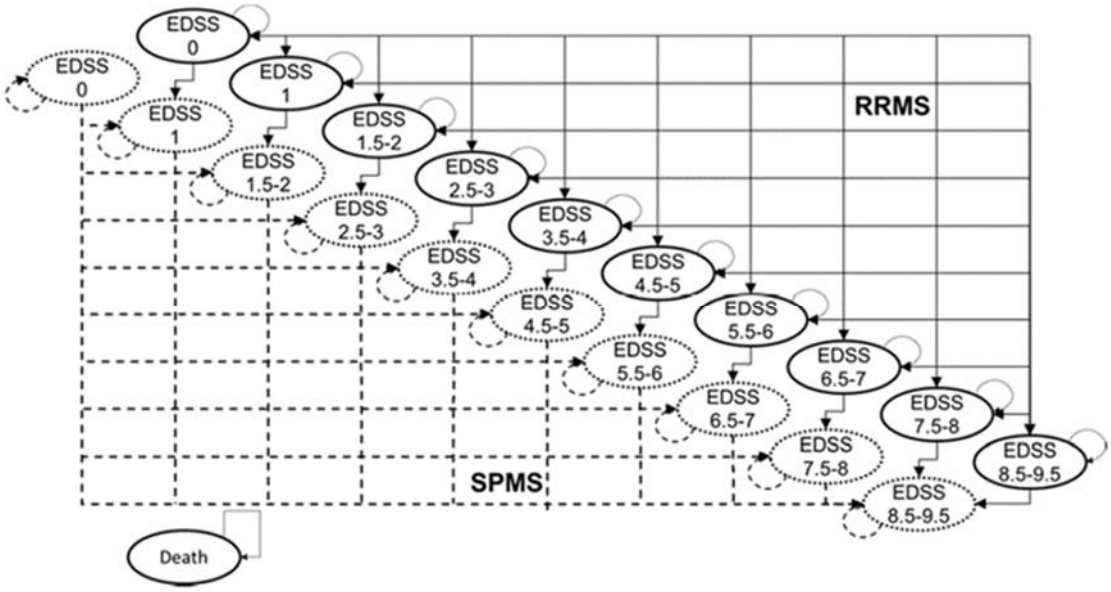
B.3.2.2.1 21-state model

The 21-state model structure has been applied in several health technology appraisal (HTA) submissions and is based on a previously published ScHARR model (Tappenden 2001). The 21-state model is a cohort-based Markov state transition model including 10 EDSS states in RRMS and 10 EDSS states in SPMS, and a single state for death. Progression and conversion to SPMS are assumed irreversible – i.e. patients can progress from the RRMS health states

to the SPMS health states but cannot move from the SPMS health states back to the RRMS states.

The structure of the 21-state model is illustrated in Figure 8. Note that the schematic does not illustrate the on-treatment and off-treatment EDSS states separately. This means that if accounting for RRMS on-treatment, RRMS off-treatment, SPMS on-treatment, and SPMS off-treatment, the 21-state model technically consists of 41 mutually exclusive states.

Figure 8. Schematic of patient flow in the cost-effectiveness model across EDSS states, 21-state model



Source: (NICE 2017d)

EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

Note that the figure does not illustrate the on-treatment and off-treatments EDSS states separately.

Note that EDSS are rounded, e.g. EDSS 4.5-5 is equivalent to EDSS 5.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention and comparators

The economic analysis presented in this submission focuses on the use of ozanimod in people with active RRMS. Celgene expects ozanimod to be used in UK clinical practice as a treatment option in patient with active RRMS. Therefore, the most relevant comparators for ozanimod are interferon beta-1a (INFβ-1a), interferon beta-1b (INFβ-1b), glatiramer acetate (GA), dimethyl fumarate and teriflunomide; i.e. treatments for active RRMS, according to the NICE scope. Ozanimod is expected to be used as a treatment for active RRMS, and Celgene does not envisage it as a treatment for the HA/RES or SOT sub-populations. However, given the breadth of treatments available in the UK, Celgene have also provided analyses versus all other treatments licenced for the treatment of RRMS in Appendix L.

The final NICE scope for this appraisal lists the following comparators in the active RRMS group:

- Alemtuzumab
- Beta-interferon

- Dimethyl fumarate
- Glatiramer acetate
- Teriflunomide
- Ocrelizumab
- Peginterferon beta-1a (subject to ongoing NICE appraisal)

The EMAs pharmacovigilance risk assessment committee started a review of alemtuzumab in April 2019, which is ongoing. The committee have advised that during the review, alemtuzumab should only be started in adults with RRMS that is highly active despite treatment with at least 2 disease-modifying therapies, or when other disease-modifying therapies cannot be used. Thus alemtuzumab, alongside ocrelizumab which is recommended for use after alemtuzumab, is not considered a relevant comparator for ozanimod. The final list of comparators is as follows:

- Beta-interferon
- Dimethyl fumarate
- Glatiramer acetate
- Teriflunomide
- Peginterferon beta-1a (subject to ongoing NICE appraisal)

The cost-effectiveness model is developed to accommodate for multiple simultaneous comparisons, which enables incremental analysis and cost-efficiency frontiers. In the base-case analysis only the relevant comparators are included. Data on all other treatments used in RRMS is provided in Appendix L.

B.3.3 Clinical parameters and variables

B.3.3.1 Natural history reference model

The model includes a natural history or best supportive care (BSC) reference arm. The natural history arm is used to estimate the long-term disability progressions and overall survival of RRMS patients, which is not possible when using clinical trial data with short follow-up (e.g. 2 years).

This approach also provides one common reference arm that allows for indirect treatment comparison of several treatment alternatives in RRMS. The natural history arm uses estimates from the British Columbia Multiple Sclerosis registry (BCMS).

The BCMS registry is a population-based database established in the 1980s capturing about 80% of people with MS in British Columbia, Canada (Palace et al. 2014). Patients that progressed from RRMS to SPMS were not censored but from 1996 onwards all patients were censored as a result of the widespread use of DMTs. Data were prospectively collected with long-term follow up (>25,000 cumulative years).

EDSS transition matrices were derived for the natural history disability progression of patients, split by median age of disease onset (<28 years, ≥28 years). The transition matrices, as presented in the study by Palace et al., were derived using a multi-state modelling method by Jackson et al. (Jackson et al. 2003) and included EDSS state 0–10 where only states 7–9 could progress to 10. Since the current model already accounts for death through background mortality and MS-related standardized mortality ratios (SMRs), EDSS 10 was excluded from this matrix when used in the model. This was further emphasized by the recent update to the

interferon beta and glatiramer acetate review appraisal where it was concluded that mortality was likely to be double-counted otherwise (NICE 2017c).

Patients included in the BCMS contained RRMS patients (84.3%) as well as SPMS patients (15.7%). One advantage of using the BCMS registry is that patients were not censored when they improved in EDSS or transitioned to SPMS stages. As the clinical trials were both active-controlled studies against Interferon beta-1a 30 µg, there is no trial evidence from a placebo arm available to supplement the BCMS registry to implement any adjustment to the current transition matrices.

The annual transition probabilities for patients ≥28 years are shown in Table 37.

Table 37. Annual transition probabilities from BCMS (MS age of onset ≥28 years)

All		To EDSS (year x + 1)										
		0	1	2	3	4	5	6	7	8	9	10
From EDSS (year x)	0	0.695	0.203	0.073	0.022	0.004	0.001	0.002	0.000	0.000	0.000	Not applicable
	1	0.058	0.695	0.158	0.061	0.016	0.005	0.006	0.000	0.000	0.000	
	2	0.016	0.121	0.608	0.168	0.045	0.018	0.022	0.002	0.001	0.000	
	3	0.006	0.050	0.120	0.544	0.091	0.058	0.117	0.010	0.004	0.000	
	4	0.002	0.022	0.067	0.115	0.489	0.104	0.168	0.026	0.007	0.001	
	5	0.001	0.005	0.029	0.059	0.087	0.487	0.273	0.039	0.019	0.001	
	6	0.000	0.001	0.004	0.025	0.031	0.041	0.741	0.109	0.044	0.004	
	7	0.000	0.000	0.001	0.002	0.007	0.004	0.117	0.693	0.161	0.016	
	8	0.000	0.000	0.000	0.000	0.001	0.001	0.019	0.056	0.903	0.021	
	9	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.006	0.174	0.818	
	10	Not applicable										

Source: (Palace 2014)

BCMS: British Columbia Multiple Sclerosis; EDSS: Expanded Disability Status Scale; MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis

Patients transition from RRMS to SPMS according to EDSS-transition probabilities used in previous cost-effectiveness models submitted to NICE and also recently used by ICER in the US (Table 38) (NICE 2007a, NICE 2014c, Mauskopf 2016).

Table 38. RRMS to SPMS conversion probabilities

EDSS	Probability of conversion (%)
0	0.0%
1	0.3%
2	3.2%
3	11.7%
4	21.0%
5	29.9%
6	23.7%
7	25.4%
8	15.3%
9	100.0%

Source: (NICE 2007a, NICE 2014c, Mauskopf 2016)

EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

B.3.3.2 Treatment adjusted model

The treatment-adjusted model was created by combining the natural history reference model with the comparative efficacy and safety of each DMT versus placebo. Treatment effects were applied to disability progression, ARR and the incidence of drug-related adverse events. The effects of treatment as well as discontinuation rates are modelled based on the results of the NMA by Celgene (see section B.2.8)

A treatment-specific HR is applied to disability progression in the reference arm and can either increase or decrease the rate of progression through the EDSS states. Due to lack of data and for simplicity reasons, the same constant HR is applied to all EDSS states. More recent MS appraisals have included a waning effect that decreases the effect size over time, as the long-term effects are unknown. In order to account for the waning effect separate transition matrices are required for each case where a different HR is applied to the reference arm.

B.3.3.3 Relapses by EDSS state

The rate corresponding to each EDSS state is applied to the number of patients occupying that state in each model cycle. A limitation of this method is that it may lead to double counting of DMT effect when the drug is assumed to act independently on EDSS and relapse rate.

The model is currently populated with ARR data from Patzold and Pocklington (Patzold 1982) (Table 39). The Patzold and Pocklington data source was chosen because it provides mid-range estimates for relapse rates of people without DMT therapies.

Table 39. ARR from Patzold and Pocklington et al, 1982

EDSS state	RRMS	SPMS
0	0.71	0.00
1	0.73	0.00
2	0.68	0.47
3	0.72	0.88
4	0.71	0.55
5	0.59	0.52
6	0.49	0.45
7	0.51	0.34
8	0.51	0.34
9	0.51	0.34

Source: (Patzold 1982)

ARR: Annualized relapse rate; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

B.3.3.4 Mortality

Background mortality rates are based on age-specific UK life tables for males and females and weighted by the gender distribution used in the model (Office for National Statistics 2018). Then an EDSS-specific mortality multiplier is applied to adjust the mortality for MS patients, using data from a prospective survey of MS people in Denmark reported in Pokorski et al. and re-analysed in Sadovnick et al. (Sadovnick 1992, Pokorski 1997). Sadovnick et al. developed

a quadrant equation for predicting SMRs conditional on EDSS state, where x is the EDSS level:

$$y = 0.0219x^3 - 0.1972x^2 + 0.6069x + 1$$

The predicted SMRs generated by this equation have been used in previous NICE appraisals TA254 for fingolimod (NICE 2012a), TA303 for teriflunomide (NICE 2014f), TA312 for alemtuzumab (NICE 2014b), and TA320 for dimethyl fumarate (NICE 2014c). A summary of the SMRs is shown in Table 40.

Table 40. SMRs by EDSS state (applies to all populations - RRMS and SPMS)

EDSS state	Mortality multiplier
0	1.000
1	1.432
2	1.600
3	1.637
4	1.674
5	1.842
6	2.273
7	3.097
8	4.447
9	6.454

Source: (Sadovnick 1992, Pokorski 1997)

EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SMR: Standardized mortality ratio; SPMS: Secondary progressive multiple sclerosis

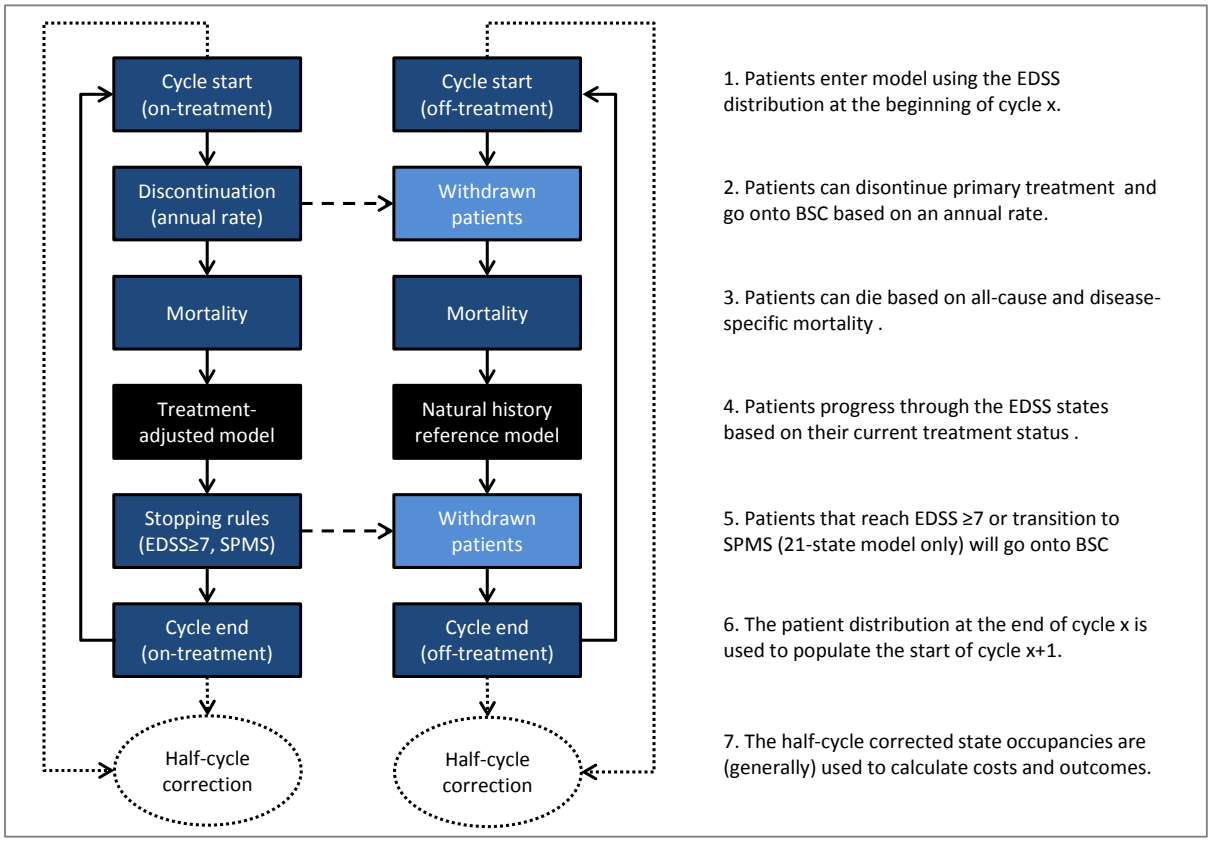
B.3.3.5 Order of transitions and half-cycle correction

The order of the model health state transitions and the calculation process for patients in the model follow common practice in MS and are illustrated in Figure 9.

The half-cycle corrected EDSS state occupancy is calculated for the on-treatment and off-treatment states separately as: (start-of-cycle x + end-of-cycle x)/2 and will therefore represent the mid-cycle estimate. This estimate is less likely to underestimate or overestimate costs and health benefits compared with using the start-of-cycle or end-of-cycle estimates.

The half-cycle corrected health state occupancy is used to calculate all disease-related costs and health benefits, such as EDSS and relapse costs and health state utilities.

Figure 9. Transition flow and calculation process for patients on primary treatment in the model



BSC: Best supportive care; EDSS: Expanded Disability Status Scale; SPMS: secondary progressive multiple sclerosis

B.3.3.6 Treatment stopping rules and withdrawal

The model considers three possible rules for patients to stop treatment (Table 41). Once patients stop primary treatment, they are assumed to be treated with BSC and remain on BSC until death, irrespective of primary treatment and current disease state. Once patients are treated with BSC they move through the EDSS and experience relapses using the natural history reference model. Patients on BSC experience no maintenance of treatment effect and may experience a higher rate of disability progression. To accommodate for this, all the EDSS states in the model engine were duplicated to include both off-treatment EDSS states and on-treatment EDSS states:

- Off-treatment (BSC) transitions are based on a natural history reference model
- On-treatment transitions are based on the treatment-adjusted models

A fourth, obvious, stopping rule not included in the table occurs when patients die. Death is an all-absorbing state; from that point onwards, patients incur £0 costs and 0.0 utilities.

Table 41. Treatment stopping rules and withdrawal

Stopping rule	Comment
Conversion to SPMS	• The ABN clinical guideline and the NHS England Commissioning Policy for disease modifying therapies in MS states that treatment should be stopped if patients have confirmed SPMS • The model base case follows this recommendation and patients discontinue primary treatment when transitioning to SPMS • From this point onwards all patients would progress through the model and experience costs and events based on the natural history reference model
EDSS ≥7	• The ABN clinical guideline and the NHS England Commissioning Policy for disease modifying therapies in MS states that treatment should be stopped if patients are unable to walk, which seems to coincide with a disability score of EDSS 7 (patients restricted to wheelchair) • The model base case follows this recommendation and patients discontinue primary treatment when reaching EDSS 7 • After reaching EDSS ≥7, patients stop the primary treatment and move onto BSC but can remain in RRMS based on the natural history reference model
Treatment discontinuations	Patients can discontinue treatment due to lack of efficacy or tolerability. This is applied through an annual discontinuation rate.

Source: (Scolding 2015, NHS England; 2019)

ABD: Association of British Neurologists; BSC: Best supportive care; EDSS: Expanded Disability Status Scale; MS: Multiple sclerosis; NHS: National Health Service; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

The treatment discontinuation rates used in the model are all-cause and therefore include withdrawals due to adverse events. Adverse events are applied irrespectively of the treatment stopping rules in the model.

B.3.3.7 Data input and sources

This section contains a summary of the data inputs and sources used to model the effect of DMTs on disability progression, relapses, and adverse events. The main source of data is from the NMA; see Section B.2.8 for further details on the NMA. Both random and fixed effects models were evaluated and the best fitting model, based on the deviance information criterion (DIC), was selected for each endpoint.

B.3.3.7.1 Treatment adjusted model – disability progression

The effect of DMT on disability progression is modelled using data on the time to CDP. The model includes options to evaluate outcomes based on disability progression that is confirmed at two or more consecutive visits separated by either 3 or 6 months.

The preferred option is the 6-month definition of progression (CDP-6M), which is considered the most appropriate measure of effect in clinical trials by the EMA (European Medicines Agency 2012). Previously, the 3-month definition (CDP-3M) was the recommended endpoint, and hence older studies had reported 3-month progression data only, which restricts the scope of analyses that can be conducted. Due to the lack of data available at CDP-6M for older comparators a combined analysis was performed where CDP-3M and CDP-6M were analysed in a single model by assuming that the HR of CDP-6M between treatments arms is proportional to the HR of CDP-3M. In this way estimates of CDP-6M relative efficacy can be

generated for treatments with no reported CDP-6M. In the base case analysis data for the combined CDP-6M from the NMA were used which is in line with recent submissions and the ICER model (ICER 2017, NICE 2017a, NICE 2018d). CDP-3M data are used in a scenario analysis (see Section B.3.8.3.2 Scenario analysis). Based on the DIC, the best fitting model was the fixed effects model for CDP-6M combined and for CPD-3M.

As highlighted in the clinical section of this submission (section B.2.6) the number of disability progression events in the pooled ozanimod Phase III trials (RADIANCE Part B and SUNBEAM) was low and the data on patients with both a CDP-3M and CDP-6M exhibited high variability and wide statistical range, with no evidence of statistical difference between the two treatment groups (Celgene 2019c). Given that ozanimod has demonstrated statistically significant favourable results versus IFN β-1a in the broad range of traditional (ARR, T2 lesions, and Gd-E lesions) and novel endpoints (BVL, NEDA-3 and NEDA-4) it would appear implausible that IFN β-1a could lead to a lower rate of disability progression compared to ozanimod 1 mg (especially considering that BVL and NEDA 4 have both been associated with a reduction in disability progression over time). Therefore, in the base case, the HR for ozanimod was set equal to interferon beta-1a 30 µg.

Table 42. HR of treatment effects on 3-month and 6-month disability progression

Treatment	CDP-6M-combined (base case) *	CDP-6M-combined, NMA result	CDP-3M
Ozanimod	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg**	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 20 mg	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 40 mg	[redacted]	[redacted]	[redacted]

Source: (Pharmerit International 2018b) Note: [redacted] **(Pharmerit International 2018b)

CDP: Confirmed disability progression; CDP3M: Confirmed disability progression at 3 months; CDP6M: Confirmed disability progression at 6 months; HR: Hazard ratio;

B.3.3.7.1.1 Hazard ratio

The effect of treatment is measured in terms of the HR, which is defined as:

$$Hazard\ Ratio\ (HR) = \frac{Treatment\ hazard\ rate}{Placebo\ hazard\ rate}$$

The HRs of each DMT versus placebo were used to adjust transition rates in the reference model using the method adopted by the ERG in the fingolimod NICE submission (NICE 2012a). This is described in the following steps:

1. For each EDSS state, calculate the combined risk of disability progression (sum of all future EDSS progression states)

2. Convert the combined risk of disability progression for each EDSS state to an annual rate using formula: 'annual rate = -LN(1 - CDP)'
3. Apply the HR (treatment versus placebo) multiplicatively to the combined rate of disability progression (in step two) as: 'treatment-adjusted rate = annual rate * HR'
4. Convert the resulting treatment-adjusted rate back to an annual probability of disability progression using the formula: 'treatment-adjusted disability progression=1–EXP(–treatment-adjusted rate)'
5. Proportionally redistribute the combined probability of disability progression for patients on treatment (in step 4) amongst the future EDSS progression states using the distribution of probabilities from the original natural history reference model
6. Rescale the probability of remaining in the same state to ensure that the sum of probabilities in each row of the matrix is equal to one (i.e. 1–sum of all regression and progressions)

B.3.3.7.1.2 Waning of treatment effect

The model has an option to apply a treatment waning effect to disability progression, which can explore uncertainty in the long-term benefits of drug therapy. In the base case, effectiveness of all treatments is set 100% for the first 2 years of treatment and then decreases over time from year 3 onwards. This is a conservative assumption and it is consistent with previous NICE appraisals (NICE 2017a, 2018).

The waning effect is applied by adjusting the proportional reduction in drug effect via the following equation:

$$\mathrm{HR_w} = (1 - (1 - \mathrm{HR_{NW}}) \times \mathrm{W})$$

where *HRw* is the drug effect adjusted for waning, *HRnw* is the drug effect without adjustment, and W is the proportional waning effect.

The periods over which drug effect were allowed to wane comprise years 0 to 2, 3, 4, 5, 6 to 9, and 10 and beyond (see Table 43). If a treatment's hazard ratio on disability progression is >1, no treatment waning effect is applied, regardless of the waning inputs. The results with no waning of treatment effect are included in a scenario analysis (see Section B.3.8 Sensitivity analyses).

Table 43. Waning of treatment effect over time

Treatment	Y0 – Y2	Y3	Y4	Y5	Y6 – Y9	Y10+
Ozanimod	100%	75%	75%	75%	50%	50%
Interferon beta-1a 30µg	100%	75%	75%	75%	50%	50%
Interferon beta-1a 22µg	100%	75%	75%	75%	50%	50%
Interferon beta-1a 44µg	100%	75%	75%	75%	50%	50%
Glatiramer acetate, 20 mg	100%	75%	75%	75%	50%	50%
Teriflunomide	100%	75%	75%	75%	50%	50%
Dimethyl fumarate	100%	75%	75%	75%	50%	50%
Interferon beta-1b 250µg	100%	75%	75%	75%	50%	50%
Peg-Interferon beta-1a 125µg	100%	75%	75%	75%	50%	50%
Glatiramer acetate, 40 mg	100%	75%	75%	75%	50%	50%

Source: (NICE 2017a, NICE 2018d)
Y: Year

B.3.3.7.2 Treatment adjusted model – relapse events

A rate ratio for each DMT was applied to the natural history EDSS-specific ARRs, based on the NMA (section B.2.8). The fixed effects model resulted in the best fit based on the DIC criteria.

Table 44. Rate ratios for relapse rates

Treatment	Rate ratio
Ozanimod	0.48
Interferon beta-1a 30µg	0.84
Interferon beta-1a 44µg	0.66
Glatiramer acetate 20 mg	0.66
Teriflunomide 14 mg	0.67
Dimethyl fumarate 240 mg	0.54
Interferon beta-1b 250 µg	0.66
Peg-Interferon beta-1a 125µg	0.64
Glatiramer acetate 40mg	0.66

Source: (Celgene 2019f)

B.3.3.7.3 Treatment adjusted model – adverse events

Treatment-related adverse events are applied as rates to calculate costs and disutilities; the rates are applied as one-off events at the start of the simulation with the exception of injection-site reactions which are applied continuously while on treatment.

Adverse event data were sourced from 45 studies identified by the NMA (section B.2.8). The incidence rates were obtained by combining raw data related to specific adverse events of interest reported for each comparator (Pharmerit International 2018a). Table 45 presents the adverse event incidence rates for each DMT.

Table 45. Incidence of adverse events by treatment (%)

	Ozanimod	Interferon beta-1a 30µg	Interferon beta-1a 22 µg/44µg	Glatiramer acetate 20mg	Terifluno mide 14 mg	Dimethyl fumarate 240 mg(bid)	Interferon beta-1b 250µg	Peg-Interferon beta-1a 125µg	Glatiramer acetate 40mg
Injection-site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Ozanimod	Interferon beta-1a 30µg	Interferon beta-1a 22 µg/44µg	Glatiramer acetate 20mg	Terifluno mide 14 mg	Dimethyl fumarate 240 mg(bid)	Interferon beta-1b 250µg	Peg-Interferon beta-1a 125µg	Glatiramer acetate 40mg
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: (Pharmerit International 2018a)

* Adverse event rates for interferon beta-1a 22µg were set equal to interferon beta-1a 44µg due to absence of data

ALT: Alanine aminotransferase test

B.3.3.7.3.1 Treatment discontinuations

The probability of treatment discontinuation (independent of EDSS progression) is modelled based on constant transition probabilities that are applied annually from Year 1 to 9, and then the same rate is applied for years 10+. This is on the basis that withdrawal of therapy is likely to vary over time with the influence of adverse events, compliance, and patient preference. Discontinuation probabilities are expected to be highest in the first few years as the incidence of treatment-limiting adverse events are expected to peak during this period. Later, it is assumed that the probability of discontinuation will decline as patients who are persistent on treatment are likely to comprise those who tolerate therapy. Patients that discontinue treatment are assumed to retain treatment effect up to the point of discontinuation when they switch to the natural history (BSC) model.

Annual discontinuation rates (not differentiated by years on treatment) were sourced from the NMA (section B.2.8), using the random effects model which had lower DIC. The NMA outputs included the median HR versus placebo or versus ozanimod for each treatment. Using the HRs relative to placebo, and ozanimod as a reference treatment, the following process was used to generate the discontinuation rates for each intervention included:

1. Calculate the annual natural logarithm of the hazard for ozanimod, which is the anchor for the calculations, using raw trial data (29 of 447 patients discontinued ozanimod over 2 years (Celgene International 2017):

$$Anchor_{oza} = -Log(1 - x) / t$$, where t=2 and x is 29/447

2. Based on NMA data, calculate the natural logarithm of the hazard ratio relative to placebo for all treatments
3. Calculate the natural logarithm of the hazard ratio ozanimod relative to each treatment by subtracting the annual hazard of ozanimod relative to placebo from each treatment's annual hazard relative to placebo:

$$Log(HR_{DMT,oza}) = Log(HR_{DMT,PBO}) - Log(HR_{oza,PBO})$$

1. By taking the exponential of the sum of the anchor and the hazard rate relative to ozanimod, the discontinuation rates for each DMT can be calculated and input in the model:

$$Discontinuation\ rate_{DMT} = EXP(Log(HR_{DMT,oza}) + Anchor_{oza})$$

Discontinuation rates are provided in Table 46.

Table 46. Annual discontinuation rates by treatment

Treatment	Discontinuation rates
Ozanimod	[redacted]
Interferon beta-1a 30µg	[redacted]
Interferon beta-1a 22µg	[redacted]
Interferon beta-1a 44µg	[redacted]
Glatiramer acetate, 20 mg	[redacted]
Teriflunomide	[redacted]
Dimethyl fumarate	[redacted]

Treatment	Discontinuation rates
Interferon beta-1b 250µg	[redacted]
Peg-Interferon beta-1a 125µg	[redacted]
Glatiramer acetate 40mg	[redacted]

Source: (Pharmerit International 2018b)

The model also allows for an option where patients discontinue treatment when they reach SPMS or when they reach a specific EDSS level. In the base case, in line with previous NICE submissions, both of these discontinuation rules are applied.

B.3.3.7.3.2 Mortality

No treatment effect is applied to mortality due to limited evidence to support long-term effect of DMT on mortality rates. However, using EDSS-dependent SMRs assumes an indirect effect on mortality.

B.3.4 Measurement and valuation of health effects

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

EQ-5D data were not collected within the ozanimod clinical trials (RADIANCE Part B and SUNBEAM). In line with appraisals of other multiple sclerosis treatments in the UK, a systematic literature review was undertaken to identify potential health state utility values for the individual EDSS health states from a UK perspective. Details of the SLR are provided in Appendix H.

B.3.4.2 Mapping

Mapping analyses were not performed as EQ-5D data were available in the literature for the individual EDSS health states.

B.3.4.3 Adverse reactions

The systematic review did not identify studies reporting the health state utilities for treatment-related adverse events in patients with MS.

Ad-hoc searches were conducted in order to identify any relevant data from previous appraisals for RRMS. The duration and disutilities of adverse events are presented in

	Standard events			
	Disutility	Average duration, days	Annual disutility	Source
Injection-site reaction	-0.01	13	-0.004	Cladribine NICE submission (TA493)
ALT increased	0			Assumption
Arthralgia	-0.25	93.1%: 10.5 6.9%: 24.5	-0.008	Ocrelizumab NICE submission (TA533)

Back pain	93.1%: -0.25 6.9%: -0.5	93.1%: 10.5 6.9%: 24.5	-0.009	Ocrelizumab NICE submission (TA533)
Bronchitis	-0.01	14	-0.0004	Ocrelizumab NICE submission (TA533)
Cough	0			Assumption
Depression	93.1%: -0.165 6.9%: -0.56	93.1%: 75 6.9%: 365.25	-0.07	Ocrelizumab NICE submission (TA533)
Dizziness	0			Assumption
Fatigue	0			Assumption
Headache	93.1%: -0.14 6.9%: -0.493	93.1%: 10.5 6.9%: 24.3	-0.006	Ocrelizumab NICE submission (TA533)
Hypoaesthesia	0			Assumption
Influenza	0			Assumption
Influenza-like illness	-0.08	1	-0.0002	Ocrelizumab NICE submission (TA533)
Nasopharyngitis	0			Ocrelizumab NICE submission (TA533)
Oral herpes			-0.046	Alemtuzumab NICE submission (TA312)
Oropharyngeal pain	0			Assumption
Pain in extremity	0			Assumption
Pharyngitis	0			Assumed the same as nasopharyngitis
Pyrexia	0			Assumption
Rash	0			Assumption
Upper respiratory tract infection	-0.2	93.1%: 7 6.9%: 14	-0.004	Ocrelizumab NICE submission (TA533)
Urinary tract infection	-0.1	5	-0.001	Ocrelizumab NICE submission (TA533)

, along with the calculated annual disutility per event.

Treatment-related adverse events led to QALY losses ranging from -0.0002 for influenza-life illness to -0.07 for depression on an annual basis. Events such as back pain (-0.009) had large impacts on total QALYs, however these persisted for shorter periods of time (e.g. less than 10.5 days) and therefore potentially had a reduced impact on QALYs on an annual basis.

Table 47. Disutilities of adverse events

	Standard events			
	Disutility	Average duration, days	Annual disutility	Source
Injection-site reaction	-0.01	13	-0.004	Cladribine NICE submission (TA493)
ALT increased	0			Assumption
Arthralgia	-0.25	93.1%: 10.5 6.9%: 24.5	-0.008	Ocrelizumab NICE submission (TA533)
Back pain	93.1%: -0.25 6.9%: -0.5	93.1%: 10.5 6.9%: 24.5	-0.009	Ocrelizumab NICE submission (TA533)
Bronchitis	-0.01	14	-0.0004	Ocrelizumab NICE submission (TA533)
Cough	0			Assumption
Depression	93.1%: -0.165 6.9%: -0.56	93.1%: 75 6.9%: 365.25	-0.07	Ocrelizumab NICE submission (TA533)
Dizziness	0			Assumption
Fatigue	0			Assumption
Headache	93.1%: -0.14 6.9%: -0.493	93.1%: 10.5 6.9%: 24.3	-0.006	Ocrelizumab NICE submission (TA533)
Hypoaesthesia	0			Assumption
Influenza	0			Assumption
Influenza-like illness	-0.08	1	-0.0002	Ocrelizumab NICE submission (TA533)
Nasopharyngitis	0			Ocrelizumab NICE submission (TA533)
Oral herpes			-0.046	Alemtuzumab NICE submission (TA312)
Oropharyngeal pain	0			Assumption
Pain in extremity	0			Assumption
Pharyngitis	0			Assumed the same as nasopharyngitis
Pyrexia	0			Assumption
Rash	0			Assumption
Upper respiratory tract infection	-0.2	93.1%: 7 6.9%: 14	-0.004	Ocrelizumab NICE submission (TA533)
Urinary tract infection	-0.1	5	-0.001	Ocrelizumab NICE submission (TA533)

Source: (NICE 2017a, NICE 2018d) ALT: Alanine Aminotransferase;

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Published health-related quality of life studies in RRMS were identified via a systematic literature review conducted by searching biomedical literature databases in accordance with the NICE methods guide (NICE 2013).

The systematic review methodology was based on the recommendations and standards stated in the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA), and related Health Technology Assessment (HTA) guidance for identifying HSU for economic models (Papaioannou 2011).

The following electronic databases were searched for health-related quality of life studies in RRMS:

- Excerpta Medica Database (Embase®)
- Medical Literature Analysis and Retrieval System Online (MEDLINE®)
- CENTRAL
- EconLit

The searches were performed on July 24, 2019. The study design filters developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) for MEDLINE and EMBASE were used in the search strategies (CADTH 2019). Because there are no validated study design filters for EconLit and CENTRAL, searches in these databases were run with population and intervention terms only.

In addition, manual searches of the conference proceedings were conducted in the ECTRIMS and ISPOR-EU for 2017 and 2018. Finally, a targeted search of HTAs meeting the eligibility criteria published in the last 10 years by NICE was also conducted.

The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to the decision problem are provided in Appendix H.

In summary, 37 unique published studies, including 5 HTA submission documents were included. Of the 37 published studies, 18 reported HSU data considered applicable to the health state structure of the cost-effectiveness model, out of which only 10 reported the change in utilities from baseline utility values.

Two potential sources were identified in the literature that provided a set of HSU from a UK perspective.

Hawton et al (Hawton 2016a) used data from a UK prospective, longitudinal, cohort study of people with MS (1406 participants and 6066 completed EQ-5D questionnaires) to estimate HSUVs by EDSS scores according to MS type. The mean age of the sample was 51 years and 26.1% were males.

Orme et al (Orme 207) used a postal questionnaire sent to 12,968 people in a database managed by a UK charity (the MS Trust). A total of 2708 (20.9%) questionnaires were returned and 2048 (15.8%) respondents provided data suitable for analysis. The mean age of the sample was 51 years, and 22.5% of people were aged 60 years or more.

In the NICE submission for Ocrelizumab (TA533) (NICE 2018c) the HSUV from the OPERA clinical trials were used supplemented with information from the Orme et al study for the advanced RRMS health states that lacked robust trial data (EDSS 7–9). To derive HSUV for

SPMS, the SPMS utility decrement (-0.045) from the regression analysis of the Orme et al study was applied to the RRMS HSUV.

The patient population in both the Hawton et al and Orme et al studies (mean 51 years) is much older that the patient population from the Ozanimod clinical trials (mean 36 years) which more closely align to the OPERA trial population (37 years). Furthermore, the patient characteristics of the population enrolled in the OPERA trials is very similar to that from the ozanimod Phase III clinical studies (RADIANCE Part B and SUNBEAM).

Health state utility values from the OPERA trials adjusted using the regression analysis by Orme et al. were used in the base case analysis as they more closely represent the population from the ozanimod clinical trials. HSU used in the base case are shown in Table 48.

Table 48. Health state utilities by EDSS state for RRMS and SPMS

EDSS state	RRMS	SPMS
0	0.811	0.836
1	0.843	0.798
2	0.77	0.725
3	0.705	0.66
4	0.644	0.599
5	0.601	0.556
6	0.493	0.448
7	0.309	0.263
8	-0.038	-0.083
9	-0.184	-0.229

Source: OPERA and Orme et al. (2007)

EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

Disutility associated with a relapse was sourced from the Hawton et al study (Hawton 2016a). Data show that experiencing a relapse was associated with a decrement of 0.076 in the EQ-5D value.

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

The costs of managing MS are calculated by combining the time spent in each EDSS state and number of relapses, with the costs assigned to each state and to relapses. The health care costs considered in the model include the costs of managing the disease, costs of drug acquisition, administration, and monitoring, and drug-related adverse events. A detailed description of how these costs were identified is given in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment costs

Treatment costs comprise three components:

- Drug acquisition
- Drug administration
- Drug monitoring

The costs of acquisition and administration are assumed to apply for the duration that people remain on therapy in the model. For continuously administered therapies, monitoring costs are also applied for the duration patients are on therapy. The number of people on therapy is estimated from the EDSS status of the population considering those that discontinue in the previous cycle. All patients are assumed to adhere to therapy and consume the full course in a given year.

For fixed course therapies, all patients are treated in the first year and a proportion of patients receive retreatment in years 2 through 5; after year 5 it is assumed no patients receive retreatment. Patients are monitored for a specific number of years after the first dose.

B.3.5.1.1.1 Drug acquisition and administration

Drug acquisition costs for the UK were sourced from the British National Formulary (BNF) and are presented in Table 49. All drug acquisition costs are presented at list price due to the confidential nature of the PAS for the relevant comparators.

Table 49. Annual drug acquisition costs at list price

Treatment	Package dose	Vials/caps per pack	Package (£)	Vials/caps per year		Annual acquisition cost (£)	
				Year 1	Years 2+	Year 1	Years 2+
Ozanimod	0.25/0.5/1 mg	4/3/28	343 initiation 1373 per 28-pack	365.25	365.25	17,910	17,910
Interferon beta-1a 30µg	30µg	12	1,962	52.18	52.18	8,531	8,531
Interferon beta-1a 22µg	22µg	12	614	156.54	156.54	8,003	8,003
Interferon beta-1a 44µg	44µg	12	813	156.54	156.54	10,608	10,608
Glatiramer acetate 20mg	20mg/1ml	28	514	365.25	365.25	6,704	6,704
Teriflunomide	14mg	28	1,038	365.25	365.25	13,538	13,538
Dimethyl fumarate	120mg	14	343	14	0	17,910	17,910
	240mg	56	1,373	716.50	730.50		
Interferon beta-1b 250µg	250µg	15	597	182.63	182.63	7,264	7,264
Peg-Interferon beta-1a 125µg	125µg	6	1,962	26.09	26.09	8,531	8,531
Glatiramer acetate 40mg	40mg/1ml	12	514	156.54	156.54	6,704	6,704

Source: (BNF 2019)

Drug administration resource use was sourced from the ocrelizumab submission (TA533) (NICE 2018d). Table 50 shows the drug administration and annual administration costs for each treatment, and Table 51 shows the unit costs associated with each resource.

Table 50. Drug administration instructions and annual administration costs

	Administration instructions	Annual administration cost (£)	
		Year 1	Year 2
Ozanimod	None	0	0
Interferon beta-1a 30µg	Dose 1: 3 hours of day nurse's time to teach self-administration	159	0
Interferon beta-1a 44µg	Dose 1: 3 hours of day nurse's time to teach self-administration	159	0
Glatiramer acetate 20mg	Dose 1: 3 hours of day nurse's time to teach self-administration	159	0
Teriflunomide	None	0	0
Dimethyl fumarate	None	0	0
Interferon beta-1b 250µg	Dose 1: 3 hours of day nurse's time to teach self-administration	159	0
Peg-Interferon beta-1a 125µg	Dose 1: 3 hours of day nurse's time to teach self-administration	159	0
Glatiramer acetate 40mg	Dose 1: 3 hours of day nurse's time to teach self-administration	159	0

Source: (NICE 2018d)

Table 51. Drug administration unit costs

	Unit cost (£)	Source
Day nurse (3 hours)	159.00	Curtis L, Burns A. PSSRU Unit Costs of Health and Social Care 2018. University of Kent, Canterbury, Unit PSSR; 2018 (Nurse band 7)

Source: (Curtis 2016, Department of Health 2016a, Department of Health 2016b)(Curtis and Burns 2018)

B.3.5.1.1.2 Drug monitoring

Drug monitoring resource use was sourced from the ocrelizumab submission (TA533) (NICE 2018d). Table 52 shows the drug monitoring instructions and annual monitoring costs for each treatment, and Table 53 shows the unit costs associated with each resource. The unit costs are sourced from the NHS Reference Costs 2017-2018, with the exception of urinalysis and tuberculin skin test which use the same cost sources as used in the alemtuzumab (TA312) NICE submission (NICE 2014b) .

Table 52. Drug monitoring instructions and annual monitoring costs

	Monitoring instructions	Annual monitoring cost (£)	
		Year 1	Year 2
Ozanimod[1]	Year 1: 1 neurology visit, 2 MS nurse visits, 3 CBC, 6 LFT Year 2+: 1 neurology visit, 2 MS nurse visits, 1 CBC, 4 LFT	216	209
Interferon beta-1a 30µg	Year 1: 1 neurology visit, 2 MS nurse visits, 4 CBC, 4 LFT, 4 urinalyses Year 2+: 1 neurology visit, 2 MS nurse visits, 2 CBC, 2 LFT, 2 urinalyses	218	210
Interferon beta-1a 22 and 44µg	Year 1: 1 neurology visit, 2 MS nurse visits, 4 CBC, 4 LFT, 4 urinalysis, 1 thyroid Year 2+: 1 neurology visit, 2 MS nurse visits, 2 CBC, 2 LFT, 2 urinalyses	220	210
Glatiramer acetate 20mg	Year 1: 1 neurology visit, 2 MS nurse visits Year 2+: 1 neurology visit, 2 MS nurse visits	202	202
Teriflunomide	Year 1: 1 neurology visit, 2 MS nurse visits, 1 tuberculin skin test, 3 CBC, 16 LFT Year 2+: 1 neurology visit, 2 MS nurse visits, 2 CBC, 7 LFT	246	215
Dimethyl fumarate	Year 1: 1 neurology visit, 2 MS nurse visits (30 min), 5 CBC, 4 LFT, 4 urinalysis, 1 MRI scan Year 2+: 1 neurology visit, 2 MS nurse visits (30 min), 4 CBC, 2 LFT, 2 urinalyses	361	188
Interferon beta-1b 250µg	Year 1: 1 neurology visit, 2 MS nurse visits, 3 CBC, 3 LFT, 2 RFT Year 2+: 1 neurology visit, 2 MS nurse visits, 2 CBC, 2 LFT, 2 RFT	220	210
Peg-Interferon beta-1a 125µg	Year 1: 1 neurology visit, 2 MS nurse visits, 4 CBC, 4 LFT, 4 urinalyses Year 2+: 1 neurology visit, 2 MS nurse visits, 2 CBC, 2 LFT, 2 urinalyses	218	210
Glatiramer acetate 40mg	Year 1: 1 neurology visit, 2 MS nurse visits Year 2+: 1 neurology visit, 2 MS nurse visits	202	202

Source: (NICE 2017a, NICE 2018d)

1 Assumed same as for fingolimod, excluding ophthalmology visit and varicella zoster virus Ab test/vaccine

CBC: Complete blood count; LFT: Liver function test; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; RFT: Renal function test

Table 53. Drug monitoring unit costs

	Unit cost (£)	Source
CBC	2.51	NHS Reference Costs 2017-18: Haematology, (DAPS05)
RFT	1.11	NHS Reference Costs 2017-18: Clinical Biochemistry, (DAPS04)
Urinalysis	0.35	Midmeds (2017). Available: https://www.midmeds.co.uk/siemens-bayer-multistix-p-234.html
LFT	1.11	NHS Reference Costs 2017-18: Clinical Biochemistry, (DAPS04)
MRI	140.60	NHS Reference Costs 2017-18: Imaging: Direct Access, (RD01A)
Tuberculin skin test	19.08	NICE (2014) TA312: Alemtuzumab for treating relapsing-remitting multiple sclerosis. Available: https://www.nice.org.uk/guidance/ta312
Neurologist visit	148.01	NHS Reference Costs 2017-18: Neurology, (WF01A)
MS nurse visit	27.00	NHS Reference Costs 2017-18: Neurology, (WF01D)

Source: (NICE 2014b, MidMeds 2017, Health 2018)

CBC: Complete blood count; LFT: Liver function test; MRI: Magnetic resonance imaging; NHS: National Health System; NICE: National Institute for Health and Care Excellence; RFT: Renal function test

Monitoring is applied while on treatment. In the base case, 6 years of monitoring from the first dose is assumed.

B.3.5.2 Health-state unit costs and resource use

Relevant studies were identified through a search of the following databases: EMBASE, MEDLINE, CENTRAL, and EconLit databases. The searches were executed on July 24, 2019. The study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN 2019) for MEDLINE and EMBASE were used to identify economic studies. As there are no validated study design filters for EconLit and CENTRAL, searches in these databases were run with population and intervention terms only and the results were screened for economic burden (costs and health care resource utilization and cost-benefit analyses). In addition, manual searches of the conference proceedings were conducted for European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR)—European Union (EU) for 2017 and 2018. Finally, a targeted search of HTAs meeting the eligibility criteria published in the last 10 years by NICE was also conducted.

Hawton et. 2016 (Hawton 2016b) and Tyas 2007 (Tyas 2007) were identified through hand search of the cladribine and ocrelizumab HTA assessments, respectively, which also characterise the cost and HCRU outcomes for the patients with RRMS. These studies were not captured in the SLR screening process as the PICOS criteria were restricted to specific interventions.

The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making are provided in Appendix I.

B.3.5.2.1 Annual disease state costs

B.3.5.2.1.1 EDSS costs

Tyas et al. 2007 was chosen as the base case because it presented costs by individual EDSS state consistent with the model structure and with the largest sample size (2048). Hawton et al. 2016 with information from Karampampa et al. (2012) reported costs by EDSS state though based on a smaller sample size (289 with EDSS information for Hawton et a.l and 119 for Karampampa et a.l) (Karampampa 2012, Hawton 2016).

Table 54. Annualized costs by EDSS state for medical direct costs/health care and social worker costs (£)

	Direct medical costs (RRMS) [1]	Other direct costs (RRMS)	Direct medical costs (SPMS)	Other direct costs (SPMS)
EDSS 0	354	3595	751	3595
EDSS 1	120	4907	517	4907
EDSS 2	302	6257	699	6257
EDSS 3	1205	8805	1602	8805
EDSS 4	1142	5709	1539	5709
EDSS 5	2011	8977	2408	8977
EDSS 6	3064	9327	3461	9327
EDSS 7	9331	15,320	9728	15,320
EDSS 8	15,253	21,742	15,650	21,742
EDSS 9	21,433	14,403	21,830	14,403

Source: (Tyas 2007)

[1] DMT costs have been excluded from total direct medical costs

EDSS: Expanded Disability Status Scale; RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

The costs were reported in 2007 and have been inflated to 2019 using the hospital and community health services (HCHS) index.

B.3.5.2.1.2 Relapse costs

The three studies reporting health state costs also report costs of relapses (Tyas et al. 2007; Karampampa et al. 2012; Hawton et al. 2016). Hawton et al. reported six monthly costs associated with no relapses, relapses not treated with steroids, relapses that limited everyday activities, relapses that required steroid therapy (oral, intravenous) and relapses that resulted in hospital admission (Hawton 2016).

Table 55. Cost of relapse reported in Hawton et al. 2016

Relapse state	% of patients	Cost per event (£)
Sample size n=1,630		
Relapse not treated with steroids n=625	40.61%	381
Relapse limited everyday activities n=634	43.60%	557
Relapse resulted in oral steroids n=196	9.14%	738
Relapse resulted in intravenous steroids n=85	3.53%	1,860
Relapse resulted in hospital admission n=90	3.12%	3,579

Source: (Hawton 2016)

Given Hawton et al. 2016 values provided a comprehensive view of the type of relapses, these values were used to estimate an average cost per relapse. A weighted value was calculated combining all type of relapses. This value was then adjusted for inflation to 2019 using the HCHS index. For the base case, the direct cost per relapse not leading to a hospitalisation is £630 while the direct cost per relapse leading to a hospitalisation is £4,116.

B.3.5.3 Adverse reaction unit costs and resource use

The resource use associated with each adverse event was based on that used in the ocrelizumab submission (TA533) for standard events (NICE 2018d). The costs use recent PSSRU or NHS Reference Costs and are presented in Table 56. Within the ocrelizumab submission, 6.9% of the events were considered serious.

Table 56. Costs associated with adverse events

	Cost (£)	Resource use	Source
Injection-site reaction	2.59	Ocrelizumab submission as injection site pain Non-serious: None Serious: 1 GP consultation	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50)
ALT increased	0.00	None	
Influenza	0.00	None	
Depression	2549.50	Non-serious: 4 GP consultations, Citalopram: 20 mg per day for 6 months, 12 psychotherapy sessions Serious: 9 GP consultations, Citalopram: 40 mg per day for 6 months; 52 Psychotherapy sessions	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50); eMIT 2019: Citalopram 20 mg tablets / Pack size 10; NHS 2017-2018: Non-admitted face-to-face, follow-up (WF01A)
Arthralgia	20.00	Non-serious: NSAIDs: 350 mg 3 x daily for 6 days Serious: 1 MS specialist visit; 1 Rheumatologist visit	eMIT 2016: Ibuprofen 400 mg tablets / Pack size 24 National Reference Cost 2017-18, WF01A, Neurology and Rheumatology
Back pain	54.92	Non-serious: None Serious: 1 MS specialist visit; 12 physical therapy sessions	National Reference Cost 2017-18, WF01A, Neurology PSSRU: "Physiotherapy", one-to-one.
Bronchitis	75.05	Non-serious: 2 GP consultations, 1 course of amoxicillin Serios: 2 GP consultations, 1 course of amoxicillin	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50); eMIT 2019: Amoxicillin 500 mg capsules / Pack size 21
Cough	0.00	None	
Dizziness	0.00	None	
Fatigue	4.08	Non-serious: None Serious: 1 GP visit; Provigil 200 mg / day for 2 months	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50); eMIT 2019: Modafinil 200 mg / Pack size 30

	Cost (£)	Resource use	Source
Headache	10.21	Non-serious: None Serious: 1 Neurology consultation	National Reference Cost 2017-18, WF01A, Neurology
Hypoaethesia	0.00	None	
Influenza like illness	0.00	None	Same assumption as in the ocrelizumab submission
Nasopharyngitis	2.59	Non-serious: None Serious: 1 GP consultation	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50)
Oral herpes	0.00	None	
Oropharyngeal pain	0.00	None	
Pain in extremity	0.00	None	
Pharyngitis	0.00	None	
Rash	0.00	None	
Upper respiratory tract infection	37.50	Non-serious: 1 GP consultation Serious: 1 GP consultation	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50)
Urinary tract infection	64.94	Non-serious: Ciprofloxacin:100 mg twice daily for 3 days Serious: 1 Hospital visit	eMIT 2019: Ciprofloxacin 100mg tablets / Pack size 1 National Reference Cost 2017-18. Sample weighted average of LA04H, J, K, L, M, N, P, Q, R, S

Source: (Curtis 2018, Health 2018, NICE 2018d, Health 2019)

ALT: Alanine aminotransferase test; eMIT: Electronic market information tool; GP: General practitioner; NHS: National Health System; NSAIDS: Non-steroidal anti-inflammatory drugs; PSSRU: Personal Social Services Research Unit

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

A summary of the base case settings for the model is shown in Table 57.

Table 57. Base case settings for the cost-effectiveness model

Setting	Section	Input
Perspective		NHS and PSS
Time horizon		Lifetime (50 years)
Population	B.3.2.1 Patient population	Active RRMS
Model structure	B.3.2.2.1 21-state model	21-health state
Comparison method	B.3.3.1 Natural history reference model	Natural history model
CDP outcome	B.3.3.7.1 Treatment adjusted model – disability progression	CDP-6M combined
Half-cycle correction	B.3.3.5 Order of transitions and half-cycle correction	Yes
Include carer disutility	B.3.4.3 Adverse reactions	Yes
Discount rate	B.3.8.1. Deterministic sensitivity analysis	3.5% costs and outcomes
WTP threshold per incremental QALY	N/A	£30,000
Comparators included	B.3.2.3 Intervention technology and comparators	Interferon beta-1a 30 µg Interferon beta-1a 22 µg Interferon beta-1a 44 µg Glatiramer acetate, 20 mg and 40 mg Teriflunomide 14 mg Dimethyl fumarate 240 mg (bid) Interferon beta-1b 250 µg Peg-interferon beta-1a 125µg EOW
Within RRMS disability progression source		British Columbia MS Registry (≥28 years)

Within SPMS disability progression source	B.3.3.1 Natural history reference model	British Columbia MS Registry (≥28 years)
RRMS to SPMS conversion source		London Ontario (method aligns with natalizumab TA127, dimethyl fumarate TA320 NICE assessments)
Increase in one EDSS score along with conversion?		No
Natural history relapse rate source	B.3.3.1 Natural history reference model	Patzold et. 1982
Mortality multiplier data source	B.3.3.4 Mortality	Pokorski et. 1997, interpolated
Treatment effect multiplier on conversion to SPMS	B.3.3.7.1.2 Waning of treatment effect	None
Waning of treatment effect		Yes
Continue treatment in SPMS?	B.3.3.6 Treatment stopping rules and withdrawal	No
RRMS DMT limit		EDSS 7
Frequency of adverse events while on treatment	B.3.4.3 Adverse reactions	One-off except injection-site reaction which is modelled contentiously for patients on treatment
Utility data source	B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis	Ocrelizumab NICE submission TA533 with SPMS adjustment from Orme et al.

Source: (Patzold 1982, Pokorski 1997, Orme 2007, NICE 2014c, Palace 2014)

CDP: Confirmed disability progression; DMT: Disease modifying therapy; EDDS: Expanded Disability Status Scale; MS: Multiple sclerosis; QALY: Quality-adjusted life year; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; WTP: Willingness to pay

B. 3.6.1 Assumptions

A summary of the key structural assumptions in the base case model is outlined in Table 58.

Table 58. Summary of basic structural assumptions

Aspect	Assumption	Justification
Health states	EDSS adequately captures the main health problems associated with MS	Numerous studies have shown a strong correlation between EDSS and resource consumption and health related quality of life. EDSS is the preferred tool for measuring disability in people with MS as recommended by the EMA
Half-cycle correction	There is an option to model EDSS and drug-related costs and QALYs based on midpoint estimates assuming patients, on average, transition mid-way through the model cycle	Standard approach required by HTA agencies to mitigate the risk of under or over-estimating costs and effects
Natural history of MS – disability progression	Disability progression is modelled assuming a constant transition probability matrix over time	Consistent with approaches taken in previous economic models Constant transition probability matrix shown to accurately predict EDSS status over 10 years
Natural history of MS – relapse	In the base case, relapses are modelled as a function of EDSS state	Consistent with approaches taken in previous economic models Model includes the option of evaluating relapses independently from EDSS state to avoid double counting of DMT effect
Effectiveness of DMT - application	CDP and relapses are modelled independently, with independent treatment effects applied.	Consistent with approaches taken in previous economic models Some treatments may be more effective in reducing relapses than slowing disease progression
Discontinuation of DMT or cessation of treatment effect	People who discontinue initial treatment are assumed to follow the natural history progression of disease In the base case, people with MS discontinue treatment after transitioning to SPMS, and upon progression to EDSS 7 or greater The health benefits of DMT that are accrued up to the point of discontinuation or cessation of therapy benefits is maintained with future progression rates modelled based on a natural history data set	This is consistent with approaches taken in past economic models Clinical trials in RRMS have typically focused on patients who have non-ambulatory RRMS including patients with EDSS <6.5 in study enrolment. No data are available on the effects of DMT in people with EDSS ≥7.0

Aspect	Assumption	Justification
Effectiveness of DMT – waning over time	The model allows for an assumption that the effectiveness of DMTs wanes over time	This is consistent with approaches taken in past economic models Long-term treatment with interferon beta can lead to the development of neutralising antibodies that can reduce the effectiveness of these therapies

CDP: Confirmed disability progression; DMT: Disease-modifying therapy; EDSS: Expanded Disability Status Scale; EMA: European Medicines Agency; HTA: Health technology assessment; MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; QALY: Quality-adjusted life year

B.3.7 Base-case results

B.3.7.1 Summary and incremental results versus ozanimod

The total costs, QALYs, life years (LYs) and relapses from the base-case analysis are summarized in Table 59 and Table 60, and show the incremental differences in these outcomes versus ozanimod. Over a lifetime horizon (50 years), the total cost per patient associated with ozanimod treatment was [redacted], while the total cost at list price of the other comparators ranged from [redacted] (peg-interferon beta-1a 125µg) to [redacted] (dimethyl fumarate). Treatment with ozanimod was associated with [redacted] versus a range of [redacted] (glatiramer acetate, 40 mg) to [redacted] (dimethyl fumarate) with the other comparators.

The estimates of clinical outcomes included in the cost-effectiveness analysis and the disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix J.

Table 59. Total costs, QALYs, LYs, and relapses from base-case analysis

Treatment	Costs (discounted) (£)	QALYs (discounted) (n)	LYs (discounted) (n)	Relapses (discounted) (n)	
				Not leading to hospitalisation	Leading to hospitalisation
Ozanimod 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LY: Life year; QALY: Quality-adjusted life year

Table 60. Incremental base-case results for ozanimod versus comparator treatments (ozanimod minus comparator)

Treatment	Costs (discounted) (£)	QALYs (discounted)	LYs (discounted)	Incr. cost (£) per QALY	Incr. cost (£) per LY	Incr. cost per relapse avoided (£)	
						Not leading to hospitalisations	Leading to hospitalisation
Ozanimod 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LY: Life year; QALY: Quality-adjusted life year

B.3.8 Sensitivity analyses

B.3.8.1. Deterministic sensitivity analysis

The DSA was run for the base-case analysis using the settings as detailed in Section B.3.6; the parameters that are varied and the magnitude of the variations are presented in Table 61. The tornado diagram is presented in

Figure 10.

Table 61. DSA inputs and results in the primary analysis, ozanimod versus interferon beta-1a 30 µg

Parameter		Parameter values			Absolute change (results)			% change		
		Lower value	Base case	Upper value	Lower value	Base case	Upper value	Lower value	Base case	Upper value
Discount rate	Costs	0.0%	3.5%	6.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Outcomes	0.0%	3.5%	6.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment efficacy on disability progression	Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment efficacy on relapse	Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapses leading to hospitalization	Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Waning of treatment effect multiplier	Ozanimod	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation multiplier	Ozanimod	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event incidence multiplier	Ozanimod	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RRMS	Direct medical costs multiplier	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter		Parameter values			Absolute change (results)			% change		
		Lower value	Base case	Upper value	Lower value	Base case	Upper value	Lower value	Base case	Upper value
	Other direct costs multiplier	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Direct cost per relapse	Not leading to hospitalization	567	630	693	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Leading to hospitalization	3704	4116	4528	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acquisition costs multiplier	Ozanimod	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs multiplier	Ozanimod	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs multiplier	Ozanimod	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Interferon beta-1a 30µg	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs multiplier		0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average utility multiplier	RRMS	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of relapse	Not leading to hospitalization	-0.01	-0.01	-0.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Leading to hospitalization	-0.01	-0.01	-0.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of adverse events multiplier		0.9	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter		Parameter values			Absolute change (results)			% change		
		Lower value	Base case	Upper value	Lower value	Base case	Upper value	Lower value	Base case	Upper value
Carer disutility multiplier	RRMS	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS	0.90	1.00	1.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DSA: Deterministic sensitivity analysis; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

Figure 10. Tornado diagram from the DSA of the model results, ozanimod versus interferon beta-1a 30 µg

DSA: Deterministic sensitivity analysis; ICER: Incremental cost-effectiveness ratio; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; QALY: Quality-adjusted life year. If both bars for a parameter are in the same direction (both positive or both negative), at least one of the ICERs is dominant

B.3.8.2 Probabilistic sensitivity analysis

A PSA using 5,000 iterations was run for the base-case analysis using the settings as detailed in Section B.3.6 and the probability distributions described in Table 62.

Table 62. PSA distributions according to parameter

Parameter	Distribution	Comment
Natural history transitions	Dirichlet	Normalized sum of independent gamma variables
EDSS distribution at baseline	Dirichlet	
Natural history progression accelerator	Lognormal	Likely skewed nature of relative effect measures, and their constraint to positive values
Natural history relapse rates	Lognormal	
Mortality multiplier	Lognormal	
HR of treatment effect	N/A	The CODA was sampled from to preserve correlations in parameter estimates
ARR	N/A	The CODA was sampled from to preserve correlations in parameter estimates
Proportion of relapses leading to hospitalization	Beta	Bounded between 0 and 1
Waning effect	Beta	
Discontinuation	N/A	The CODA was sampled from to preserve correlations in parameter estimates
Adverse event rates (incidence)	Beta	Bounded between 0 and 1
Proportion serious adverse events	Beta	
Costs	Gamma	Likely skewed nature of health care costs, and their constraint to positive values
Health state utilities	Lognormal	As utility values may be negative, a transformation of D=1-U where D is a utility decrement was performed so utilities became constrained on the interval 0 to positive infinity and a lognormal distribution was used
Disutilities	Lognormal	Bounded between 0 and infinity, and skewed

The average results of all PSA iterations are shown in Table 63. The results were similar to the base-case deterministic results (Section B.3.7).

Table 63. Average results from the PSA (discounted cumulative results)

Treatment	Total Costs (£)	Total QALYs	Total LY	ICER (versus ozanimod)	
				£/QALY	£/LY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Total Costs (£)	Total QALYs	Total LY	ICER (versus ozanimod)	
				£/QALY	£/LY
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: Incremental cost-effectiveness ratio; LY: Life year; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life year

B.3.8.3 Cost-effectiveness plane

The cost-effectiveness plane is show in Figure 11.

Figure 11. Cost-effectiveness plane vs. all comparators

B.3.8.3.1 Cost-effectiveness acceptability curve

The CEAC is shown in

Figure 12 where peg-interferon beta-1a has the highest likelihood of being cost effective between a threshold of £20,000 to £30,000 per QALY.

Figure 12. Cost-effectiveness acceptability curve, ozanimod versus all comparators

B.3.8.3.2 Scenario analysis

A range of scenario analyses were conducted to explore the impact on varying specific inputs or model assumptions. The results of these scenarios are presented in Table 64 through to Table 77. The scenarios included exploring the impact of using the London Ontario Canada natural history dataset (Table 64) to understand how it could change the results, using different sources for CDP values (Table 65 to Table 66), using Harding et al's mortality estimates (Table 68), a different relapse cost (Table 74), excluding other direct non-medical costs (Table 75), and excluding carer disutilities (Table 76). Other scenarios included using values from the RSS analysis for starting EDSS distribution (Table 67), treatment discontinuation (Table 69), CDP HRs (Table 71), utility values (Table 72), and health state costs (Table 73).

Table 64. Results of scenario: Alternative natural history of disease source; London Ontario Canada active RRMS group and the SPMS data from the Scalfari 2010 publication

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 65. Results of scenario: CDP using 6M combined-based approach with ozanimod set to NMA output

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 66. Results of scenario: CDP using 3M

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Quality-adjusted life year;

Table 67. Results of scenario: EDSS starting distribution using the RSS analysis

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 68. Results of scenario: Mortality multiplier using Harding et al

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 69. Results of scenario: Treatment discontinuation using the RSS setting of 5% discontinuation per year

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 70. Results of scenario: No treatment waning

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 71. Results of scenario: CDP HR for ozanimod, IFNs, and GA set to the RSS value (HR = 0.79)

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 72. Results of scenario: Utility values set to the same as the RSS model

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 73. Results of scenario: Health state costs set to the RSS values adjusted with current inflation rates

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Glatiramer acetate, 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 74. Results of scenario: Relapse cost set to the value used in Tyas, the same cost is used independently of hospitalisation (£2,300.50)

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Quality-adjusted life year;

Table 75. Results of scenario: Other non-medical direct costs excluded

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 76. Results of scenario: Carer disutility excluded

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg Interferon beta-1a 125 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

Table 77. Results of scenario: Glatiramer acetate using the biosimilar price

Treatment	Costs (£)	QALYs	Incr. cost (£)	Incr. QALY	Incr. £/QALY
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY: Quality-adjusted life year;

B.3.8.4 Summary of sensitivity analyses results

The results of the PSA (Table 63), showed similar results to the base-case deterministic results (Section 3.7). While ozanimod produced comparable QALYs and LYs of the included treatments, [redacted]

For the DSA, ozanimod was compared with interferon beta-1a at a 30µg dose. The resulting tornado diagram (Figure 11) showed that the waning of treatment effect parameter for ozanimod and interferon beta-1a had the largest (change between [redacted] and second largest change between [redacted]) impacts on the ICER respectively, and the next highest were the treatment effect on disability progression for interferon beta-1a (change between [redacted] and ozanimod (change between [redacted]).

In all of the explored scenarios, ozanimod [redacted] except when the CDP HR for ozanimod, the IFNs and the glatiramer acetate doses were set to the value in the RSS analysis (HR = 0.79, Table 71[redacted]. Similarly, ozanimod was not dominated by interferon beta-1a 22 µg or interferon beta-1a 30 µg in any scenarios [redacted]. Ozanimod was never dominated by glatiramer acetate 40 mg in any of the scenarios.

Out of all the scenarios, the following generally improved the estimated cost-effectiveness of ozanimod:

- EDSS starting distribution using the RSS analysis (Table 67)
- No treatment waning (Table 70)
- CDP HR for ozanimod, IFNs, and GA set to the RSS value (HR = 0.79) (Table 71)
- Health state costs set to the RSS values adjusted with current inflation rates (Table 73)
- Relapse cost set to the value used in Tyas, the same cost is used independently of hospitalisation (Table 74)

The following scenarios generally reduced the estimated cost-effectiveness of ozanimod:

- Alternative natural history of disease source; London Ontario Canada active RRMS group and the SPMS data from the Scalfari 2010 publication (Table 64)
- CDP using 6M combined-based approach with ozanimod set to NMA output (Table 65)
- Using CDP 3M (Table 66)
- Mortality multiplier using Harding et al (Table 68)
- Treatment discontinuation using the RSS setting of 5% discontinuation per year, except when compared with glatiramer acetate 40mg (Table 69)
- Utility values set to the same as the RSS model (Table 72)
- Other non-medical direct costs excluded (Table 75)
- Carer disutility excluded (Table 76)

B.3.9 Subgroup analysis

Subgroup analysis was not carried out as part of this analysis. Celgene does not envisage ozanimod being used in the RRMS sub-populations, i.e. RES/HA and SOT population.

B.3.10 Validation

To validate the model, it was compared against the RSS model built to support the risk-sharing scheme for the use of DMTs in the NHS (Palace et al. 2019). Estimates of whole cohort mean EDSS and utility progression were compared between the models, without treatment (natural history) and with treatment.

B.3.10.1 Model assumptions

The model types differed between the two studies as the RSS model was a multi-level model instead of the discrete Markov model developed for this submission. Other assumptions made regarding treatment effect, waning and discontinuation were not described in the RSS model so it is unclear how they may have differed.

B.3.10.2 EDSS progression

The first comparison was on whole cohort mean EDSS progression from baseline simulated for the first 10 years, considering both the untreated (natural history) population and the treated population.

B.3.10.2.1 EDSS progression in the natural history population

The natural history progression in the untreated population was simulated and compared with the corresponding information from Palace et al. 2019. The whole cohort mean EDSS progression from baseline was plotted and visually compared (Figure 13).

Figure 13. Natural history progression in the untreated population. Whole cohort mean EDSS progression from baseline

Table 78. Whole cohort EDSS progression from baseline

	Palace 2019	Ozanimod CE model
Time (years)	Untreated	BSC
0	0	[redacted]
2	0.631	[redacted]
4	1.088	[redacted]
6	1.473	[redacted]
8	1.800	[redacted]
10	2.132	[redacted]

Source: (Palace 2019)

As demonstrated in Figure 13, EDSS progression simulated by both models is similar. This is supported by the results in Table 78 that show minimal difference at the 2-year milestone, which reduces at the later milestones. To minimise any difference in the starting populations, the RSS initial EDSS patient distribution was used in the Celgene model for this comparison.

B.3.10.2.2 EDSS progression in the on-treatment population

The results for a population with DMT treatment are presented below; with the results assuming no treatment discontinuation and no waning in the ozanimod model shown in Figure 14 and Table 79, and those results where treatment discontinuation and waning are assumed in Figure 15 and Table 80.

Figure 14. Whole cohort mean EDSS progression from baseline, showing the treatment effect. No treatment waning or discontinuation are assumed in the ozanimod CE model

[redacted]

Table 79. Whole cohort mean EDSS progression from baseline, with and without treatment. No treatment waning or discontinuation are assumed in the ozanimod CE model

Time (years)	Palace 2019		Ozanimod CE model	
	Untreated (Palace)	RSS treated (Palace)	BSC (Ozanimod model)	Pooled RSS (Ozanimod model)
0	0	0	[redacted]	[redacted]
2	0.631	0.292	[redacted]	[redacted]
4	1.088	0.631	[redacted]	[redacted]
6	1.473	0.963	[redacted]	[redacted]
8	1.800	1.277	[redacted]	[redacted]
10	2.132	1.521	[redacted]	[redacted]

Source: (Palace 2019)

Figure 15. Whole cohort mean EDSS progression from baseline, showing the treatment effect. Treatment waning and discontinuation are assumed in the ozanimod CE model

Table 80. Whole cohort mean EDSS progression from baseline, with and without treatment. Treatment waning and discontinuation are assumed in the ozanimod CE model

Time (years)	Palace 2019		Ozanimod CE model	
	Untreated (Palace)	RSS treated (Palace)	BSC (Ozanimod model)	Pooled RSS (Ozanimod model)
0	0	0	[redacted]	[redacted]
2	0.631	0.292	[redacted]	[redacted]
4	1.088	0.631	[redacted]	[redacted]
6	1.473	0.963	[redacted]	[redacted]
8	1.800	1.277	[redacted]	[redacted]
10	2.132	1.521	[redacted]	[redacted]

Source: (Palace 2019)

The results of this comparison show that the Ozanimod CE model simulates a reduced treatment effect both visually and in the mean values. This treatment effect is more pronounced when treatment discontinuation and waning is assumed. Palace et al. 2019 does not provide sufficient detail regarding treatment waning and treatment discontinuation modelling assumptions to concretely determine whether it is these factors that are driving the differences between the results of the two approaches.

B.3.10.2.1 Utility progression with Palace et al. 2019 utility set, used in the RSS model

Figure 16 illustrates that the mean utility progression from Palace et al. 2019 for an untreated population aligns with the utility progression within the Ozanimod CE model.

Figure 16. Mean utility progression from baseline in the untreated population

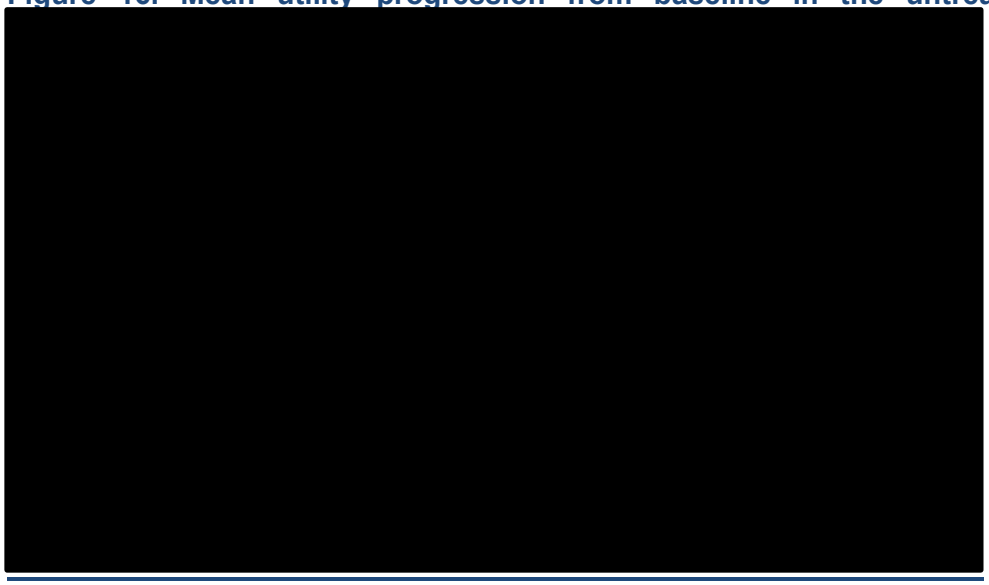
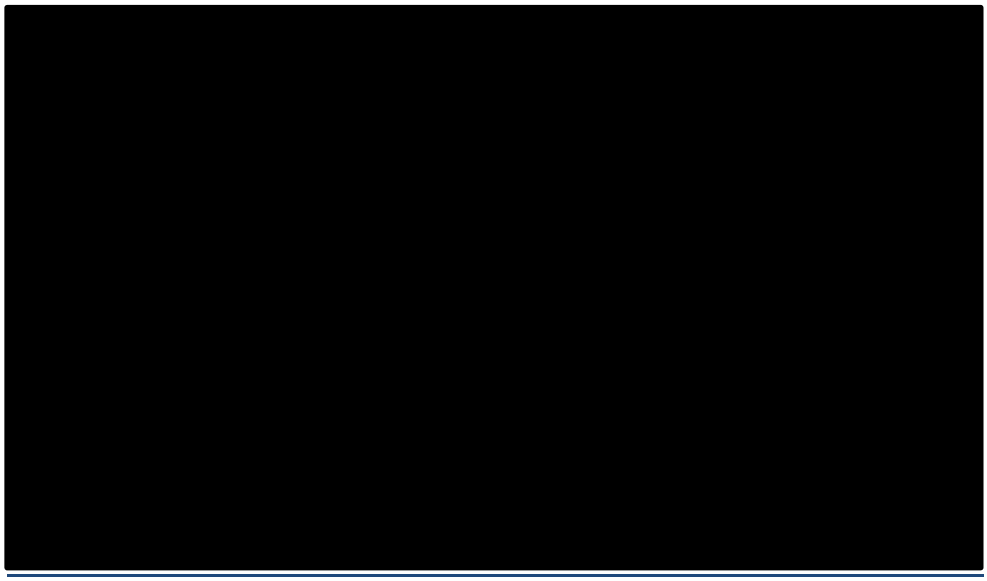


Figure 17. Whole cohort utility progression from baseline, showing the treatment effect. No treatment waning or discontinuation are assumed in the ozanimod CE model



B.3.11 Interpretation and conclusions of economic evidence

A *de novo* economic analysis was developed to assess the incremental cost-effectiveness of ozanimod versus alternative treatments within its expected marketing authorisation for active RRMS. The economic analysis examines the use of ozanimod in people with active RRMS and included beta-interferons, dimethyl fumarate, glatiramer acetate, teriflunomide, and peginterferon beta-1a therapies as comparators. An extensive series of economic analyses were performed using the best currently available evidence on the costs and clinical outcomes of treatment in active RRMS whilst following the precedent set in previous NICE appraisals.

The results of the base case analysis demonstrate that ozanimod has comparable or improved outcomes compared with the interferon beta-1a, glatiramer acetate, and teriflunomide in the active RRMS population. Dimethyl fumarate, interferon beta-1b are the comparators with relatively improved outcomes versus ozanimod. Over a lifetime horizon, the model predicts fewer discounted relapses than the other comparators with [redacted] total discounted relapses.

The deterministic results are primarily influenced by the assumptions of the 6-month CDP HR. As was noted earlier, this parameter is unstable due to the low event rate in the ozanimod clinical trials. The numerical (but not statistical) difference favouring ozanimod in CDP-3M and favouring IFNβ-1a in CDP-6M indicates that the differences are unlikely driven by a true underlying treatment effect but are likely the result of statistical variability. In settings with low event rates, estimated hazard ratios may numerically distort the magnitude of differences, whereas “absolute differences” between estimated probabilities may better reflect practical differences.

The structure of cost-effectiveness analyses within MS rely on CDP progression as a critical efficacy parameter, using estimated hazard ratios. The uncertainty around the comparable effectiveness of ozanimod and the long-term uncertainty of all treatments addressed by testing treatment waning assumptions together contribute to uncertainty in the long-term costs and outcomes within a cost-effectiveness framework. The statistically significant improvements in relapse rates for ozanimod compared with interferon beta-1a, teriflunomide, interferon beta-1b, and glatiramer acetate are not directly reflected in the cost-effectiveness analysis because of the structural assumption where CDP progression is independent and not influenced by relapse rates. This structural assumption is also present in other cost-effectiveness evaluations of DMTs for RRMS.

A comprehensive set of scenario analyses were performed to assess the robustness of the economic analysis. These scenarios included alternative assumptions around the HR for CDP, the exclusion of direct non-medical costs, the assumption of no treatment waning, a conservative assumption that applied the same waning assumptions across all comparators following NICE precedent, and the consideration of alternative input parameters. Overall, these scenarios show the variability of the results with regards to the underlying CDP assumptions. The outcomes, incremental QALYs, remain largely unchanged across the other scenarios demonstrating the robustness of the economic analysis to alternative assumptions around costs, treatment waning, carer disutility, and other setting or input assumptions.

In summary, ozanimod is an oral treatment demonstrating effects similar to other DMTs for disease progression with improved efficacy in terms of relapse rates. With a list price of £17,910 annually, it aligns with the list price of dimethyl fumarate (£17,910 – list price), another oral DMT used in patients with non-highly active RRMS. Indirect treatment comparisons have suggested no statistically significant differences in ARR or disability compared to dimethyl fumarate. Other DMTs have an agreed discount with the NHS so it is difficult to comment on the cost-effectiveness outside of relying on list prices. The results of the economic analysis support the case that ozanimod is an effective treatment in this population.

Consistency with published economic literature

None of the studies identified in the systematic literature review of economic evaluations in RRMS included ozanimod as a comparator. Therefore, the results of this analysis cannot be directly compared with other studies.

As outlined in B.3.10, the model with ozanimod does reliably reproduce outcomes comparable with the RSS model over 10 years.

Relevance to all groups of patients who could potentially use the technology

In line with the expected marketing authorisation for ozanimod and the final scope for this appraisal, the economic analysis focused on the use of ozanimod in a population with active RRMS.

Relevance of the analysis to clinical practice in England

Where possible, the analyses have used input values from literature sources and/or previous NICE appraisals that have been considered generalisable to clinical practice in England. This input includes the selection of cost inputs corresponding to the NHS and PSS perspective from patients with RRMS in England, where available, and the inclusion of HSU values derived from UK social preferences. In addition, the natural history model used to generate EDSS progression was based on the model used in the UK risk sharing scheme, which was developed with the intention of modelling the EDSS of the UK RRMS population.

Strengths and weaknesses

The key strengths of the analysis are shown below:

- Includes the long-term waning in drug efficacy for all therapies including ozanimod
- Allows for improvements and progression in EDSS as modelled using the preferred BC natural history data set
- Use of NICE preferred endpoint of 3 month combined with 6 month confirmed disability progression as the base case
- Use of the European Medicines Agency preferred endpoint of 6 month confirmed disability progression as a scenario
- Use of health state utility values representing the UK population

The key weaknesses of the analysis are:

- The model structure relies on CDP as the primary influence of the results. Relapse rates are only incorporated as annual costs and disutility. In addition to relapse rates, other meaningful clinical endpoints are not reflected within the accepted model structures for DMTs. Benefits seen in other meaningful clinical endpoints are not captured due to the CDP-based model structure. As discussed in Section B.1.3.2, the EDSS scale has a number of limitations, and as CDP is defined as an increase in EDSS score over a period of time, it has been regarded as inaccurate in the measurement of disease progression in MS.
- The analysis does not consider the cost-effectiveness of ozanimod or its comparators when given in a sequence of therapies. This is in line with NICE precedent.
- DMT are assumed to only impact on EDSS progression and relapse rate. There is no effect of DMT on mortality.
- The health benefits of an oral drug are not fully captured in the QALY estimates given the need to assume the same utilities across different formulations. Similarly, in TA303 and TA320 it was recognized that oral drugs provide quality of life benefits other than those captured in the QALY calculations.

Further analyses

The discounts agreed in the patient access schemes for comparators are commercial in confidence and are hence unknown to the company. All base case analyses presented here are based on the list price for these therapies. Further analyses should be performed using the actual discounts agreed with these therapies, as available to the evidence review group and NICE Committee.

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B.5 Appendices

Appendix C: Summary of product characteristics or information for use, European public assessment report, scientific discussion or drafts

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Post-hoc Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Confidential information checklist

Appendix L: Non-relevant comparators

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Clarification questions

November 2019

File name	Version	Contains confidential information	Date
	V1	Yes/no	09/12/2019

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Trials of ozanimod

A1. Table 9 company submission: Please clarify the meaning of the numbers in square brackets in the Kaplan-Meier estimate row for the pooled analysis. If appropriate, please provide the similar data for the RADIANCE Part B and SUNBEAM trials.

The numbers outside square brackets (i.e. 0.741 and 0.822) are the Kaplan-Meier estimates of the relapse-free rates, evaluated at month 12, for patients treated with IFN-β1a and ozanimod 1.0mg respectively, calculated in the pooled analysis of RADIANCE Part B and SUNBEAM trials. The numbers in square brackets (i.e. 0.623 and 0.755) are the Kaplan-Meier estimates of the relapse-free rates for the pooled analysis but evaluated at month 24. The Kaplan-Meier estimates for the individual trials is also provided in the same table; RADIANCE Part B (calculated at month 24) and SUNBEAM (calculated at month 12).

A2. Please provide the rate ratio (95% confidence interval [CI]) for the pooled analysis of number of gadolinium-enhancing (Gd-E) brain magnetic resonance imaging (MRI) lesions for the comparison of ozanimod versus interferon beta-1a, 30 µg which is missing from Table 11 of the company submission.

The rate ratio (95% CI) for the pooled analysis of Gd-E brain MRI lesions for ozanimod vs. IFN-β1a is as follows:

- At month 12: 0.392 (95% CI: 0.300, 0.512)
- At month 24: 0.471 (95% CI: 0.306, 0.725)

This calculation is based on the negative binomial regression model, adjusted for each study (SUNBEAM or RADIANCE Part B), region (Eastern Europe vs rest of the world), age at baseline, and the baseline number of GdE lesions. The offset term in the model was the logarithmic transformation of the number of MRI scans at 12 or 24 months.

A3. Please provide rationale for quoting p-values from the ranked based ANCOVA model adjusted for region and Expanded Disability Status Scale category per Interactive Voice Response System within Tables 12, 13 and 14 of the company submission (MRI measures of disease activity). The ERG notes that this model is not pre-specified in any of the statistical analysis plans for RADIANCE Part B (Celgene 2015d), SUNBEAM (Celgene 2015e) or the integrated analysis (Celgene 2017b).

The raked based ANCOVA was performed out of concerns regarding the assumption of normality. However, given the large sample size of the two studies and the central limit theorem the pre-specified parametric analyses should also be acceptable. We note that both the ranked based ANCOVA and the pre-specified parametric analysis produced the same conclusions regarding these endpoints.

A4. <u>Priority question</u>: Please clarify if the proportional hazard assumption is valid for the analyses of RADIANCE Part B, SUNBEAM and the pooled analysis for the confirmed disability progression (CDP) outcomes at 3 months (CDP-3M) and 6 months (CDP-6M) and provide results of a statistical test (e.g. a test of Schoenfeld Residuals) to verify the validity of the proportional hazards assumption.

To check the proportional hazard assumption for the 0.5mg ozanimod and 1.0mg ozanimod treatment groups (relative to IFN) we applied the methodology of Grambsch & Therneau 1995 as implemented in the R function cox.zph() (Grambsch 1994).

For the pooled studies of CDP-3M, the model p-values for the 0.5mg ozanimod and 1.0mg ozanimod arms are 0.154 and 0.622, respectively; For Study 201B (RADIANCE Part B), the CDP-3M model p-values are 0.412 and 0.682 (respectively), and for Study 301 (SUNBEAM) the CDP-3M model p-values are 0.105 and 0.413 (respectively).

For the pooled studies of CDP-6M, the model p-values for the 0.5mg ozanimod and 1.0mg ozanimod arms are 0.105 and 0.901 (respectively). For Study 201B (RADIANCE Part B), the CDP-6M model p-values are 0.214 and 0.678 (respectively), and for Study 301 (SUNBEAM) the CDP-6M model p-values are 0.509 and 0.412 (respectively).

Considering p-values <0.05 to indicate violation of the proportional hazard assumption, the above results suggest that there is no statistically significant departure from the proportional; hazard assumption.

A5. It is stated on pages 44 to 45 of the company submission that the observed Kaplan-Meier estimates for CDP-3M and CDP-6M in the interferon beta-1a, 30 µg group was “lower than anticipated”. Please clarify what the anticipated Kaplan-Meier estimates for CDP-3M and CDP-6M were (including any references as appropriate).

For CDP-3M and CDP-6M, it was insufficient to detect a significant treatment difference between ozanimod and IFN β-1a arm due to the low number of events associated with limited follow-up time in all three treatment arms. The CDP endpoint was powered based on rates of disability progression at 3 months seen in other 1- and 2-year RMS studies with an S1P modulator (Cohen 2010, Kappos 2010). The lower than anticipated rate of disability

progression for the IFN β-1a group (vs historical rates) reduced the ability to detect a meaningful difference between ozanimod and IFN β-1a.

Table 1 – CDP3M values for IFNβ-1a vs ozanimod

	Powering Assumptions		Pooled Observed Rates	
	IFNβ-1a	Ozanimod	IFNβ-1a	Ozanimod
CDP-3M	12-24%	6-18%	7.8%	7.6%

A6. The ERG notes that the outcome of no evidence of disease activity (NEDA-3) is listed as an endpoint for which an integrated analysis "may be performed" in the statistical analysis plan of the pooled analysis (Celgene 2017b, pages 11 to 12). If performed, please provide the pooled analysis results for NEDA-3.

No evidence of disease activity (NEDA) is a comprehensive measure of treatment response in patients with RMS. It is believed to be able to predict MS disease activity, disease progression, and treatment efficacy. There are currently eight levels of NEDA, with NEDA-3 and NEDA-4 regarded as the most commonly utilised tools in MS. NEDA-3 is defined by no relapses, no increase in disability, and no new or active (enhancing) lesions on MRI scans.

Please see below the results of the pooled analysis for NEDA-3.

The results of the pooled analysis for NEDA-3 are consistent with the NEDA-3 analysis of SUNBEAM (12 month) and RADIANCE Part B (24 months) and show a statistically significant favourable response in patients treated with ozanimod compared to IFN β-1a.

Table 2 – Proportion of subjects with NEDA-3 (month 24): Observed cases Pooled Phase 3 Studies, (ITT)

	RADIANCE Part B and SUNBEAM pooled analysis	
Treatment	IFN β-1a 30 µg (N = 889)	Ozanimod 1 mg (N = 880)
Proportion No Evidence of Disease Activity (95% CI)	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)a	[redacted]	[redacted]
p-value[b]	[redacted]	0.0244

[a] Based on Wald 95% CI.
[b] Based on the Cochran-Mantel-Haenszel test stratified by region and EDSS category per IVRS.
Note: No evidence of disease activity is defined as no protocol-defined relapses, no 3 month confirmed disability progression, no new or enlarging T2 lesions, and no new GdE lesions.

A7. Please clarify why the post-hoc pooled analysis of NEDA-4 was conducted at 24 months rather than 12 months (which is the time point of the other pooled analyses presented in Section B.2.6 of the company submission).

NEDA-4 is defined as no evidence of relapses, new or enlarged T2 lesions and CDP-6M (as defined in NEDA-3), and a mean annualised rate brain volume loss (BVL) of less than 0.4%. In the submission, both 24 month and 12 month data were presented, and the same table has been reproduced here.

Table 3 – Proportion of Subjects with No Evidence of Disease Activity through Month 24: Observed Cases. Pooled Phase 3 Studies, (ITT)

	RADIANCE Part B and SUNBEAM pooled analysis	
Treatment	**IFN β-1a 30 µg (N = 889)**	**Ozanimod 1 mg (N = 880)**
Proportion No Evidence of Disease Activity at month 12 (95% CI)	[redacted]	24.5 (21.44, 27.52)
Difference in proportions vs IFN β-1a (95% CI)[a]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]
Odds ratio ozanimod vs IFN β-1a (95% CI)b	[redacted]	[redacted]
Proportion No Evidence of Disease Activity at month 24 (95% CI)	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)[a]	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]
Odds ratio ozanimod vs IFN β-1a (95% CI)[b]	[redacted]	[redacted]

[a] Based on Wald 95% CI.
[b] Based on the Cochran-Mantel-Haenszel test stratified by region and EDSS category per IVRS.
Note: No evidence of disease activity is defined as no protocol-defined relapses, no 3 month confirmed disability progression, no new or enlarging T2 lesions, and no new GdE lesions, and annualized brain volume loss (AR-BVL) <= 0.4%.

A8. Please also provide NEDA-4 results for the individual trials (RADIANCE Part B and SUNBEAM) in the format of Table 20 of the company submission.

The NEDA-4 analysis for the individual trials is presented in Table 4 and Table 5. Please note, for SUNBEAM the study duration was 12 months, therefore no data for NEDA-4 at 24 months is available.

The results of the pooled analysis for NEDA-4 are consistent with the NEDA-4 analysis of SUNBEAM (12 month) and RADIANCE Part B (24 months) and show a statistically significant favourable response in patients treated with ozanimod compared to IFN β-1a.

Table 4 – Proportion of Subjects with No Evidence of Disease Activity through Month 12 — Observed Cases 301 Study (SUNBEAM), (ITT)

Treatment	**IFN β-1a 30 µg (N = 448)**	**Ozanimod 1 mg (N = 447)**
Proportion No Evidence of Disease Activity (95% CI)	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)a	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]

[a] Based on Wald 95% CI.
[b] Based on the Cochran-Mantel-Haenszel test stratified by region and EDSS category per IVRS.
Note: No evidence of disease activity is defined as no protocol-defined relapses, no 3 month confirmed disability progression, no new or enlarging T2 lesions, and no new GdE lesions, and annualized brain volume loss (AR-BVL) <= 0.4%. (NEDA-4)
-- 301 Study had a 12-month study period.

Table 5 – Proportion of Subjects with No Evidence of Disease Activity through Month 24 — Observed Cases 201b Study (RADIANCE Part B), (ITT)

Treatment	IFN β-1a 30 µg (N = 441)	Ozanimod 1 mg (N = 433)
Proportion No Evidence of Disease Activity (95% CI)	[redacted]	[redacted]
Difference in proportions vs IFN β-1a (95% CI)a	[redacted]	[redacted]
p-value[b]	[redacted]	[redacted]

[a] Based on Wald 95% CI.
[b] Based on the Cochran-Mantel-Haenszel test stratified by region and EDSS category per IVRS.
Note: No evidence of disease activity is defined as no protocol-defined relapses, no 3 month confirmed disability progression, no new or enlarging T2 lesions, and no new GdE lesions, and annualized brain volume loss (AR-BVL) <= 0.4%. (NEDA-4)

Network meta-analyses (NMAs)

A9. <u>Priority question</u>: Please clarify if any studies included in the NMAs in the Institute for Clinical and Economic Review [ICER] 2017 report and NICE 2017a document were excluded from the NMAs in the company's submission and if so, why?

A comparison of the included studies in the NICE and ICER NMA with Celgene's NMA identified three studies that were excluded in the Celgene NMA but included in the NICE/ICER NMA. The NICE/ICER research question was broader than the NICE scope and therefore the rational for excluding these studies was because the treatment of interest in the studies were not included in the NICE scope. The following studies were excluded from the Celgene NMA:

- Hauser 2008: included by ICER but excluded in our NMA as rituximab is not included in the NICE scope (Hauser 2008)
- Gold 2013: included by ICER and NICE but excluded in our NMA as daclizumab is not included in the NICE scope (Gold 2013)
- Kappos 2015: included by ICER and NICE but excluded in our NMA as daclizumab is not included in the NICE scope (Kappos 2015)

A10. <u>Priority question</u>: The company highlights in its submission (Section B.2.6.1) that in the RADIANCE Part B and SUNBEAM trials: "Patients had a wide range of disease activity and approximately 70% had received no prior DMT treatment for MS." It is also noted in Appendix D1.1.5 to the company submission that "No evidence of treatment-effect modifying characteristics was noted in the clinical trials or the general MS literature with the exception

of prior treatment exposure and disease severity." Please provide further information on any important differences between the studies included in the NMAs in the company's submission in relation to prior treatment exposure and disease severity.

In our assessment of the clinical trial literature, there are two clinically meaningful factors that could contribute to differential outcomes: disease severity and prior treatment exposure. Disease severity was often measured in terms of patient classifications such as "high disease activity" or "rapidly evolving severe"[1]. Categorizations into these groups were not provided in the patient characteristics to enable evaluation of differences among trials. Prior treatment exposure was reported as the proportion of patients with any prior treatment or the proportion with prior DMT. A few trials examined treatment-naïve patients exclusively, such as Coles 2008 (Coles 2008). Among the rest, the reported proportions of patients with prior DMT were similar to the proportions of the RADIANCE and SUNBEAM trials.

These observations, along with the fact that most of these studies had been compared in prior analyses (ICER 2017, NICE 2017a, NICE 2018) led us to conclude that there was no evidence of clinically meaningful differences among the trials in the current evaluation. Detailed patient characteristics are provided in the table below.

[1] Rapidly Evolving Severe (RES) = ≥1 T1 Gd+ lesion AND ≥2 relapses in last year; High Disease Activity (HDA) = Treated with IFN or GA for ≥1 yr AND ≥1 relapse previous year while on therapy AND ≥1 T1 Gd+ lesion or ≥9 T2 lesions at baseline

Table 6 – Updated version of Table 8. Summary of patient characteristics for the included studies

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Boiko 2018	Placebo	12 mo	28	4 (median)							1 Year: 1.21 (0.42)	
	Glatiramer acetate (Generic), 20mg		61	5 (median)							1 Year: 1.28 (0.49)	
	Glatiramer acetate (Copaxone), 20mg		61	3 (median)							1 Year: 1.28 (0.64)	
Bornstein 1987	Placebo	24 mo	23	31.1	60			6.4		3.1	2 Years: 3.9	
	Glatiramer acetate (Copaxone), 20mg		25	30	56			4.9		2.9	2 Years: 3.8	
Cadavid 2009/BECOME	Glatiramer acetate (Copaxone), 20mg	2 yr	39	36 (22,55)	64			1.2		2		
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		36	36 (18,49)	75			0.9		2		

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Calabrese 2012	Glatiramer acetate (Copaxone), 20mg	2 yrs	48	38.9 (10.2)	72.9			5.5 (6.1)		2.1 (1.1)		
	Interferon beta-1a (Avonex) 30mcg		47	34.8 (9.6)	68			5.3 (5.1)		1.9 (0.8)		
	Interferon beta-1a (Rebif), 44mcg		46	35.9 (9.1)	69.5			5.7 (4.9)		1.9 (1.0)		
Calabresi 2014a/FREEDOMS II	Placebo	24 mo	355	40.1 (8.4)	81	73	IFN 59 GA 41 Nat 7		10.6 (7.9)	2.4 (1.3)	1 Year: 1.5 (0.9), 2 Years: 2.2 (1.5)	1.2 (3.2)
	Fingolimod (Gilenya), 0.5mg		358	40.6 (8.4)	77	74	IFN 61 GA 36 Nat 5		10.4 (8.0)	2.4 (1.3)	1 Year: 1.4 (0.9), 2 Years: 2.2 (1.4)	1.3 (3.4)
Calabresi 2014b/ADVANCE	Placebo	48 wks	500	36.3 (9.7)	72	17		3.5 (4.6)	6.3 (6.3)	2.44 (1.18)	1 Year: 1.6 (0.67), 3 Years: 2.6 (1.0)	1.6 (3.8)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Peg-Interferon beta-1a (Plegridy), 125mcg EOW		512	36.9 (9.8)	71	17		4.0 (5.1)	6.9 (6.6)	2.47 (1.26)	1 Year: 1.6 (0.6.7), 3 Years: 2.9 (0.99)	1.2 (3.4)
Cohen 2010/TRANSFORMS	Fingolimod (Gilenya), 0.5mg	12 mo	431	36.7 (8.8)	65.4	55.2	IFN 50.8 GA 13.2 Nat 0.9		7.5 (6.2)	2.24 (1.33)	1 Year: 1.5 (1.2), 2 Years: 2.3(2.2)	0.98 (2.81)
	Interferon beta-1a (Avonex) 30mcg		435	36 (8.3)	67.8	56.3	IFN 47.6 GA 15.4 Nat 0.2		7.4 (6.3)	2.19 (1.26)	1 Year: 1.5 (0.8), 2 Years: 2.3 (1.2)	1.06 (2.80)
Cohen 2012b/CARE-MS I	Alemtuzumab (Lemtrada), 12mg	24 mo	376	33.0 (8.03)	65				2.1 (1.4)	2.0 (0.81)	1 Year: 1.8 (0.8)	2.3 (5.1)
	Interferon beta-1a (Rebif), 44mcg		187	33.2 (8.48)	65				2.0 (1.3)	2.0 (0.79)	1 Year: 1.8 (0.8)	2.2 (4.9)
Cohen 2015/ GATE	Placebo	9 mo	84	32.6 (8.7)	67.9	88.1			5.7 (6.0)	2.7 (1.2)	2 Years: 1.9 (0.9)	2.8 (4.1)
	Glatiramer acetate (Copaxone), 20mg		357	33.8 (9)	66.7	82.6			6.4 (6.0)	2.7 (1.2)	2 Years: 1.8 (0.9)	2.5 (3.9)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Glatiramer acetate (generic), 20mg		353	32.6 (8.6)	66	84.1			5.5 (5.3)	2.6 (1.2)	2 Years: 1.9 (0.9)	2.5 (3.5)
Cohen 2016/ RADIANCE Part A	Placebo	24 wks	88	39.0 (8.7)	70			8.1 (7.0)	4.6 (5.1)	2.9 (1.3)	1 Year: 1.3 (0.6) 2 Years: 1.8 (1.0)	1.4 (3.4)
	Ozanimod, 0.5mg		87	38.1 (9.2)	69			6.0 (6.4)	6.0 (6.4)	2.9 (1.3)	1 Year: 1.5 (1.2) 2 Years: 2.0 (1.8)	0.9 (1.4)
	Ozanimod, 1.0mg		83	38.4 (9.8)	71			6.2 (5.8)	3.6 (4.4)	2.9 (1.2)	1 Year: 1.3 (0.7) 2 Years: 1.9 (1.1)	1.3 (2.8)
Coles 2008/CAMMS223	Alemtuzumab (Lemtrada), 12mg	36 mo	112	31.9 (8.0)	64.3		0			1.9 (0.74)		
	Interferon beta-1a (Rebif), 44mcg		111	32.8 (8.8)	64		0			1.9 (0.83)		
Coles 2012/CARE-MS II	Alemtuzumab (Lemtrada), 12mg	24 mo	426	34.8 (8.36)	66	100	multiple drugs listed		4.5 (2.68)	2.7 (1.26)	1 Year: 1.7 (0.86)	2.28 (6.02)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1a (Rebif), 44mcg		202	35.8 (8.77)	65	100			4.7 (2.86)	2.7 (1.21)	1 Year: 1.5 (0.75)	2.10 (4.95)
Comi 2001/EU/C GASG	Placebo	9 mo	120	34.0 (7.5)				8.3 (5.5)		2.4 (1.2)	2 Years: 2.5 (1.4)	4.4 (7.1)
	Glatiramer acetate (Copaxone), 40mg		119	34.1 (7.4)				7.9 (5.5)		2.3 (1.1)	2 Years: 2.8 (1.8)	4.2 (4.8)
Comi 2017/GOLDEN	Fingolimod (Gilenya), 0.5mg	18 mo	80	40.23 (9.09)	71.25	52.5		4.97 (6.67)		2.78 (1.34)	1 Year: 1.45 (0.79) 2 Years: 1.90 (0.84)	0.75 (1.15)
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		28	37.64 (9.29)	67.86	46.43		4.71 (6.47)		2.09 (1.05)	1 Year: 1.18 (0.48) 2 Years: 1.54 (0.84)	0.89 (1.91)
Confavreux 2014/TOWER	Placebo	48 wks	389	38.1 (9.1)	70	35	multiple drugs listed		7.64 (6.7)	2.69 (1.36)	1 Year: 1.4 (0.8), 2 Years: 2.1 (1.1)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Teriflunomide (Aubagio), 14mg		372	38.2 (9.4)	69	34			8.18 (6.73)	2.71 (1.35)	1 Year: 1.4 (0.7), 2 Years: 2.1 (1.2)	
	Teriflunomide (Aubagio), 7mg		408	37.4 (9.4)	74	30			8.18 (6.75)	2.71 (1.39)	1 Year: 1.4 (0.7) 2 Years: 2.1 (1.1)	
De Stefano 2010, 2012/ IMPROVE	Placebo	16 wks	60	35.2 (10.5)	70							
	Interferon beta-1a (Rebif), 44mcg		120	34.0 (7.8)	73							
Durelli 2002/INCOMIN	Interferon beta-1a (Avonex) 30mcg	24 mo	92	34.9 (7.9)	62			6.7 (5.4)		1.96 (0.7)	2 Years (annualized): 1.38 (0.52)	
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		96	38.8 (7.1)	68.8			5.9 (4.2)		1.97 (0.7)	2 Years (annualized): 1.52 (0.67)	
Etemadifar 2006	Interferon beta-1a (Avonex) 30mcg	24 mo	30	28.1 (1.2)	80			2.9 (2.3)		1.9 (1.1)	1 Year: 2.0 (0.8)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1a (Rebif), 44mcg		30	27.4 (1.2)	77			3.0 (2.2)		2.1 (1.0)	1 Year: 2.4 (1.0)	
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		30	29.9 (1.4)	70			3.7 (2.3)		1.9 (0.7)	1 Year: 2.2 (0.7)	
Fox 2012/ CONFIRM	Placebo	96 wks	363	36.9 (9.2)	69		31	4.8 (5.0)		2.6 (1.2)	1 Year: 1.4 (0.8)	
	Dimethyl fumarate (Tecfidera), 240mg (bid)		359	37.8 (9.4)	68		28	4.9 (5.1)		2.6 (1.2)	1 Year: 1.3 (0.6)	
	Glatiramer acetate (Copaxone), 20mg		350	36.7 (9.1)	71		29	4.4 (4.7)		2.6 (1.2)	1 Year: 1.4 (0.6)	
Giovannoni 2010/CLARITY	Placebo	96 wks	437	38.7 (9.9)	65.9		32.5	8.9 (7.4)		2.9 (1.3)		0.8 (2.1)
	Cladribine, 3.5 mg/kg		433	37.9 (10.3)	68.8		26.1	7.9 (7.2)		2.8 (1.2)		1.0 (2.7)
	Placebo	96 weeks	408	38.5 (9.1)	75	42		5.8 (5.8)		2.48 (1.24)	1 Year: 1.3 (0.7)	1.6 (3.4)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Gold 2012/DEFINE	Dimethyl fumarate (Tecfidera), 240mg (bid)		410	38.1 (9.1)	72.2	40		5.6 (5.4)		2.4 (1.29)	1 Year: 1.3 (0.7)	1.2 (3.3)
Hauser 2017a/OPERA I	Interferon beta-1a (Rebif), 44mcg	96 wks	411	36.9 (9.3)	66.2		28.6	3.71 (4.63)	6.25 (5.98)	2.75 (1.29)	1 Year: 1.33 (0.64)	
	Ocrelizumab (Ocrevus), 600mg		410	37.1 (9.3)	65.9		26.2	3.82 (4.80)	6.74 (6.37)	2.86 (1.24)	1 Year: 1.31 (0.65)	
Hauser 2017b/OPERA II	Interferon beta-1a (Rebif), 44mcg	96 wks	418	37.4 (9)	67		24.7	4.13 (5.07)	6.68 (6.13)	2.84 (1.38)	1 Year: 1.34 (0.73)	
	Ocrelizumab (Ocrevus), 600mg		417	37.2 (9.1)	65		27.1	4.15 (4.95)	6.72 (6.10)	2.78 (1.30)	1 Year: 1.32 (0.69)	
IFNb MSSG 1993	Placebo	2 yr	123	36 (0.6, SE)	71.5			3.9 (0.3, SE)		2.8 (0.1, SE)	2 Years: 3.6 (0.1, SE)	
	Interferon beta-1b (Betaseron; Betaferon), 8 mIU		124	35.2 (0.6, SE)	69.4			4.7 (0.4, SE)		3.0 (0.1, SE)	2 Years: 3.4 (0.2, SE)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Jacobs 1996/MS CRG	Placebo	104 wks	143	36.9 (0.64, SE)	72			6.4 (0.49, SE)		2.3 (0.07, SE)	1 Year: 1.2 (0.05, SE)	2.32 (0.37, SE)
	Interferon beta-1a (Avonex) 30mcg		158	36.7 (0.57, SE)	75			6.6 (0.46, SE)		2.4 (0.06, SE)	1 Year: 1.2 (0.05, SE)	3.17 (0.62, SE)
Johnson 1995/Copolymer 1 Trial	Placebo	24 mo	126	34.3 (6.5)	76.2			6.6 (5.1)		2.4 (1.3)	2 Years: 2.9 (1.1)	
	Glatiramer acetate (Copaxone), 20mg		125	34.6 (6)	70.4			7.3 (4.9)		2.8 (1.2)	2 Years: 2.9 (1.3)	
Kappos 2010/FREEDOMS	Placebo	24 mo	418	37.2 (8.6)	71.3		40.4		8.1 (6.4)	2.5 (1.3)	1 Year: 1.4 (0.7), 2 Years: 2.2 (1.2)	1.3 (2.9)
	Fingolimod (Gilenya), 0.5mg		425	36.6 (8.8)	69.6		42.6		8.0 (6.6)	2.3 (1.3)	1 Year: 1.5 (0.8), 2 Years: 2.1 (1.1)	1.6 (5.6)
Kappos 2011	Placebo	24 wks	54	38 (8.8)	67	30		2.7	4.8	3.2 (1.4)		1.6 (4.05)
	Interferon beta-1a (Avonex) 30mcg		54	38.1 (9.3)	59	31		3.3	5.3	3.1 (1.5)		2.3 (5.26)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Ocrelizumab (Ocrevus), 600mg		55	35.6 (8.5)	64	53		3.6	6.5	3.5 (1.5)		3.9 (9.88)
Khan 2013/GALA	Placebo	12 mo	461	38.1 (9.2)	67.9		13.7		7.6 (6.4)	2.7 (1.2)	1 Year: 1.3 (0.6), 2 Years: 1.9 (0.9)	1.4 (3.7)
	Glatiramer acetate (Copaxone), 40mg		943	37.4 (9.4)	68		13.6		7.7 (6.7)	2.8 (1.2)	1 Year: 1.3 (0.6), 2 Years: 1.9 (0.9)	1.7 (4.7)
Knobler 1993	Placebo	24 wks	7	34.5	71			7		3.1		
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		6	35.4	33			4.2		2.7		
Lublin 2013/CombiRx	Glatiramer acetate (Copaxone), 20mg	36 mo	259	39 (9.5)	71.4			1.0 (2.9)		1.9 (1.2)	1 Year: 1.6 (0.7)	4.6 (7.6)
	Interferon beta-1a (Avonex) 30mcg		250	37.6 (10.2)	69.2			1.4 (4.0)		2.0 (1.2)	1 Year: 1.7 (0.9)	4.1 (5.5)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Mikol 2008/REGARD	Glatiramer acetate (Copaxone), 20mg	96 wks	378	36.8 (9.5)	72					2.33 (1.31)		1.65 (4.7)
	Interferon beta-1a (Rebif), 44mcg		386	36.7 (9.8)	69					2.35 (1.28)		1.47 (4.95)
Mokhber 2015/ IRCT201404195280N16	Interferon beta-1a (Avonex) 30mcg	12 mo	20	31.11 (6.76)	60							
	Interferon beta-1a (Rebif), 44mcg		22	27.78 (8.01)	60.9							
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		23	28.95 (8.78)	72.7							
O'Connor 2006	Placebo	36 wks	61	39.2 (8.7)	67			4.4 (5.7), 8.6 (7.9)		2.5	1 Year: 1 3 Years: 3	2.1 (0.62, SE)
	Teriflunomide (Aubagio), 7mg		61	40.1 (9.3)	75			6.0 (5.6), 10.3 (8.1)		2.5	1 Year: 1 3 Years: 2	1.23 (0.6, SE)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Teriflunomide (Aubagio), 14mg		57	40.1 (9.1)	78.9			5.4 (6.2), 8.5 (7.1)		2.0	1 Year: 1, 3 Years: 3	2.32 (0.61, SE)
O'Connor 2009/BEYOND	Glatiramer acetate (Copaxone), 20mg	2 yr	448	35.2 (27,43, IQR)	68.3			5.1		2.28	1 Year: 1.6	1.8 (0,2) [median, (IQR)]
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		897	35.8 (28,43, IQR)	69.9			5.3		2.35	1 Year: 1.6	2.3 (0,2) [median, (IQR)[
O'Connor 2011/TEMSO	Placebo	108 wks	363	38.4 (9)	75.8		24.8		8.6 (7.1)	2.68 (1.34)	1 Year: 1.4 (0.7), 2 Years: 2.2 (1)	1.66 (3.55)
	Teriflunomide (Aubagio), 7mg		366	37.4 (9)	69.7		27.9		8.8 (6.8)	2.68 (1.34)	1 Year: 1.4 (0.7), 2 Years: 2.3 (1.2)	1.5 (3.96)
	Teriflunomide (Aubagio), 14mg		359	37.8 (8.2)	71		28.4		8.7 (6.7)	2.67 (1.24)	1 Year: 1.3 (0.7), 2 Years: 2.2 (1)	1.81 (5.17)
Panitch 2002/EVIDENCE	Interferon beta-1a (Rebif), 44mcg	48 weeks	339	38.3	74.9			6.5		2.3	2 Years: 2.6	1.9

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1a (Avonex) 30mcg		338	37.4	74.6			6.7		2.3	2 Years: 2.6	2.5
Polman 2006/AFFIRM	Placebo	2 yrs or more	315	36.7 (7.8)	67			6		2.3 (1.2)	1 Year: 1.5 (0.77)	2.0 (4.8)
	Natalizumab (Tysabri), 300mg		627	35.6 (8.5)	72			5		2.3 (1.2)	1 Year 1.53 (0.91)	2.2 (4.7)
PRISMS 1998	Placebo	24 mo	187	34.6	75			4.3		2.4 (1.2)	2 Years: 3 (1.3)	
	Interferon beta-1a (Rebif), 22mcg		189	34.8	67			5.4		2.5 (1.2)	2 Years: 3 (1.1)	
	Interferon beta-1a (Rebif), 44mcg		184	35.6	66			6.4		2.5 (1.3)	2 Years: 3 (1.1)	
RADIANCE Part B	Interferon beta-1a (Avonex) 30mcg	24 mo	441	35.1 (9.07)	68.9	92.3	28.6	3.63 (4.613)	6.36 (6.065)	2.49 (1.158)	1 Year: 1.3 (0.58), 2 Year: 1.8 (0.86)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Ozanimod, 0.5mg		439	35.4 (8.82)	65.4	92	29.8	3.5 (4.207)	6.23 (5.547)	2.48 (1.166)	1 Year: 1.4 (0.64), 2 Years: 1.8 (0.9)	
	Ozanimod, 1.0mg		433	36 (8.89)	67.2	92.8	28.4	3.97 (5.171)	6.92 (6.201)	2.55 (1.145)	1 Year: 1.3 (0.56), 2 Years: 1.7 (0.82)	
Saida 2012	Placebo	6 mo	57	35 (8.9)	68.4				8.2 (7.3)	2.1 (1.7)	1 Year: 1.7 (1.6), 2 Years 2.8 (3.0)	1.6 (3.05)
	Fingolimod (Gilenya), 0.5mg		57	35 (9)	70.2				8.2 (6.8)	2.3 (1.9)	1 Year: 1.4 (1.0), 2 Years: 2.2 (1.4)	1.2 (2.08)
Saida 2017	Placebo	24 weeks	47	35.1 (8.2)	68	85		5.1 (4.9)	6.8 (5.5)	2.1 (1.5)	1 Year: 1.9 (1.0)	0.7 (1.9)
	Natalizumab (Tysabri), 300mg		47	37.7 (8.6)	72	91		5.9 (5.0)	8.7 (5.7)	2.5 (1.6)	1 Year: 2.0 (1.2)	0.9 (2.7)
Saida 2019	Placebo	24 weeks	113	36.0 (7.5)	74	57				1.9 (1.3)	1 Year: 1.4 (0.7) 3 Years: 2.3 (1.5)	1.5 (3.2)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Dimethyl fumarate (Tecfidera), 240mg (bid)		111	37.3 (8.3)	70	57				2.2 (1.3)	1 Year: 1.4 (0.7) 3 Years: 2.5 (1.7)	1.6 (4.9)
Singer 2012/RE FORMS	Interferon beta-1a (Rebif), 44mcg	12 wks	65	40.26 (9.80)	70.8			1.01 (2.35)	4.51 (6.70)		1 Year: 1.36 (0.52) out of 55 w/relapse	
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		64	40.78 (9.56)	68.8			1.93 (4.02)	5.74 (6.66)		1 Year: 1.30 (0.46) out of 50 w/relapse	
SUNBEA M	Interferon beta-1a (Avonex) 30mcg	24 mo	448	35.9 (9.11)	67	95.3	33.7	3.71(4.36 1)	6.88 (5.877),	2.62 (1.138)	1 Year: 1.3 (0.55), 2 Years: 1.7 (0.84)	1.7 (3.22)
	Ozanimod, 0.5mg		451	36 (9.43)	69	92.5	29.3	3.70(4.51 8)	7.16 (6.255),	2.65 (1.135)	1 Year: 1.3 (0.57), 2 Years: 1.7 (0.84)	1.6 (2.95)
	Ozanimod, 1.0mg		447	34.8 (9.24)	63.3	94.4	28.6	3.60(4.19 3)	6.85 (6.449)	2.61 (1.160)	1 Year: 1.3 (0.57), 2 Years: 1.8 (0.86)	1.8 (3.41)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	% prior Tx	% prior DMT	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Vermersch 2014/TENERE	Interferon beta-1a (Rebif), 44mcg	48 wks	104	37 (10.6)	68.3		24.0a		7.7 (7.6)	2.0 (1.2)	1 Year: 1.2 (1.0), 2 Years: 1.7 (1.1)	
	Teriflunomide (Aubagio), 7mg		109	35.2 (9.2)	64.2		21.1a		7.0 (6.9)	2.0 (1.2)	1 Year: 1.3 (0.8), 2 Years: 1.7 (0.9)	
	Teriflunomide (Aubagio), 14mg		111	36.8 (10.3)	70.3		11.7a		6.6 (7.6)	2.3 (1.4)	1 Year: 1.4 (0.8), 2 Years: 1.7 (0.9)	
Vollmer 2014/BRAVO	Placebo	24 mo	450	37.5	71.3		6	1.2	4.7	2.5	1 Year: 1 (1,2) [median, (IQR)[2 Years: 2 (1,2) [median, (IQR)[	
	Interferon beta-1a (Avonex) 30mcg		447	38.5	68.7		9.4	1.4	5.3	2.5	1 Year: 1 (1,2) [median, (IQR)[2 Years: 2 (1,2) [median, (IQR)[	

Source: (Pharmerit International 2019a)

A11. <u>Priority question</u>: Please provide the following information:

a. The source of all data for each outcome in the NMAs in the company's submission (e.g. whether the data used are from a published trial report, from the ICER 2017 report, etc).

Data sources for ARR, CDP, and discontinuation outcomes are reported in the Appendix tables 1.1-1.4 (Pharmerit International 2019b). Data for AEs, serious AEs, and lesion counts were all taken from the trial publications (or CSR for RADIANCE and SUNBEAM). This tables are reproduced below.

Table 7 – Data input for ARR NMA (Table 1.1 from Appendix)

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Boiko 2018	Publication	Placebo	7	28	Glatiramer acetate (Copaxone), 20mg	22	122			
Bornstein 1987*	ICER[a]	Placebo	62	45.1	Glatiramer acetate (Copaxone), 20mg	16	47.5			
Cadavid 2009/BECOME*	ICER[b]	Glatiramer acetate (Copaxone), 20mg	23	70.59	Interferon beta-1b (Betaseron; Betaferon), 250mcg	25	68.04			
Calabrese 2012*	ICER[c]	Glatiramer acetate (Copaxone), 20mg	48	96	Interferon beta-1a (Avonex) 30mcg	47	94	Interferon beta-1a (Rebif), 44mcg	37	92
Calabresi 2014a/FREEDOMS II*	ICER[d]	Placebo	246	615	Fingolimod (Gilenya), 0.5mg	131	623.8			
Calabresi 2014b/ADVANCE*	ICER[e]	Placebo	167	420.9	Peg-Interferon beta-1a (Plegridy), 125mcg EOW	103	404.3			

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Cohen 2010/TRANSFORMS*	ICER[f]	Fingolimod (Gilenya), 0.5mg	68	424.6	Interferon beta-1a (Avonex) 30mcg	137	415.7			
Cohen 2012/CARE-MS I*	ICER[g]	Alemtuzumab (Lemtrada), 12mg	119	661.11	Interferon beta-1a (Rebif), 44mcg	122	312.82			
Cohen 2015/GATE	NICE	Placebo	24	61.88	Glatiramer acetate (Copaxone), 20mg	182	512.26			
Coles 2008/CAMM223*	ICER	Alemtuzumab (Lemtrada), 12mg	34	309.09	Interferon beta-1a (Rebif), 44mcg	89	247.22			
Cohen 2016/RADIANCE PART A(Cohen 2016)(Cohen 2016)(Cohen 2016)(Cohen 2016)	Publication[h]	Placebo	22	44	Ozanimod, 0.5 mg	15	43.5	Ozanimod, 1.0 mg	10	41.5
Coles 2012/CARE-MS II*	ICER, NICE	Alemtuzumab (Lemtrada), 12mg	236	907.69	Interferon beta-1a (Rebif), 44mcg	201	386.54			

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Confavreux 2014/TOWER*	ICERi	Placebo	296	608.4	Teriflunomide (Aubagio), 7mg	235	614	Teriflunomide (Aubagio), 14mg	177	573.6
De Stefano 2010/IMPROVE	NICE	Placebo	6	18.14	Interferon beta-1a (Rebif), 44mcg	5	35.96			
Durelli 2002/INCOMIN*	ICER[j]	Interferon beta-1a (Avonex) 30mcg	126	180	Interferon beta-1b (Betaseron; Betaferon), 250mcg	95	190			
Etemadifar 2006*	ICER[k]	Interferon beta-1a (Avonex) 30mcg	36	60	Interferon beta-1b (Betaseron; Betaferon), 250mcg	21	60	Interferon beta-1a (Rebif), 44mcg	18	60
Comi 2001/EU/CGASG	NICE	Placebo	91	75.21	Glatiramer acetate (Copaxone), 20mg	61	75.31			
Comi 2017/GOLDEN	Publication[l]	Fingolimod (Gilenya), 0.5mg	20	166.67	Interferon beta-1b (Betaseron; Betaferon), 250mcg	22	56.41			

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Fox 2012/CONFIRM*	ICER, NICE	Placebo	212	561.43	Dimethyl fumarate (Tecfidera), 240mg (bid)	124	552.99	Glatiramer acetate (Copaxone), 20mg	163	569.62
Giovannoni 2010/CLARITY	NICE	Placebo	252	741.1	Cladribine, 3.5 mg/kg	109	767.1			
Gold 2012/DEFINE*	ICER, NICE	Placebo	246	612.35	Dimethyl fumarate (Tecfidera), 240mg (bid)	128	628.61			
Hauser 2008/HERMES*	ICER	Placebo	19	27.2	Rituximab (Rituxan), 1000mg	21	59.2			
Hauser 2017a/OPERA I*	ICER	Interferon beta-1a (Rebif), 44mcg	219	756.2	Ocrelizumab (Ocrevus), 600mg	121	754.3			
Hauser 2017b/OPERA II*	ICER	Interferon beta-1a (Rebif), 44mcg	223	769.1	Ocrelizumab (Ocrevus), 600mg	123	767.2			
IFNB Multiple Sclerosis Study Group 1993*	ICER, NICE	Placebo	266	209.2	Interferon beta-1b (Betaseron; Betaferon), 250mcg	173	207			

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Jacobs 1996*	ICER	Placebo	225	274	Interferon beta-1a (Avonex) 30mcg	196	293			
Johnson 1995/Copolymer1 Trial*	ICER[m]	Placebo	210	250	Glatiramer acetate (Copaxone), 20mg	161	273			
Kappos 2010/FREEDOMS*	ICER[n]	Placebo	307	766.3	Fingolimod (Gilenya), 0.5mg	146	810.3			
Kappos 2011	ICER, publication[o]	Placebo	16	28.73	Interferon beta-1a (Avonex) 30mcg	9	24.73	Ocrelizumab (Ocrevus), 600mg	3	23.62
Khan 2013/GALA*	ICER[p]	Placebo	223	442.5	Glatiramer acetate (Copaxone), 40mg	293	884.4			
Knobler 1993	NICE	Placebo	5	2.8	Interferon beta-1b (Betaseron; Betaferon), 250mcg	2	2.3			
Lublin 2013/CombiRx*	ICER, NICE	Glatiramer acetate (Copaxone), 20mg	70	650.7	Interferon beta-1a (Avonex) 30mcg	97	604.4			

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Mikol 2008/REGARD*	ICER, NICE	Glatiramer acetate (Copaxone), 20mg	194	669.5	Interferon beta-1a (Rebif), 44mcg	201	669.5			
O'Connor 2006	NICE	Placebo	33	40.85	Teriflunomide (Aubagio), 7mg	24	41.19	Teriflunomide (Aubagio), 14mg	19	35.31
O'Connor 2009/BEYOND*	ICER, NICE	Glatiramer acetate (Copaxone), 20mg	374	1099.5	Interferon beta-1b (Betaseron; Betaferon), 250mcg	814	2260			
O'Connor 2011/TEMSO*	ICER[q]	Placebo	335	627.7	Teriflunomide (Aubagio), 7mg	233	633.7	Teriflunomide (Aubagio), 14mg	227	615
Panitch 2002/EVIDENCE*	ICER, NICE	Interferon beta-1a (Avonex) 30mcg	195	304.2	Interferon beta-1a (Rebif), 44mcg	165	304.71			
Polman 2006/AFFIRM*	ICER[r]	Placebo	422	578	Natalizumab (Tysabri), 300mg	276	1200			
PRISMS 1998*	ICER[s]	Placebo	479	374.22	Interferon beta-1a (Rebif), 22mcg	344	378.02	Interferon beta-1a (Rebif), 44mcg	318	365.52

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
RADIANCE Part B	CSR	Interferon beta-1a (Avonex) 30mcg	236	809.88	Ozanimod, 0.5mg	186	810.26	Ozanimod, 1.0mg	143	816.81
Saida 2012	NICE	Placebo	27	27	Fingolimod (Gilenya), 0.5mg	13	26.25			
Saida 2017	NICE	Placebo	36	20.7	Natalizumab (Tysabri), 300mg	11	21.39			
Saida 2019/APEX	Publication[h]	Placebo	34	52.15	Dimethyl fumarate (Tecfidera), 240mg (bid)	23	51.23			
Singer 2012/REFORMS	NICE	Interferon beta-1b (Betaseron; Betaferon), 250mcg	7	14.61	Interferon beta-1a (Rebif), 44mcg	10	13.92			
SUNBEAM	CSR	Interferon beta-1a (Avonex) 30mcg	184	504.92	Ozanimod, 0.5mg	125	510.72	Ozanimod, 1.0mg	97	507.59
Vermersch 2014/TENERE*	ICER[t]	Interferon beta-1a (Rebif), 44mcg	25	112.1	Teriflunomide (Aubagio), 7mg	58	136.2	Teriflunomide (Aubagio), 14mg	35	132.2

Study	Data source	Arm 1	Number of relapses	Person-years exposure	Arm 2	Number of relapse	Person-years exposure	Arm 3	Number of relapse	Person-years exposure
Vollmer 2014/BRAVO*	ICER[u]	Placebo	275	809	Interferon beta-1a (Avonex) 30mcg	215	825			

Source: (Pharmerit International 2019b)

*Included in the ICER analysis of ARR

aNICE used 46 and 47 person-years of exposure, respectively

bNICE used 69.7 and 67.57 person-years of exposure, respectively

cNICE used 52, 51, 40 number of relapses and 103, 102, 101 person-years of exposure, respectively

dNICE used 623.81 person-years of exposure

eNICE used 181, 116 number of relapses and 445.25, 425.74 person-years of exposure, respectively.

fNICE used 89, 179 relapses and 423.81, 416.28 person-years of exposure, respectively

gNICE has the same data

hCalculated from ARR and sample size, based on 0.6 mo of follow-up.

iNICE used 592, 602.56, 553.125 person-years of exposure, respectively

jNICE has the same data

kNICE used 57, 65, 66 for relapses and 60, 90, 60 for person-years of exposure, respectively

lCalculated from reported number of relapses and ARR

mNICE used 272.88 rather than 273

nNICE used 246, 131 for number of relapses and 615, 623.81 person-years of exposure, respectively

oNICE used 24.38, 28.84 for person-years of experience, respectively, for placebo and Avonex.

pNICE used 215, 290 for number of relapses and 445.5, 901 person-years of experience, respectively

qNICE used 620.37, 629.73, 613.51 for person-years of experience, respectively

rNICE used 472, 204 for number of relapses and 738, 1338 person-years of exposure, respectively

sNICE used 354, 366, 363 for person-years of experience, respectively

tNICE used 29, 63, 39 for number of relapses and 126.09, 143.16, 144.44 for person-years of experience, respectively

uNICE used 808.82, 826.52 for person-years of experience, respectively.

Table 8 – Data input for CDP12* (Table 1.2 from Appendix)

Study	Data Source	Duration (yrs)	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Bornstein 1987	NICE	2	Placebo	11/23	47.8	Glatiramer acetate (Copaxone), 20mg	5/25	20.0			
Calabresi 2014a/FREEDOMS II	ICER, NICE	2	Placebo	103/355	29.0	Fingolimod (Gilenya), 0.5mg	91/358	25.4			
Calabresi 2014b/ADVANCE	ICER	2	Placebo	50/500	10.0	Peg-Interferon beta-1a (Plegridy), 125mcg EOW	31/512	6.1			
Cohen 2010/TRANFORMS	ICER[a]	2	Fingolimod (Gilenya), 0.5mg	25/429	5.8	Interferon beta-1a (Avonex) 30mcg	34/431	7.9			
Coles 2008/CAMMS223	ICER[b]	3	Alemtuzumab (Lemtrada), 12mg	16/112	14.3	Interferon beta-1a (Rebif), 44mcg	30/111	27.0			
Confavreux 2014/TOWER	ICER[c]	2	Placebo	76/388	19.6	Teriflunomide (Aubagio), 7mg	86/407	21.1	Teriflunomide (Aubagio), 14mg	58/370	15.7
Fox 2012/CONFIRM	ICER[d]	2	Placebo	62/363	17.1	Dimethyl fumarate (Tecfidera), 240mg (bid)	47/359	13.1	Glatiramer acetate (Copaxone), 20mg	56/350	16
Giovannoni 2010/CLARITY	Publication[e]	2	Placebo	90/437	20.6	Cladribine, 3.5 mg/kg	62/433	14.3			
Gold 2012/DEFINE	ICER[f]	2	Placebo	110/408	27.0	Dimethyl fumarate (Tecfidera), 240mg (bid)	65/409	15.9			
Hauser 2017a/OPERAI	ICER[g]	2	Interferon beta-1a (Rebif), 44mcg	53/411	12.9	Ocrelizumab (Ocrevus), 600mg	34/410	8.3			

Study	Data Source	Duration (yrs)	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Hauser 2017b/OPERA II	ICER[g]	2	Interferon beta-1a (Rebif), 44mcg	73/418	17.5	Ocrelizumab (Ocrevus), 600mg	47/417	11.3			
IFNb MSSG 1993	ICER[h]	2	Placebo	56/122	45.9	Interferon beta-1b (Betaseron; Betaferon), 8 mIU	43/122	35.2			
Johnson 1995/Copolymer 1 trial	ICER, NICE	2	Placebo	31/126	24.6	Glatiramer acetate (Copaxone), 20mg	27/125	21.6			
Kappos 2010/FREEDOMS	ICER, NICE	2	Placebo	101/418	24.2	Fingolimod (Gilenya), 0.5mg	75/425	17.6			
Khan 2013/GALA	ICER	1	Placebo	17/461	3.7	Glatiramer acetate (Copaxone), 40mg	42/943	4.5			
O'Connor 2009/BEYOND	ICER[i]	2	Glatiramer acetate (Copaxone), 20mg	90/448	20.1	Interferon beta-1b (Betaseron; Betaferon), 250mcg	188/897	21.0			
O'Connor 2011/TEMSO	NICE[a]	2	Placebo	99/363	27.3	Teriflunomide (Aubagio), 7mg	79/365	21.6	Teriflunomide (Aubagio), 14mg	72/358	20.1
Panitch 2002/EVIDENCE	ICER	1	Interferon beta-1a (Rebif), 44mcg	43/339	12.7	Interferon beta-1a (Avonex) 30mcg	49/338	14.5			
Polman 2006/AFFIRM	ICER, NICE	2	Placebo	91/315	28.9	Natalizumab (Tysabri), 300mg	107/627	17.1			
PRISMS 1998/PRISMS	ICER[j]	2	Placebo	77/187	41.2	Interferon beta-1a (Rebif), 22mcg	64/189	33.9	Interferon beta-1a (Rebif), 44mcg	54/184	29.3
RADIANCE PART B	CSR	2	Interferon beta-1a (Avonex) 30mcg	50/441	11.3	Ozanimod, 0.5mg	41/439	9.3	Ozanimod, 1.0mg	54/433	12.5
SUNBEAM	CSR	1.13	Interferon beta-1a (Avonex) 30mcg	19/448	4.2	Ozanimod, 0.5mg	17/451	3.8	Ozanimod, 1.0mg	13/447	2.9

Study	Data Source	Duration (yrs)	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Vollmer 2014/BRAVO	ICER, NICE	3	Placebo	60/450	13.3	Interferon beta-1a (Avonex) 30mcg	46/447	10.3			

Source: (Pharmerit International 2019b)

*The NICE Cladribine assessment frequently used denominators including patients randomized, but never receiving treatment. The ICER assessment (and the current assessment) excluded these patients

aCalculated from Kaplan-Meier curve

bNICE used 11/113, 24/111 respectively

cData from Figure 2; NICE used 76/389, 86/408, 58/372

dNICE used 62/363, 47/362, 56/360, respectively

eWeek 0-96 patients are reported in post-hoc analysis; NICE used 103/437, 65/433, respectively

fNICE used 89/410, 57/411, respectively

gITT results reported in supplement

hNICE used 56/123, 43/124 respectively

iNICE used 92/448,244/857, respectively

jNICE used 68/187, 49/189, 47/184, respectively

Table 9 – Data input for CDP24* (Table 1.3 from Appendix)

Study	Data Source	Duration (yrs)	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Cadavid 2009/BECOME	NICE	2	Glatiramer acetate (Copaxone), 20mg	6/39	15.4	Interferon beta-1b (Betaseron; Betaferon), 250mcg	4/36	11.1			
Calabresi 2014a/FREEDOMS II	ICER, NICE	2	Placebo	63/355	17.7	Fingolimod (Gilenya), 0.5mg	49/358	13.7			
Cohen 2012b/CARE-MS I	ICER[a]	2	Interferon beta-1a (Rebif), 44mcg	20/187	10.7	Alemtuzumab (Lemtrada), 12mg	30/376	8.0			

Study	Data Source	Duration (yrs)	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Coles 2008/CAMMS223	ICER[b]	3	Interferon beta-1a (Rebif), 44mcg	24/111	21.6	Alemtuzumab (Lemtrada), 12mg	8/112	7.1			
Coles 2012/CARE-MS II	ICER[c]	2	Interferon beta-1a (Rebif), 44mcg	40/202	19.8	Alemtuzumab (Lemtrada), 12mg	54/426	12.7			
Confavreux 2014/TOWER	NICE	2	Placebo	46/388	11.9	Teriflunomide (Aubagio), 7mg	61/407	15.0	Teriflunomide (Aubagio), 14mg	43/370	11.6
Durelli 2002/INCOMIN	ICER, NICE	2	Interferon beta-1a (Avonex) 30mcg	28/92	30.4	Interferon beta-1b (Betaseron; Betaferon), 250mcg	13/96	13.5			
Fox 2012/CONFIRM	ICER[d]	2	Placebo	45/363	12.4	Dimethyl fumarate (Tecfidera), 240mg (bid)	28/359	7.8	Glatiramer acetate (Copaxone), 20mg	38/350	10.9
Giovannoni 2010/CLARITY	Publication[e]	2	Placebo	56/366	15	Cladribine, 3.5 mg/kg	35/393	8.9			
Gold 2012/DEFINE	ICER[f]	2	Placebo	69/408	16.9	Dimethyl fumarate (Tecfidera), 240mg (bid)	52/409	12.7			
Hauser 2017a/OPERAI	ICER[g]	2	Interferon beta-1a (Rebif), 44mcg	43/411	10.5	Ocrelizumab (Ocrevus), 600mg	27/410	6.6			
Hauser 2017b/OPERAII	ICER[g,h]	2	Interferon beta-1a (Rebif), 44mcg	56/418	13.4	Ocrelizumab (Ocrevus), 600mg	36/417	8.6			
IFNb MSSG 1993	Publication[i]	3	Placebo	34/122	27.9	Interferon beta-1b (Betaseron; Betaferon), 8 mIU	25/122	20.5			
Jacobs 1996/MSCRG	ICER, NICE	2	Placebo	50/143	35.0	Interferon beta-1a (Avonex) 30mcg	35/158	22.2			

Study	Data Source	Duration (yrs)	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Kappos 2010/FREEDOMS	ICER, NICE	2	Placebo	79/418	18.9	Fingolimod (Gilenya), 0.5mg	53/425	18.6			
Lublin 2013/CombiRx	ICER	3	Glatiramer acetate (Copaxone), 20mg	61/246	24.8	Interferon beta-1a (Avonex) 30mcg	52/241	25.3			
Mikol 2008/REGARD	ICER, NICE	2	Glatiramer acetate (Copaxone), 20mg	33/378	8.7	Interferon beta-1a (Rebif), 44mcg	45/386	8.5			
O'Connor 2011/TEMSO	ICER[i]	2	Placebo	68/363	18.7	Teriflunomide (Aubagio), 7mg	51/365	18.6	Teriflunomide (Aubagio), 14mg	49/358	13.7
Panitch 2002/EVIDENCE	ICER	1	Interferon beta-1a (Rebif), 44mcg	20/339	5.9	Interferon beta-1a (Avonex) 30mcg	28/338	8.3			
Polman 2006/AFFIRM	ICER, NICE	2	Placebo	72/315	22.9	Natalizumab (Tysabri), 300mg	69/627	1.5			
RADIANCE PART B	CSR	2	Interferon beta-1a (Avonex) 30mcg	29/441	6.6	Ozanimod, 0.5mg	32/439	6.6	Ozanimod, 1.0mg	42/433	9.7
SUNBEAM	CSR	1.13	Interferon beta-1a (Avonex) 30mcg	7/448	1.6	Ozanimod, 0.5mg	11/451	1.6	Ozanimod, 1.0mg	9/447	2.0
Vollmer 2014/BRAVO	ICER, NICE	2	Placebo	46/450	10.2	Interferon beta-1a (Avonex) 30mcg	35/447	7.8			

Source: (Pharmerit International 2019b)

*The NICE Cladribine assessment frequently used denominators including patients randomized, but never receiving treatment. The ICER assessment (and the current assessment) excluded these patients

aNICE used 21/195, 30/386, respectively

bNICE used 19/111, 4/113, respectively

cNICE used 43/231, 54/436, respectively

dNICE used 28/362 rather than 28/359, and 38/360 instead of 38/350

eWeek 0-96 patients are reported in post-hoc analysis (Giovannoni 2011(Giovannoni 2011))

fNICE used 69/410, 52/411

gITT results reported in supplement;
hNICE used 48/418, 33/417, respectively
iICER used 56/122, 43/122, respectively, which are the CDP12 data from the NICE cladribine assessment. These values are reported in the study.
jNICE used 51/366 rather than 51/365 and 49/359 rather than 49/358.

Table 10 –: Data input for discontinuations (Table 1.4 from Appendix)

Study	Data Source	Study Duration	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Boiko 2017	Publication		Placebo	4/31	12.9	Glatiramer acetate (Copaxone), 20mg	15/124	12.1			
Cadavid 2009/ BECOME	Publication	2 yr	Glatiramer acetate (Copaxone), 20mg	8/39	20.5	Interferon beta-1b (Betaseron; Betaferon), 250mcg	11/36	30.6			
Calabresi 2014a/ FREEDOMS II	Publication	24 mo	Placebo	100/355	28.2	Fingolimod (Gilenya), 0.5mg	86/358	24.0			
Calabresi 2014b/ ADVANCE	NCT	48 wk	Placebo	44/500	8.8	Peg-Interferon beta-1a (Plegridy), 125mcg EOW	76/515	14.8			
Cohen 2010/ TRANSFORMS	NCT	12 mo	Fingolimod (Gilenya), 0.5mg	33/431	7.7	Interferon beta-1a (Avonex) 30mcg	49/435	11.4			
Cohen 2012b/ CARE-MS I	Publication	24 mo	Alemtuzumab (Lemtrada), 12mg	24/386	6.2	Interferon beta-1a (Rebif), 44mcg	31/195	15.9			
Cohen 2015/ GATE	Publication	9 mo	Placebo	3/84	3.6	Glatiramer acetate (Generic), 20mg	58/712	8.2			
Cohen 2016/RADIANCE PART A(Cohen 2016)(Cohen 2016)(Cohen 2016)(Cohen 2016)	Publication	24 wk	Placebo	3/88	3.4	Ozanimod, 0.5 mg	2/87	2.3	Ozanimod, 1.0 mg	1/83	1.1

Study	Data Source	Study Duration	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Coles 2008/ CAMM223	Publication	36 mo	Alemtuzumab (Lemtrada), 12mg	19/113	16.8	Interferon beta-1a (Rebif), 44mcg	45/111	40.5			
Coles 2012/ CARE-MS II	NCT	24 mo	Alemtuzumab (Lemtrada), 12mg	20/436	4.6	Interferon beta-1a (Rebif), 44mcg	56/231	27.7			
Comi 2001/European and Canadian Glatiramer trial	Publication	9 mo	Placebo	7/120	5.8	Glatiramer acetate (Copaxone), 40mg	7/119	5.9			
Comi 2017/GOLDEN	Publication		Fingolimod (Gilenya), 0.5mg	9/106	8.4	Interferon beta-1b (Betaseron; Betaferon), 250mcg	21/51	41.1			
Confavreux 2014/ TOWER	NCT	48 wk	Placebo	126/389	32.4	Teriflunomide (Aubagio), 7mg	135/408	33.1	Teriflunomide (Aubagio), 14mg	128/372	34.4
Durelli 2002/ INCOMIN	Publication	24 mo	Interferon beta-1a (Avonex) 30mcg	19/92	20.7	Interferon beta-1b (Betaseron; Betaferon), 250mcg	11/96	11.5			
Fox 2012/ CONFIRM	Publication	96 wk	Placebo	85/363	23.4	Dimethyl fumarate (Tecfidera), 240mg (bid)	78/362	21.6	Glatiramer acetate (Copaxone), 20mg	68/360	18.9
Giovannoni 2010/ CLARITY	Publication	96 wk	Placebo	57/437	13.0	Cladribine, 3.5 mg/kg	35/433	8.1			
Gold 2012/ DEFINE	Publication	96 wk	Placebo	93/410	22.7	Dimethyl fumarate (Tecfidera), 240mg (bid)	96/411	23.4			
Hauser 2008/ HERMES	Publication	48 wk	Placebo	14/35	40.0	Rituximab (Rituxan), 1000mg	11/69	15.9			
Hauser 2017a/ OPERA I	Publication	96 wk	Interferon beta-1a (Rebif), 44mcg	71/411	17.3	Ocrelizumab (Ocrevus), 600mg	44/410	10.7			
Hauser 2017b/ OPERA II	Publication	96 wk	Interferon beta-1a (Rebif), 44mcg	98/418	23.4	Ocrelizumab (Ocrevus), 600mg	57/417	13.7			

Study	Data Source	Study Duration	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
IFNB Multiple Sclerosis Study Group 1993	Publication	2 yr	Placebo	23/112	20.5	Interferon beta-1b (Betaseron; Betaferon), 250mcg	24/115	20.9			
Jacobs 1996	Publication	104 wk	Placebo	9/143	6.3	Interferon beta-1a (Avonex) 30mcg	14/158	8.9			
Kappos 2010/ FREEDOMS	Publication	24 mo	Placebo	86/418	20.6	Fingolimod (Gilenya), 0.5mg	56/425	13.2			
Kappos 2011	Publication	24 wk	Placebo	0/54	0	Interferon beta-1a (Avonex) 30mcg	4/55	7.3	Ocrelizumab (Ocrevus), 600mg	5/56	8.9
Khan 2013/ GALA	Publication	12 mo	Placebo	31/461	6.7	Glatiramer acetate (Copaxone), 40mg	84/943	8.9			
Lublin 2013/ CombiRx	Publication	36 mo	Glatiramer acetate (Copaxone), 20mg	36/259	13.9	Interferon beta-1a (Avonex) 30mcg	56/250	22.4			
Mikol 2008/ REGARD	Publication	96 wk	Glatiramer acetate (Copaxone), 20mg	54/378	13.6	Interferon beta-1a (Rebif), 44mcg	85/386	22.0			
Mokhber 2015	Publication	12 mo	Interferon beta-1a (Rebif), 44mcg	3/23	13.0	Interferon beta-1a (Avonex) 30mcg	3/23	13.0			
O'Connor 2006	Publication	36 wk	Placebo	4/61	6.6	Teriflunomide (Aubagio), 7mg	3/61	4.9	Teriflunomide (Aubagio), 14mg	12/57	21.1
O'Connor 2009/ BEYOND	Publication	2 yr	Glatiramer acetate (Copaxone), 20mg	74/448	16.5	Interferon beta-1b (Betaseron; Betaferon), 250mcg	113/897	12.6			
O'Connor 2011/ TEMSO	NCT	108 wk	Placebo	104/363	28.7	Teriflunomide (Aubagio), 7mg	92/366	25.1	Teriflunomide (Aubagio), 14mg	96/359	26.7
Panitch 2002/ EVIDENCE	Publication	48 wk	Interferon beta-1a (Avonex) 30mcg	25/339	7.4	Interferon beta-1a (Rebif), 44mcg	21/338	6.2			
Polman 2006/ AFFIRM	Publication	2 yr	Placebo	34/315	10.8	Natalizumab (Tysabri), 300mg	52/627	8.3			
PRISMS 1998	Publication	24 mo	Placebo	17/187	9.1	Interferon beta-1a (Rebif), 22mcg	22/189	11.6	Interferon beta-1a (Rebif), 44mcg	19/184	10.3
RADIANCE PART B	CSR	24 mo	Interferon beta-1a (Avonex) 30mcg	65/441	14.7	Ozanimod, 0.5mg	65/439	14.8	Ozanimod, 1.0mg	45/433	10.4

Study	Data Source	Study Duration	Arm 1	r/N	%	Arm 2	r/N	%	Arm 3	r/N	%
Saida 2012	Publication	6 mo	Placebo	6/57	10.5	Fingolimod (Gilenya), 0.5mg	9/57	15.8			
Saida 2017	Publication	24 wk	Placebo	4/47	8.5	Natalizumab (Tysabri), 300mg	1/47	2.1			
Saida 2019/APEX	Publication		Placebo	6/113	5.3	Dimethyl fumarate (Tecfidera), 240mg (bid)	6/111	5.4			
Singer 2012/ REFORMS	Publication	12 wk	Interferon beta-1b (Betaseron; Betaferon), 250mcg	1/64	1.6	Interferon beta-1a (Rebif), 44mcg	9/65	13.8			
SUNBEAM	CSR	1.13 yrs	Interferon beta-1a (Avonex) 30mcg	36/448	8.0	Ozanimod, 0.5mg	26/451	5.8	Ozanimod, 1.0mg	29/447	6.5
Vermersch 2014/TENERE	Publication	48 wk	Interferon beta-1a (Rebif), 44mcg	33/104	31.7	Teriflunomide (Aubagio), 7mg	20/109	18.3	Teriflunomide (Aubagio), 14mg	22/111	19.8
Vollmer 2014/ BRAVO	Publication	24 mo	Placebo	91/449	20.3	Interferon beta-1a (Avonex) 30mcg	69/442	15.6			

Source: (Pharmerit International 2019b)

b. Details of which studies included the annualised relapse rate (ARR) outcome directly and for which studies ARR was estimated according to the methods described on pages 19 to 20 of the Pharmerit International 2019 report.

This information is recorded in footnotes of the Appendix Table 1.1 (see footnotes of Table 7). The ICER and NICE reports were used as a data source for the ARR data used in the NMA conducted by Celgene. For the APEX study, the number of relapses was estimated from the reported ARR and follow-up time/sample size (Saida 2019). The Boiko 2018 study reported the absolute number of relapses, and person-years were estimated as number of patients multiplied by study duration (Boiko 2018). The GOLDEN study reported the absolute number of relapses and ARR, from which follow-up time was calculated (Comi 2017).

A12. <u>Priority question</u>: There appears to be an error in Table 27 of the company submission. The results for 'CDP-6M combined' for ozanimod compared with placebo and ozanimod compared with interferon beta-1a 30µg do not match the "combined" results reported in Table 3 of the Pharmerit International 2019c report, they seem to correspond to the "class based" results. Please confirm whether these are typographical errors in Table 27 of the company submission.

This was a typographical error. The results for combined CDP-6M in the submission were incorrectly pasted from the Pharmerit International 2019 report. The numbers should be a direct copy from the table on page 9 in the report; Section 1.4 Key Results Table: Summary of Key Efficacy and Safety Outcomes, ozanimod 1.0 mg vs comparator, median (95% CrI). The table is reproduced below.

Table 11 – Summary of key efficacy and safety outcomes of ozanimod 1 mg vs comparator

Comparator	ARR, Rate ratio (95% CrI)	CDP-3M, Annualized HR (95% CrI)	CDP-6M, Annualized HR (95% CrI)	CDP-3M and CDP-6M combined Annualized HR (95% CrI)	Discontinuation, Annualized HR (95% CrI)	AE, Odds ratio (95% CrI)	Serious AE Odds ratio (95% CrI)
Placebo	0.48 (0.4, 0.57)	[redacted]	[redacted]	[redacted]	[redacted]	0.98 (0.74, 1.32)	0.84 (0.49, 1.44)
Interferon beta-1a, 30µg	0.57 (0.48, 0.66)	[redacted]	[redacted]	[redacted]	[redacted]	0.53 (0.43, 0.65)	1.07 (0.68, 1.69)
Interferon beta-1a, 22µg	0.68 (0.54, 0.85)	[redacted]	[redacted]	[redacted]	[redacted]	--	--
Interferon beta-1b, 250µg	0.7 (0.58, 0.85)	[redacted]	[redacted]	[redacted]	[redacted]	2.08 (0.89, 4.89)	1.38 (0.72, 2.65)
Teriflunomide, 14mg	0.72 (0.56, 0.93)	[redacted]	[redacted]	[redacted]	[redacted]	0.77 (0.51, 1.16)	0.77 (0.42, 1.42)
Glatiramer acetate, 20mg	0.72 (0.58, 0.89)	[redacted]	[redacted]	[redacted]	[redacted]	1.2 (0.79, 1.83)	1.15 (0.65, 2.02)
Interferon beta-1a, 44 µg	0.72 (0.6, 0.87)	[redacted]	[redacted]	[redacted]	[redacted]	0.66 (0.34, 1.25)	0.95 (0.47, 1.9)
Glatiramer acetate, 40mg	0.72 (0.6, 0.87)	[redacted]	[redacted]	[redacted]	[redacted]	0.61 (0.42, 0.89)	0.75 (0.36, 1.54)

Peg-Interferon beta-1a, 125µg EOW	0.74 (0.55, 1.01)	[redacted]	[redacted]	[redacted]	[redacted]	0.32 (0.19, 0.53)	1.26 (0.66, 2.42)
Dimethyl fumarate, 240mg (bid)	0.88 (0.7, 1.1)	[redacted]	[redacted]	[redacted]	[redacted]	0.58 (0.36, 0.91)	1.07 (0.6, 1.9)

Source: (Pharmerit International 2019a, Pharmerit International 2019c)

ARR: Annualised Relapse Rate; bid: twice a day; CDP-3: Confirmed Disease Progression at 3 months; CDP-6: Confirmed Disease Progression at 6 months; CrI: Credible Interval; HR: Hazard ratio; µg: microgram; mg: milligram; OR: Odds rati

A13. The ERG notes that within Table 9, Appendix D1.2 to the company submission, in addition to placebo, two studies (Boiko 2018 and Cohen 2015) include glatiramer acetate (Copaxone) 20mg and glatiramer acetate (generic) 20mg. Please confirm whether these glatiramer acetate 20mg treatment arms were pooled to form a single GA_20 node in the networks these studies are included in or whether only the data from glatiramer acetate (Copaxone) 20mg were used.

For the GA-20 node in the NMA, data from Boiko 2018 and Cohen 2015 were combined into a single arm for the ARR, discontinuation, and AE outcomes (Cohen 2015, Boiko 2018). For lesion count outcomes, each arm of the Boiko 2018 study was analysed separately.

A14. The company submission states that 22 studies were included in the NMA of CDP-3M (Appendix D1.3.2) and 26 studies were included in the NMA of adverse events (Appendix D1.3.4). However, from Table 9 of Appendix D1.2 it appears that CDP-3M data were available for 23 studies and adverse event data were available for 28 studies. Please clarify these discrepancies and how many studies were included within the NMAs for these outcomes. If any studies were excluded please provide justification.

This is a typographical error. There are 28 studies in the adverse event and 23 in the CDP-3M analyses. The networks for each are correct as is Table 9 of Appendix D1.2.

A15. The ERG notes that the methods for evaluating heterogeneity (Q-statistic and I-squared statistics) are appropriate for meta-analysis rather than for network meta-analysis. A heterogeneity (tau) parameter can be directly estimated within Bayesian random-effects NMA models and the ERG considers this parameter to be a more appropriate statistical measure of heterogeneity for network meta-analysis. Please provide a heterogeneity parameter (and 95% credible interval) for random-effects NMAs for all outcomes.

The heterogeneity parameters for both fixed-effects and random effects DIC models, along with the heterogeneity parameter for the random-effects model are provided in the Table 12.

Table 12 – Heterogeneity parameter (and 95% credible interval) for random-effects NMAs for all outcomes

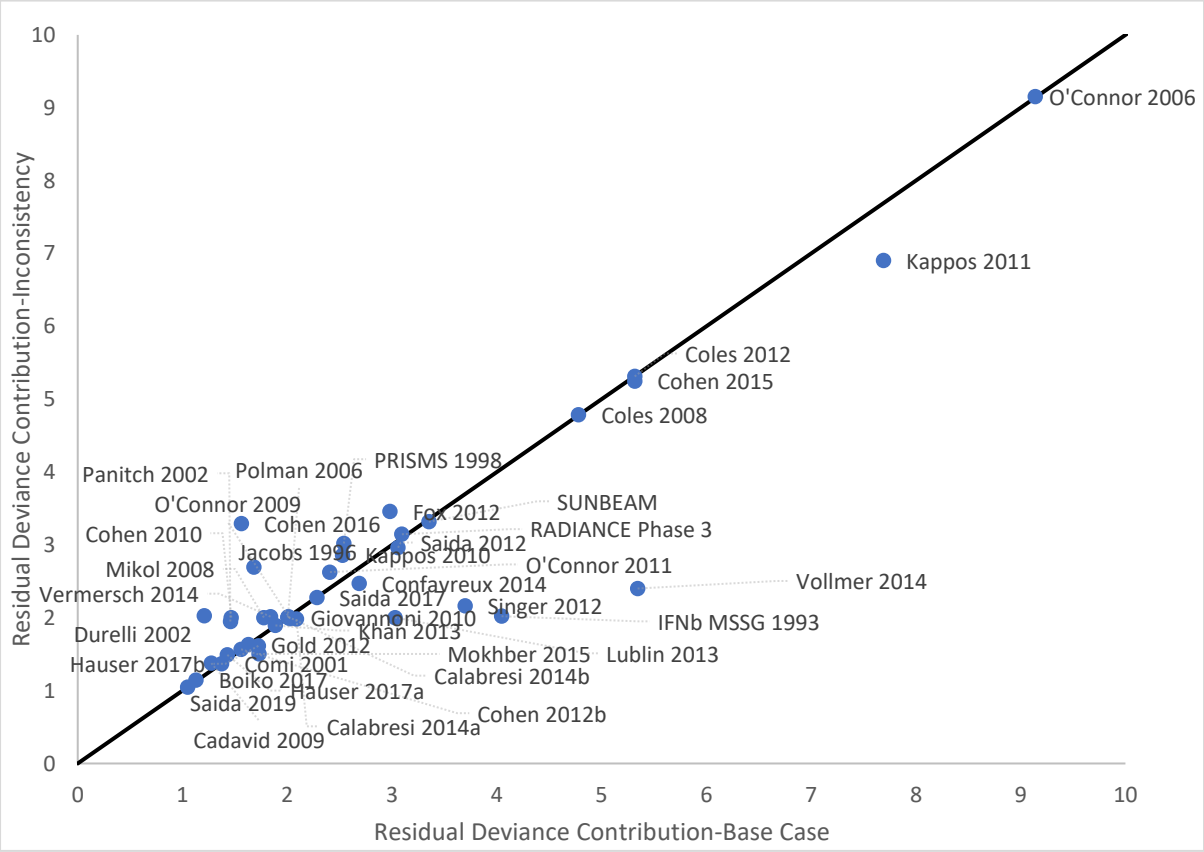
Outcome	FE DIC	RE DIC	Random effect parameter, median (95% CrI)
ARR	182.303	187.426	0.05 (0.004, 0.15)
CDP12	93.72	95.22	0.08 (0.004, 0.27)

Outcome	FE DIC	RE DIC	Random effect parameter, median (95% CrI)
CDP24	95.5	95.7	0.16 (0.01, 0.41)
Discontinuation	168.87	166.74	0.17 (0.01, 0.37)
AEs	114.727	114.879	2.49 (0.12, 4.87)
Serious AEs	117.373	117.385	2.5 (0.12, 4.88)
Gd+ lesions	84.362	83.689	0.13 (0.008, 0.45)
T2 lesions at 12 mo	37.987	38.781	0.43 (0.02, 3.58)
T2 lesions at 24 mo	37.987	38.781	0.62 (0.04, 3.69)

A16a. <u>Priority question</u>: It is stated in Appendix D1.2.1 to the company submission that "Network inconsistency of the ARR and CDP NMAs were evaluated by constructing a meta-analysis estimating only direct comparison evidence without the influence of the network or indirect treatment effects." Please also provide results of investigations of network inconsistency for the following outcome: discontinuation.

The inconsistency in the network for discontinuation is provided in Figure 1, results show that overall, discontinuation was inconsistent.

Figure 1 – Discontinuation: Residual Deviance of Fixed Effect Model vs Residual Deviance of Inconsistency Model

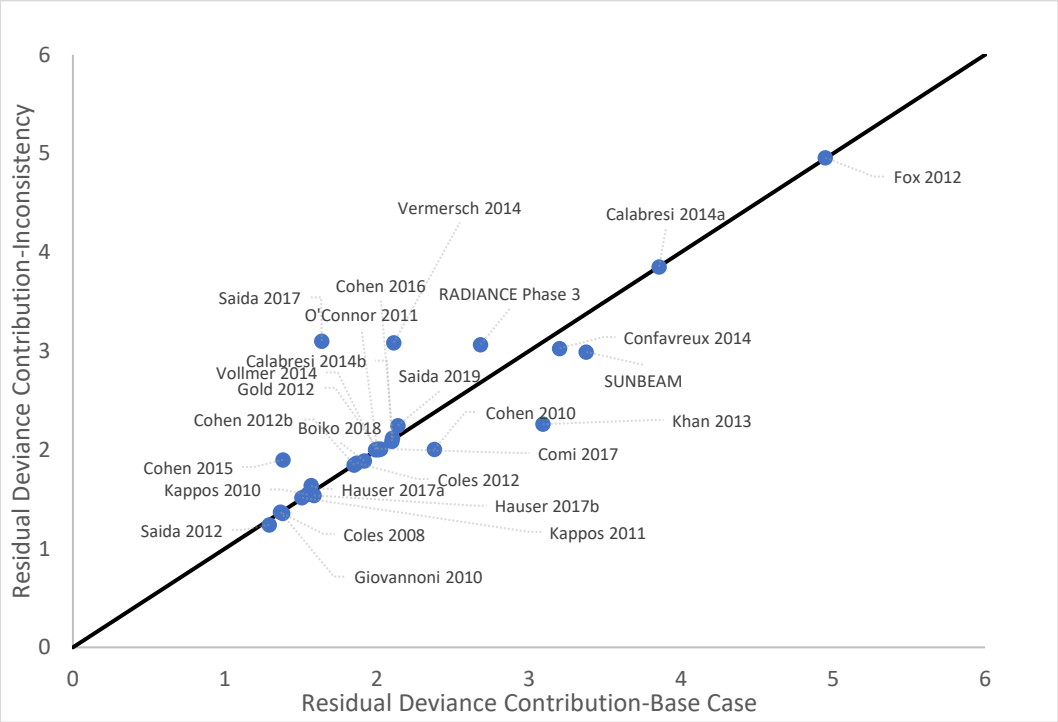


A16b. Please also provide results of investigations of network inconsistency for the following outcomes:

a. adverse events

The inconsistency in the network for adverse events is provided in Figure 2, results show that overall, the reporting of adverse events was inconsistent.

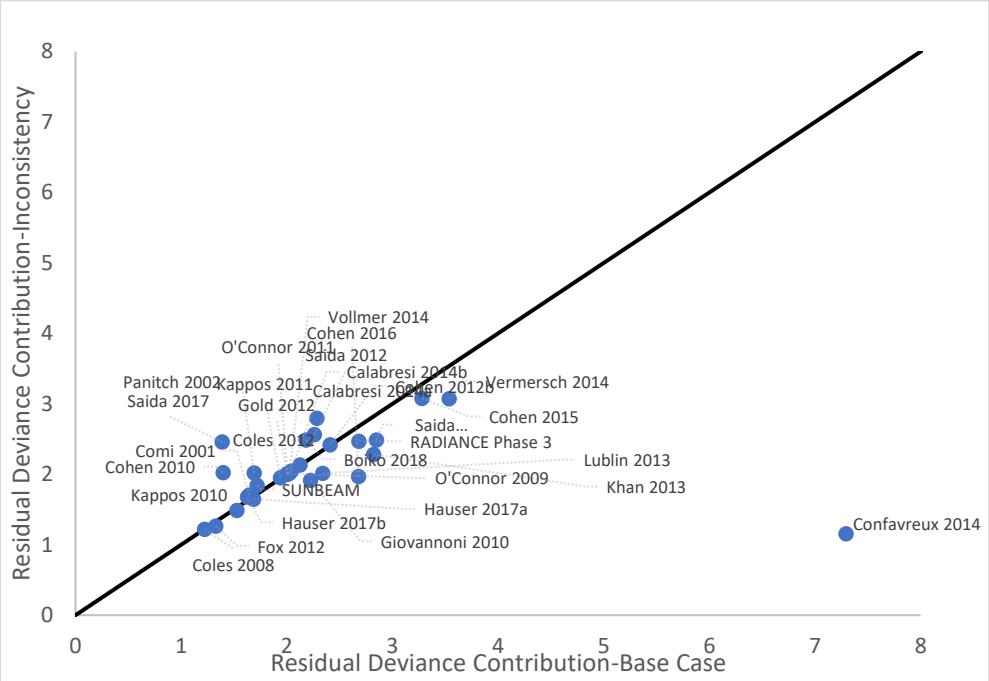
Figure 2 – AEs: Residual Deviance of Fixed Effect Model vs Residual Deviance of Inconsistency Model



b. serious adverse events

Serious adverse events were largely inconsistent, with the Confavreux 2014 study (Oral teriflunomide for patients with relapsing multiple sclerosis [TOWER]: a randomised, double-blind, placebo-controlled, phase 3 trial) resulting as an outlier Figure 3.

Figure 3 – Serious AEs: Residual Deviance of Fixed Effect Model vs Residual Deviance of Inconsistency Model



c. mean lesion counts

Overall, mean lesion counts were also inconsistent (Figure 4 and Figure 6), with the least inconsistency seen in T2 lesions at 12 months (Figure 5).

Figure 4 – Gd+ lesions: Residual Deviance of Fixed Effect Model vs Residual Deviance of Inconsistency Model

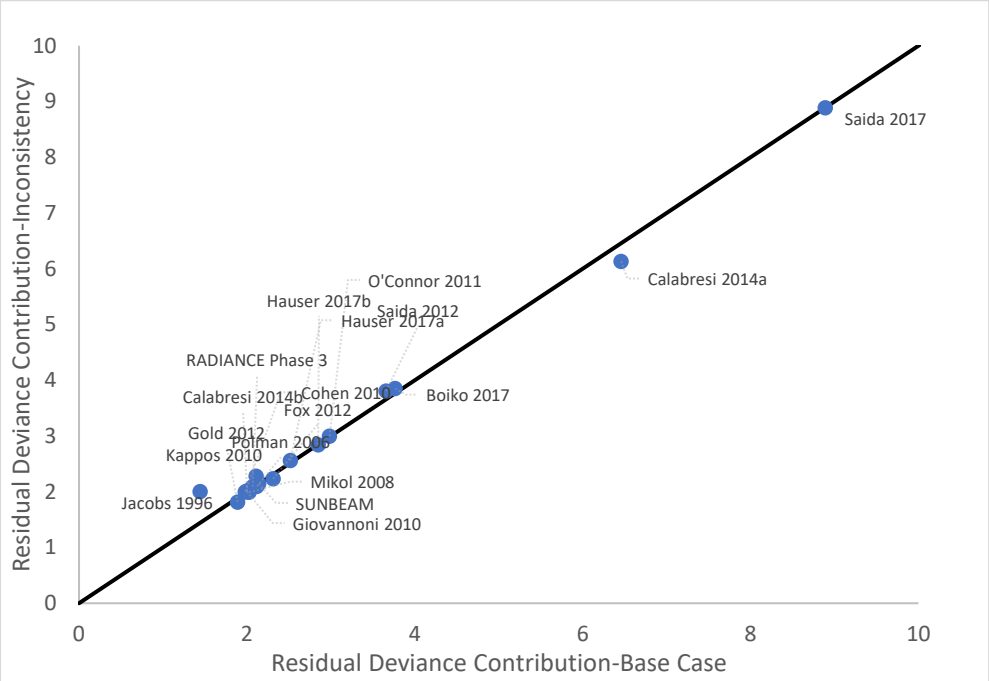


Figure 5 – T2 lesions at 12 months: Residual Deviance of Fixed Effect Model vs Residual Deviance of Inconsistency Model

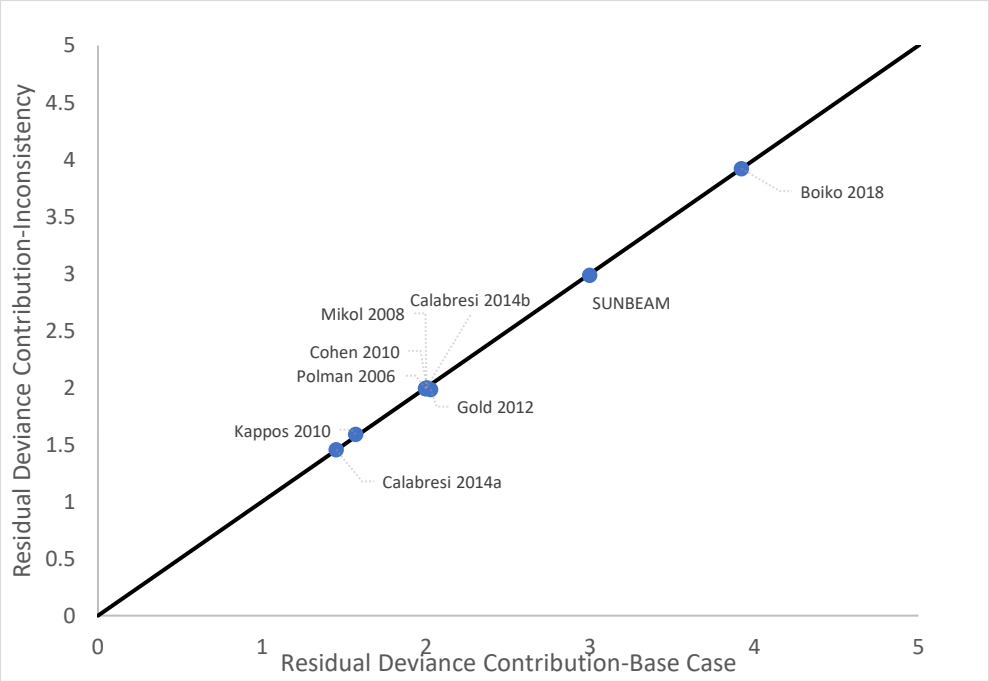
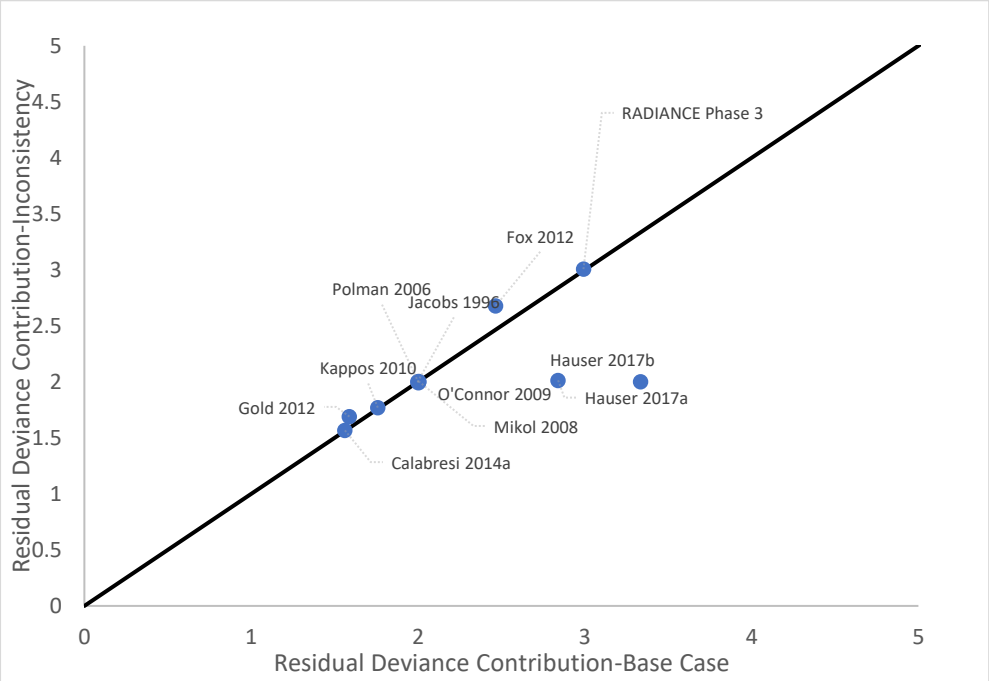


Figure 6 – T2 lesions at 24 months: Residual Deviance of Fixed Effect Model vs Residual Deviance of Inconsistency Model



A17. From the NICE quality assessment checklist used to assess the quality of the 47 trials included within the NMAs (Appendix D1.2.2 to the company submission), please clarify which prognostic factors were compared in relation to the question "Were the groups similar at the outset of the study in terms of prognostic factors?"

The reporting of patient baseline characteristics between the studies included in the NMA was not consistent. To evaluate whether patients included in each group (including their prognostic factors) were similar, baseline characteristics of patients in each treatment arm was compared. The baseline characteristics of patients in the included studies are in Table 8 of Appendix D1.1. 5 (reproduced as Table 13 below).

Table 13 – Summary of patient characteristics for the included studies

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Boiko 2018	Placebo	12 mo	28	4 (median)					1 Year: 1.21 (0.42)	
	Glatiramer acetate (Generic), 20mg		61	5 (median)					1 Year: 1.28 (0.49)	
	Glatiramer acetate (Copaxone), 20mg		61	3 (median)					1 Year: 1.28 (0.64)	
Bornstein 1987	Placebo	24 mo	23	31.1	60	6.4		3.1	2 Years: 3.9	
	Glatiramer acetate (Copaxone), 20mg		25	30	56	4.9		2.9	2 Years: 3.8	
Cadavid 2009/BECOME	Glatiramer acetate (Copaxone), 20mg	2 yr	39	36 (22,55)	64	1.2		2		
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		36	36 (18,49)	75	0.9		2		

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Calabrese 2012	Glatiramer acetate (Copaxone), 20mg	2 yrs	48	38.9 (10.2)	72.9	5.5 (6.1)		2.1 (1.1)		
	Interferon beta-1a (Avonex) 30mcg		47	34.8 (9.6)	68	5.3 (5.1)		1.9 (0.8)		
	Interferon beta-1a (Rebif), 44mcg		46	35.9 (9.1)	69.5	5.7 (4.9)		1.9 (1.0)		
Calabresi 2014a/FREEDOMS II	Placebo	24 mo	355	40.1 (8.4)	81		10.6 (7.9)	2.4 (1.3)	1 Year: 1.5 (0.9), 2 Years: 2.2 (1.5)	1.2 (3.2)
	Fingolimod (Gilenya), 0.5mg		358	40.6 (8.4)	77		10.4 (8.0)	2.4 (1.3)	1 Year: 1.4 (0.9), 2 Years: 2.2 (1.4)	1.3 (3.4)
Calabresi 2014b/ADVANCE	Placebo	48 wks	500	36.3 (9.7)	72	3.5 (4.6)	6.3 (6.3)	2.44 (1.18)	1 Year: 1.6 (0.67), 3 Years: 2.6 (1.0)	1.6 (3.8)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Peg-Interferon beta-1a (Plegridy), 125mcg EOW		512	36.9 (9.8)	71	4.0 (5.1)	6.9 (6.6)	2.47 (1.26)	1 Year: 1.6 (0.6.7), 3 Years: 2.9 (0.99)	1.2 (3.4)
Cohen 2010/TRANSFORMS	Fingolimod (Gilenya), 0.5mg	12 mo	431	36.7 (8.8)	65.4		7.5 (6.2)	2.24 (1.33)	1 Year: 1.5 (1.2), 2 Years: 2.3(2.2)	0.98 (2.81)
	Interferon beta-1a (Avonex) 30mcg		435	36 (8.3)	67.8		7.4 (6.3)	2.19 (1.26)	1 Year: 1.5 (0.8), 2 Years: 2.3 (1.2)	1.06 (2.80)
Cohen 2012b/CARE-MS I	Alemtuzumab (Lemtrada), 12mg	24 mo	376	33.0 (8.03)	65		2.1 (1.4)	2.0 (0.81)	1 Year: 1.8 (0.8)	2.3 (5.1)
	Interferon beta-1a (Rebif), 44mcg		187	33.2 (8.48)	65		2.0 (1.3)	2.0 (0.79)	1 Year: 1.8 (0.8)	2.2 (4.9)
Cohen 2015/ GATE	Placebo	9 mo	84	32.6 (8.7)	67.9		5.7 (6.0)	2.7 (1.2)	2 Years: 1.9 (0.9)	2.8 (4.1)
	Glatiramer acetate (Copaxone), 20mg		357	33.8 (9)	66.7		6.4 (6.0)	2.7 (1.2)	2 Years: 1.8 (0.9)	2.5 (3.9)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Glatiramer acetate (generic), 20mg		353	32.6 (8.6)	66		5.5 (5.3)	2.6 (1.2)	2 Years: 1.9 (0.9)	2.5 (3.5)
Cohen 2016/ RADIANCE PART A	Placebo	24 wks	88	39.0 (8.7)	70	8.1 (7.0)	4.6 (5.1)	2.9 (1.3)	1 Year: 1.3 (0.6) 2 Years: 1.8 (1.0)	1.4 (3.4)
	Ozanimod, 0.5mg		87	38.1 (9.2)	69	6.0 (6.4)	6.0 (6.4)	2.9 (1.3)	1 Year: 1.5 (1.2) 2 Years: 2.0 (1.8)	0.9 (1.4)
	Ozanimod, 1.0mg		83	38.4 (9.8)	71	6.2 (5.8)	3.6 (4.4)	2.9 (1.2)	1 Year: 1.3 (0.7) 2 Years: 1.9 (1.1)	1.3 (2.8)
Coles 2008/CAMMS223	Alemtuzumab (Lemtrada), 12mg	36 mo	112	31.9 (8.0)	64.3			1.9 (0.74)		
	Interferon beta-1a (Rebif), 44mcg		111	32.8 (8.8)	64			1.9 (0.83)		
Coles 2012/CARE-MS II	Alemtuzumab (Lemtrada), 12mg	24 mo	426	34.8 (8.36)	66		4.5 (2.68)	2.7 (1.26)	1 Year: 1.7 (0.86)	2.28 (6.02)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1a (Rebif), 44mcg		202	35.8 (8.77)	65		4.7 (2.86)	2.7 (1.21)	1 Year: 1.5 (0.75)	2.10 (4.95)
Comi 2001/EU/CGASG	Placebo	9 mo	120	34.0 (7.5)		8.3 (5.5)		2.4 (1.2)	2 Years: 2.5 (1.4)	4.4 (7.1)
	Glatiramer acetate (Copaxone), 40mg		119	34.1 (7.4)		7.9 (5.5)		2.3 (1.1)	2 Years: 2.8 (1.8)	4.2 (4.8)
Comi 2017/GOLDEN	Fingolimod (Gilenya), 0.5mg	18 mo	80	40.23 (9.09)	71.25	4.97 (6.67)		2.78 (1.34)	1 Year: 1.45 (0.79) 2 Years: 1.90 (0.84)	0.75 (1.15)
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		28	37.64 (9.29)	67.86	4.71 (6.47)		2.09 (1.05)	1 Year: 1.18 (0.48) 2 Years: 1.54 (0.84)	0.89 (1.91)
Confavreux 2014/TOWER	Placebo	48 wks	389	38.1 (9.1)	70		7.64 (6.7)	2.69 (1.36)	1 Year: 1.4 (0.8), 2 Years: 2.1 (1.1)	
	Teriflunomide (Aubagio), 14mg		372	38.2 (9.4)	69		8.18 (6.73)	2.71 (1.35)	1 Year: 1.4 (0.7), 2 Years: 2.1 (1.2)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Teriflunomide (Aubagio), 7mg		408	37.4 (9.4)	74		8.18 (6.75)	2.71 (1.39)	1 Year: 1.4 (0.7) 2 Years: 2.1 (1.1)	
De Stefano 2010, 2012/ IMPROVE	Placebo	16 wks	60	35.2 (10.5)	70					
	Interferon beta-1a (Rebif), 44mcg		120	34.0 (7.8)	73					
Durelli 2002/INCOMIN	Interferon beta-1a (Avonex) 30mcg	24 mo	92	34.9 (7.9)	62	6.7 (5.4)		1.96 (0.7)	2 Years (annualized): 1.38 (0.52)	
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		96	38.8 (7.1)	68.8	5.9 (4.2)		1.97 (0.7)	2 Years (annualized): 1.52 (0.67)	
Etemadifar 2006	Interferon beta-1a (Avonex) 30mcg	24 mo	30	28.1 (1.2)	80	2.9 (2.3)		1.9 (1.1)	1 Year: 2.0 (0.8)	
	Interferon beta-1a (Rebif), 44mcg		30	27.4 (1.2)	77	3.0 (2.2)		2.1 (1.0)	1 Year: 2.4 (1.0)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		30	29.9 (1.4)	70	3.7 (2.3)		1.9 (0.7)	1 Year: 2.2 (0.7)	
Fox 2012/ CONFIRM	Placebo	96 wks	363	36.9 (9.2)	69	4.8 (5.0)		2.6 (1.2)	1 Year: 1.4 (0.8)	
	Dimethyl fumarate (Tecfidera), 240mg (bid)		359	37.8 (9.4)	68	4.9 (5.1)		2.6 (1.2)	1 Year: 1.3 (0.6)	
	Glatiramer acetate (Copaxone), 20mg		350	36.7 (9.1)	71	4.4 (4.7)		2.6 (1.2)	1 Year: 1.4 (0.6)	
Giovannoni 2010/CLARITY	Placebo	96 wks	437	38.7 (9.9)	65.9	8.9 (7.4)		2.9 (1.3)		0.8 (2.1)
	Cladribine, 3.5 mg/kg		433	37.9 (10.3)	68.8	7.9 (7.2)		2.8 (1.2)		1.0 (2.7)
Gold 2012/DEFINE	Placebo	96 weeks	408	38.5 (9.1)	75	5.8 (5.8)		2.48 (1.24)	1 Year: 1.3 (0.7)	1.6 (3.4)
	Dimethyl fumarate (Tecfidera), 240mg (bid)		410	38.1 (9.1)	72.2	5.6 (5.4)		2.4 (1.29)	1 Year: 1.3 (0.7)	1.2 (3.3)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Hauser 2017a/OPERA I	Interferon beta-1a (Rebif), 44mcg	96 wks	411	36.9 (9.3)	66.2	3.71 (4.63)	6.25 (5.98)	2.75 (1.29)	1 Year: 1.33 (0.64)	
	Ocrelizumab (Ocrevus), 600mg		410	37.1 (9.3)	65.9	3.82 (4.80)	6.74 (6.37)	2.86 (1.24)	1 Year: 1.31 (0.65)	
Hauser 2017b/OPERA II	Interferon beta-1a (Rebif), 44mcg	96 wks	418	37.4 (9)	67	4.13 (5.07)	6.68 (6.13)	2.84 (1.38)	1 Year: 1.34 (0.73)	
	Ocrelizumab (Ocrevus), 600mg		417	37.2 (9.1)	65	4.15 (4.95)	6.72 (6.10)	2.78 (1.30)	1 Year: 1.32 (0.69)	
IFNb MSSG 1993	Placebo	2 yr	123	36 (0.6, SE)	71.5	3.9 (0.3, SE)		2.8 (0.1, SE)	2 Years: 3.6 (0.1, SE)	
	Interferon beta-1b (Betaseron; Betaferon), 8 mIU		124	35.2 (0.6, SE)	69.4	4.7 (0.4, SE)		3.0 (0.1, SE)	2 Years: 3.4 (0.2, SE)	
	Placebo	104 wks	143	36.9 (0.64, SE)	72	6.4 (0.49, SE)		2.3 (0.07, SE)	1 Year: 1.2 (0.05, SE)	2.32 (0.37, SE)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Jacobs 1996/MSCRG	Interferon beta-1a (Avonex) 30mcg		158	36.7 (0.57, SE)	75	6.6 (0.46, SE)		2.4 (0.06, SE)	1 Year: 1.2 (0.05, SE)	3.17 (0.62, SE)
Johnson 1995/Copolymer 1 Trial	Placebo	24 mo	126	34.3 (6.5)	76.2	6.6 (5.1)		2.4 (1.3)	2 Years: 2.9 (1.1)	
	Glatiramer acetate (Copaxone), 20mg		125	34.6 (6)	70.4	7.3 (4.9)		2.8 (1.2)	2 Years: 2.9 (1.3)	
Kappos 2010/FREEDOMS	Placebo	24 mo	418	37.2 (8.6)	71.3		8.1 (6.4)	2.5 (1.3)	1 Year: 1.4 (0.7), 2 Years: 2.2 (1.2)	1.3 (2.9)
	Fingolimod (Gilenya), 0.5mg		425	36.6 (8.8)	69.6		8.0 (6.6)	2.3 (1.3)	1 Year: 1.5 (0.8), 2 Years: 2.1 (1.1)	1.6 (5.6)
Kappos 2011	Placebo	24 wks	54	38 (8.8)	67	2.7	4.8	3.2 (1.4)		1.6 (4.05)
	Interferon beta-1a (Avonex) 30mcg		54	38.1 (9.3)	59	3.3	5.3	3.1 (1.5)		2.3 (5.26)
	Ocrelizumab (Ocrevus), 600mg		55	35.6 (8.5)	64	3.6	6.5	3.5 (1.5)		3.9 (9.88)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Khan 2013/GALA	Placebo	12 mo	461	38.1 (9.2)	67.9		7.6 (6.4)	2.7 (1.2)	1 Year: 1.3 (0.6), 2 Years: 1.9 (0.9)	1.4 (3.7)
	Glatiramer acetate (Copaxone), 40mg		943	37.4 (9.4)	68		7.7 (6.7)	2.8 (1.2)	1 Year: 1.3 (0.6), 2 Years: 1.9 (0.9)	1.7 (4.7)
Knobler 1993	Placebo	24 wks	7	34.5	71	7		3.1		
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		6	35.4	33	4.2		2.7		
Lublin 2013/CombiRx	Glatiramer acetate (Copaxone), 20mg	36 mo	259	39 (9.5)	71.4	1.0 (2.9)		1.9 (1.2)	1 Year: 1.6 (0.7)	4.6 (7.6)
	Interferon beta-1a (Avonex) 30mcg		250	37.6 (10.2)	69.2	1.4 (4.0)		2.0 (1.2)	1 Year: 1.7 (0.9)	4.1 (5.5)
Mikol 2008/REGARD	Glatiramer acetate (Copaxone), 20mg	96 wks	378	36.8 (9.5)	72			2.33 (1.31)		1.65 (4.7)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1a (Rebif), 44mcg		386	36.7 (9.8)	69			2.35 (1.28)		1.47 (4.95)
Mokhber 2015/ IRCT20140 4195280N1 6	Interferon beta-1a (Avonex) 30mcg	12 mo	20	31.11 (6.76)	60					
	Interferon beta-1a (Rebif), 44mcg		22	27.78 (8.01)	60.9					
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		23	28.95 (8.78)	72.7					
O'Connor 2006	Placebo	36 wks	61	39.2 (8.7)	67	4.4 (5.7), 8.6 (7.9)		2.5	1 Year: 1 3 Years: 3	2.1 (0.62, SE)
	Teriflunomide (Aubagio), 7mg		61	40.1 (9.3)	75	6.0 (5.6), 10.3 (8.1)		2.5	1 Year: 1 3 Years: 2	1.23 (0.6, SE)
	Teriflunomide (Aubagio), 14mg		57	40.1 (9.1)	78.9	5.4 (6.2), 8.5 (7.1)		2.0	1 Year: 1, 3 Years: 3	2.32 (0.61, SE)

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
O'Connor 2009/BEYOND	Glatiramer acetate (Copaxone), 20mg	2 yr	448	35.2 (27,43, IQR)	68.3	5.1		2.28	1 Year: 1.6	1.8 (0,2) [median, (IQR)]
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		897	35.8 (28,43, IQR)	69.9	5.3		2.35	1 Year: 1.6	2.3 (0,2) [median, (IQR)[
O'Connor 2011/TEMSO	Placebo	108 wks	363	38.4 (9)	75.8		8.6 (7.1)	2.68 (1.34)	1 Year: 1.4 (0.7), 2 Years: 2.2 (1)	1.66 (3.55)
	Teriflunomide (Aubagio), 7mg		366	37.4 (9)	69.7		8.8 (6.8)	2.68 (1.34)	1 Year: 1.4 (0.7), 2 Years: 2.3 (1.2)	1.5 (3.96)
	Teriflunomide (Aubagio), 14mg		359	37.8 (8.2)	71		8.7 (6.7)	2.67 (1.24)	1 Year: 1.3 (0.7), 2 Years: 2.2 (1)	1.81 (5.17)
Panitch 2002/EVIDENCE	Interferon beta-1a (Rebif), 44mcg	48 weeks	339	38.3	74.9	6.5		2.3	2 Years: 2.6	1.9
	Interferon beta-1a (Avonex) 30mcg		338	37.4	74.6	6.7		2.3	2 Years: 2.6	2.5

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Polman 2006/AFFIRM	Placebo	2 yrs or more	315	36.7 (7.8)	67	6		2.3 (1.2)	1 Year: 1.5 (0.77)	2.0 (4.8)
	Natalizumab (Tysabri), 300mg		627	35.6 (8.5)	72	5		2.3 (1.2)	1 Year 1.53 (0.91)	2.2 (4.7)
PRISMS 1998	Placebo	24 mo	187	34.6	75	4.3		2.4 (1.2)	2 Years: 3 (1.3)	
	Interferon beta-1a (Rebif), 22mcg		189	34.8	67	5.4		2.5 (1.2)	2 Years: 3 (1.1)	
	Interferon beta-1a (Rebif), 44mcg		184	35.6	66	6.4		2.5 (1.3)	2 Years: 3 (1.1)	
RADIANCE PART B	Interferon beta-1a (Avonex) 30mcg	24 mo	441	35.1 (9.07)	68.9	3.63 (4.613)	6.36 (6.065)	2.49 (1.158)	1 Year: 1.3 (0.58), 2 Year: 1.8 (0.86)	
	Ozanimod, 0.5mg		439	35.4 (8.82)	65.4	3.5 (4.207)	6.23 (5.547)	2.48 (1.166)	1 Year: 1.4 (0.64), 2 Years: 1.8 (0.9)	
	Ozanimod, 1.0mg		433	36 (8.89)	67.2	3.97 (5.171)	6.92 (6.201)	2.55 (1.145)	1 Year: 1.3 (0.56), 2 Years: 1.7 (0.82)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Saida 2012	Placebo	6 mo	57	35 (8.9)	68.4		8.2 (7.3)	2.1 (1.7)	1 Year: 1.7 (1.6), 2 Years 2.8 (3.0)	1.6 (3.05)
	Fingolimod (Gilenya), 0.5mg		57	35 (9)	70.2		8.2 (6.8)	2.3 (1.9)	1 Year: 1.4 (1.0), 2 Years: 2.2 (1.4)	1.2 (2.08)
Saida 2017	Placebo	24 weeks	47	35.1 (8.2)	68	5.1 (4.9)	6.8 (5.5)	2.1 (1.5)	1 Year: 1.9 (1.0)	0.7 (1.9)
	Natalizumab (Tysabri), 300mg		47	37.7 (8.6)	72	5.9 (5.0)	8.7 (5.7)	2.5 (1.6)	1 Year: 2.0 (1.2)	0.9 (2.7)
Saida 2019	Placebo	24 weeks	113	36.0 (7.5)	74			1.9 (1.3)	1 Year: 1.4 (0.7) 3 Years: 2.3 (1.5)	1.5 (3.2)
	Dimethyl fumarate (Tecfidera), 240mg (bid)		111	37.3 (8.3)	70			2.2 (1.3)	1 Year: 1.4 (0.7) 3 Years: 2.5 (1.7)	1.6 (4.9)
Singer 2012/REFORMS	Interferon beta-1a (Rebif), 44mcg	12 wks	65	40.26 (9.80)	70.8	1.01 (2.35)	4.51 (6.70)		1 Year: 1.36 (0.52) out of 55 w/relapse	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
	Interferon beta-1b (Betaseron; Betaferon), 250mcg		64	40.78 (9.56)	68.8	1.93 (4.02)	5.74 (6.66)		1 Year: 1.30 (0.46) out of 50 w/relapse	
SUNBEAM	Interferon beta-1a (Avonex) 30mcg	24 mo	448	35.9 (9.11)	67	3.71(4.361)	6.88 (5.877),	2.62 (1.138)	1 Year: 1.3 (0.55), 2 Years: 1.7 (0.84)	1.7 (3.22)
	Ozanimod, 0.5mg		451	36 (9.43)	69	3.70(4.518)	7.16 (6.255),	2.65 (1.135)	1 Year: 1.3 (0.57), 2 Years: 1.7 (0.84)	1.6 (2.95)
	Ozanimod, 1.0mg		447	34.8 (9.24)	63.3	3.60(4.193)	6.85 (6.449)	2.61 (1.160)	1 Year: 1.3 (0.57), 2 Years: 1.8 (0.86)	1.8 (3.41)
Vermersch 2014/TENERE	Interferon beta-1a (Rebif), 44mcg	48 wks	104	37 (10.6)	68.3		7.7 (7.6)	2.0 (1.2)	1 Year: 1.2 (1.0), 2 Years: 1.7 (1.1)	
	Teriflunomide (Aubagio), 7mg		109	35.2 (9.2)	64.2		7.0 (6.9)	2.0 (1.2)	1 Year: 1.3 (0.8), 2 Years: 1.7 (0.9)	
	Teriflunomide (Aubagio), 14mg		111	36.8 (10.3)	70.3		6.6 (7.6)	2.3 (1.4)	1 Year: 1.4 (0.8), 2 Years: 1.7 (0.9)	

Study	Treatment	Study Duration	N	Mean Age (SD) (yrs)	% Female	Mean disease duration, mean (SD), s	Mean symptom duration (SD), y	Mean (SD) EDSS	Mean prior relapses (SD)	Mean Gd+ legions (SD)
Vollmer 2014/BRAVO	Placebo	24 mo	450	37.5	71.3	1.2	4.7	2.5	1 Year: 1 (1,2) [median, (IQR)[2 Years: 2 (1,2) [median, (IQR)[	
	Interferon beta-1a (Avonex) 30mcg		447	38.5	68.7	1.4	5.3	2.5	1 Year: 1 (1,2) [median, (IQR)[2 Years: 2 (1,2) [median, (IQR)[	

Abbreviations: EDSS: Expanded Disability Status Scale; mcg: microgram; SD: Standard deviation
Source: (Pharmerit International 2019a)

Section B: Clarification on cost-effectiveness data

B1. P 15 of the company's submission states "Since ocrelizumab is only recommended by NICE to be used in patients where alemtuzumab is contraindicated or otherwise unsuitable, it is also not considered a relevant comparator to ozanimod". Figure 1 in the company submission places ozanimod in the same point in the treatment pathway as ocrelizumab, which is recommended for people with active RRMS when alemtuzumab is contraindicated or otherwise unsuitable. NICE do not consider this an appropriate exclusion. Please provide further justification for excluding ocrelizumab.

In clinical practice in England, ocrelizumab is prescribed if patients have failed or are contraindicated for alemtuzumab. In line with this, clinical experts consulted during the development of this submission stated that neither alemtuzumab or ocrelizumab are currently in use in clinical practice as first line treatments in England. This is also consistent with discussions during the recent NICE committee meeting for peginterferon beta 1a. During this appraisal ocrelizumab was excluded as a first-line comparator by the committee. Based on clinical opinion, ozanimod is most likely to be used as a first line treatment in clinical practice in England, therefore ocrelizumab is not a relevant comparator for ozanimod.

B2. In the company's decision problem form it acknowledges that the committee has previously preferred EDSS health states costs from the UK MS survey data, however has not provided analyses using this data. Please provide scenarios using EDSS health state costs from the UK MS survey.

Tyas et al 2007, used in the company base case cost-effectiveness analysis, reports the costs from the UK MS Survey published in Orme et al 2007 (Orme 2007, Tyas 2007). The sample represents respondents to postal questionnaire sent to people in February 2005 identified within a database managed by the MS Trust (UK charity). This survey provides costs for each individual EDSS health state.

This was discussed in the clarification call on Thursday 5th 2019, and NICE agreed with this approach.

Section C: Textual clarification and additional points

C1. <u>Priority question</u>: Thank you for providing a copy of the Pharmerit International 2019 report (and other cited references) alongside the company submission. Please also provide the following documents:

a. **Statistical Analysis Plan (Final, Version 1.2 dated 20 May 2014) of RADIANCE Part A.**

This document has been provided alongside this response.

b. **Appendix 2 (*Celgene_RRMS_NMA_Report_Apdx1-2_11Sep2019.docx*) to the Pharmerit International 2019 report.**

This document has been provided alongside this response. The ARR table has been updated to add additional information on the source of the data for some of the studies as requested in question A11b and the file name has been amended from '*Celgene_RRMS_NMA_Report_Apdx1-2_11Sep2019.docx'* to '*Celgene_RRMS_NMA_Report_Apdx1-2_27Nov2019.docx'* accordingly (and referenced as Pharmerit International 2019b Systematic review and network meta-analysis of treatments for RRMS: Appendices 1 and 2).

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ozanimod for treating relapsing–remitting multiple sclerosis

Confidential until published

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Ozanimod for treating relapsing–remitting multiple sclerosis [ID1294]

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Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Rui Duarte	Critical appraisal of the clinical and economic evidence, editorial input
Rachel Houten	Critical appraisal of the economic evidence
Joanne McEntee	Critical appraisal of the company submission
Ian Pomeroy	Clinical advice and critical appraisal of the clinical sections of the company submission

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List of abbreviations

ABN	Association of British Neurologists
AE	adverse event
AESI	adverse event of special interest
ARR	annualised relapse rate
BCMS	British Columbia Multiple Sclerosis
BNF	British National Formulary
BSC	best supportive care
BVL	brain volume loss
CDP	confirmed disability progression
CE	cost effectiveness
CI	confidence interval
CrI	credible interval
CS	company submission
CSR	clinical study report
DIC	deviance information criterion
DMF	dimethyl fumarate
DMT	disease modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQoL-5 dimension
ERG	Evidence Review Group
GA	glatiramer acetate
Gd-E	gadolinium-enhancing
HA	highly active
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost effectiveness ratio

IFN	interferon
ITT	Intention-to-treat
LCLA	low-contrast letter acuity
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
MSQoL	multiple sclerosis quality of life
NEDA	no evidence of disease activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analyses
OLE	open label extension
PD	pharmacokinetics
PK	pharmacodynamics
PSA	probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	randomised clinical trial
RES	rapidly-evolving severe
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SPMS	secondary progressive multiple sclerosis
TEAE	treatment-emergent adverse event
TSAP	trial statistical analysis plan
UK	United Kingdom

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal process. Clinical and economic evidence has been submitted to NICE by Celgene in support of the use of ozanimod for treating relapsing-remitting multiple sclerosis (RRMS). Currently, ozanimod does not have a marketing authorisation in the UK. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use decision is expected in [redacted] and European marketing authorisation is expected in [redacted].

One subgroup of RRMS is 'active RRMS'. More severe forms of 'active RRMS' include highly active (HA) RRMS and rapidly evolving severe (RES) RRMS. ***However, for the purpose of this report, the use of the term 'active RRMS' excludes HA RRMS and RES RRMS.***

1.1 Critique of the decision problem in the company's submission

As highlighted in Section 2.5 of this ERG report, the decision problem addressed by the company is largely in accordance with the final scope issued by NICE. The few minor differences are summarised below.

Differences in final scope issued by NICE and decision problem addressed by the company

Parameter	Final scope issued by NICE	Decision problem
Population	People with RRMS	Based on clinical feedback, the company considers that ozanimod should be a treatment option for patients with active RRMS (excluding HA RRMS and RES RRMS); the ERG has received clinical advice supporting this view and clinical advice suggesting that ozanimod may also be suitable for patients with HA RRMS. The ERG highlights that ~25% of patients recruited to the two trials (RADIANCE PART A and SUNBEAM trials) which provide clinical effectiveness evidence (ozanimod versus IFN β-1a 30µg (Avonex)) to inform this appraisal had diagnoses of other types of RRMS, including types broadly comparable to HA RRMS and RES RRMS
Comparator(s)	DMTs for active RRMS DMTs for HA RRMS DMTs for RES RRMS	The ERG considers that the comparators considered by the company are appropriate for patients with active RRMS (including peg-IFN β-1a which although being currently reviewed by NICE [ID1521], is currently used to treat patients in NHS clinical practice) The ERG also considers that ocrelizumab, which was excluded as a comparator by the company, should have been included as a comparator since it is recommended by NICE as a first-line treatment option for patients with active RRMS (TA533) and clinical advice to the ERG is that it is used to treat some of this patient population

DMT=Disease modifying therapy; HA=highly; IFN=interferon; peg-IFN=peginterferon; RES=rapidly-evolving severe; RRMS=relapsing-remitting multiple sclerosis

1.2 Summary of the key issues in the clinical effectiveness evidence

1.2.1 Systematic review methods

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence were satisfactory (Section 3.3.1).

1.2.2 Direct evidence

As highlighted in Section 3.3.1, only the RADIANCE Part B and SUNBEAM trials provide direct clinical effectiveness evidence comparing treatment with ozanimod versus a relevant comparator (Interferon beta-1a [IFN β-1a] 30µg (Avonex)]).

The following important caveats should be considered when interpreting the evidence from the two trials:

- While approximately 75% of patients had active RRMS, approximately 25% had other types of MS including types broadly comparable to HA RRMS and RES RRMS (Section 3.3.2). The company considers that ozanimod is only an appropriate treatment for patients with active RRMS only, not those with HA RRMS and RES RRMS.

- Approximately 30% of patients had received a disease modifying therapy (DMT) prior to receiving ozanimod (Section 3.3.2). However, it is unclear if these patients had stopped treatment due to poor efficacy (meaning the study drug could be considered to be a second-line treatment) or intolerability (in which case, the study drug could be considered to be an alternative first-line therapy). The ERG notes that people who could not tolerate previous treatment were a subgroup of interest specified in the final scope issued by NICE and that the company consider ozanimod to be a first-line DMT.

- Patients with specific cardiovascular conditions at screening were excluded (Section 3.3.1). It is therefore unclear if ozanimod would be a suitable treatment for such patients in clinical practice.

- The trials include a very high proportion (>90%) of white and Eastern European patients (Section 3.3.2). It is unclear if results would differ in a more diverse population as would be expected in NHS clinical practice in England and Wales.

The key findings from these trials were as follows:

- With the exception of confirmed disability progression (CDP) at 3 months (CDP-3M) or 6 months (CDP-6M), ozanimod was statistically significantly superior to IFN β-1a

(Avonex) for all efficacy outcomes, including annualised relapse rate (ARR) (Section 3.6).

- Analysis of pooled health-related quality of life (HRQoL) data from the RADIANCE Part B and SUNBEAM trials showed no statistically significant differences between treatment with ozanimod and IFN β-1a 30µg (Avonex) (Section 3.7).

- As highlighted in Section 3.8.2, treatment with ozanimod resulted in a lower, or similar, incidence of all types of adverse events (AEs) compared with IFN β-1a 30µg (Avonex). This included AEs of special interest (AESIs), specifically infections, malignancies, bradycardia and heart conduction abnormalities, pulmonary function abnormalities and ophthalmic abnormalities associated with administration of sphingosine-1-phosphate 1 receptor (S1P1R) modulators.

1.2.3 Network meta-analyses

As highlighted in Section 3.10, indirect evidence for the effectiveness of treatment with ozanimod versus other comparators listed in the final scope issued by NICE has been derived from network meta-analyses (NMAs). These include data from up to 47 different trials, including the RADIANCE Part B and SUNBEAM trials (Section 3.10). The ERG has presented the company's NMA results versus nine different DMTs (Section 3.10.4, Table 15), namely the nine DMTs that the company considered to be relevant comparators for active RRMS plus ocrelizumab (which the company had presented evidence for in Appendix D to the CS). The full list of comparator DMTs are as follows:

1. IFN β-1a 22µg (Rebif)
2. IFN β-1a 30µg (Avonex)
3. IFN β-1a 44µg (Rebif)
4. IFN β-1b (Extavia is the only NICE recommended IFN β-1b [TA 527] but evidence is actually derived from Betaferon in the NMAs)
5. Glatiramer acetate (GA) 20mg (Copaxone or generic)
6. GA 40mg (Copaxone or generic)
7. Peginterferon beta-1a (peg-IFN β-1a)
8. Teriflunomide
9. Dimethyl fumarate (DMF)
10. Ocrelizumab.

The following important caveats should be considered when interpreting the evidence from the NMAs:

- Heterogeneity may occur from:
    - Types of RRMS and line of treatment (neither of which were consistently reported in the trials but where reported appear to vary considerably) (Section 3.10.1).
    - Different follow-up durations of the trials (varying from 3 to 27 months) and the large range of dates that trials were conducted (published 1987 to 2019) (Section 3.10.1).
- The CDP-6M combined outcome (i.e. the CDP outcome used to populate the company economic model [Section 4.3.6] and which enables CDP-6M outcomes to be generated when CDP-6M data are not reported in trials) requires the assumption that the CDP-3M hazard ratio (HR) is proportional to the CDP-6M HR (Section 3.10.3). However, the assumption of a linear relationship between the CDP-3M and CDP-6M HRs for ozanimod appears to have been violated and therefore caution should be taken when drawing conclusions from the combined analysis (Section 3.10.4).

Results from the NMAs (Section 3.10.4, Table 15) are as follows:

- The only statistically significant difference in terms of CDP-6M combined was that ocrelizumab was statistically significantly superior to ozanimod.
- Treatment with ozanimod statistically significantly improved ARR versus most comparators (exceptions being peg-IFN β-1a, DMF and ocrelizumab; ocrelizumab was statistically significantly superior to ozanimod).
- Treatment with ozanimod is associated with a statistically significant later time to treatment discontinuation compared to 5/10 DMTs and statistically significantly fewer AEs (of any type and severity) compared with 4/10 DMTs. There were no statistically significant differences between ozanimod and any of the DMTs in terms of total numbers of SAEs.

Despite the issues with the NMAs highlighted by the ERG, the ERG is confident that, within the context of this appraisal, it is appropriate to use the results from the NMAs to inform decision making.

1.2.4 Other indirect evidence

NMAs were not conducted for specific types of AEs, SAEs or for HRQoL (Section 3.10). However, the company has reported incidence rates of specific types of AEs from studies of DMTs (CS, Table 45) and results show that AE incidence rates from treatment with ozanimod compare favourably with all comparators, including fingolimod, which like ozanimod, is a S1P1R modulator (Section 3.9).

1.3 Summary of the key issues in the cost effectiveness evidence

The company model structure only allows patients to receive one DMT over their lifetime; as there are now a number of treatments available to treat active RRMS this is unrealistic. A model that can simulate treatment switching or treatment sequencing would be complex to construct. Furthermore, it is unlikely that there are sufficiently robust data to populate such a model. Nevertheless, and recognising that all cost effectiveness models are simplifications of clinical reality, given the range of treatments available to treat active RMMS, results from a model that only simulates the effect of one treatment over a patient's disease course may be of limited use to decision makers. See Section 4.4.2 for further details.

The ERG considers that the company has potentially produced overly pessimistic relative cost effectiveness results for treatment with ozanimod by modelling differences in effectiveness (namely, CDP-6M combined, ARR, treatment discontinuation rates and SAE rates) between treatments which were shown by results from the company's NMAs not to be statistically significant (Section 4.4.3). The ERG considers that when generating base case cost effectiveness results, if clinical effectiveness results are not statistically significantly different, then a difference in effect should not be modelled.

The ERG considers that ocrelizumab is a relevant comparator and should have been included in the company base case (Section 4.4.4).

Treatment discontinuation rates (Section 4.4.5) in the model remain the same for each treatment over the lifetime of the model. Clinical advice to the ERG is that, within the bounds of a model that only represents one line of treatment, a more realistic approach would be to model treatment discontinuation using trial data for the first year (the period for which they are available) and then, from year 2 onwards, assume that treatment continues whilst the patient receives benefit, which, in the company model, is up until a patient reaches EDSS state 7 or enters the SPMS state.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG made the following changes to the company base case (Section 4.5)

- R1: modelling a difference in treatment effect only when the clinical outcomes used to compare relative efficacy of different treatments are shown, by results from the company NMAs, to be statistically significantly different and removing AE rates from the model (R1)
- R2: after one year, treatment is assumed to continue until progression to EDSS 7, or conversion to SPMS state (R2)
- inclusion of ocrelizumab as a comparator.

Rather than showing results of the changes against all comparators, the ERG's revised incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained are shown, using list prices only, for three comparisons:

- treatment with ozanimod versus the reference case, i.e., the comparator with the most favourable ICER per QALY gained compared to ozanimod in the company base case, which, for analyses, undertaken using list prices, is [redacted] (see Table 24)
- the comparison of treatment with ozanimod versus DMF; clinical advice to the ERG, [redacted] is that DMF is the most widely used DMT for active RRMS in the NHS (see Table 25)
- comparison of treatment with ozanimod versus ocrelizumab; the ERG considers that treatment with ocrelizumab is a valid comparator (see Table 26).

The results are summarised in the following tables:

ERG exploratory analyses R1: results generated using list prices

Comparator	Ozanimod		Comparator		Incremental		ICER £/QALY	Change from base case
	QALYs	Costs	QALYs	Costs	QALYs	Costs		
Reference case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* For this analysis, the reference case is [redacted]
ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

ERG exploratory analyses R2: results generated using list prices

Comparator	Ozanimod		Comparator		Incremental		ICER £/QALY	Change from base case
	QALYs	Costs	QALYs	Costs	QALYs	Costs		
Reference case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* For this analysis, the reference case is [redacted]
ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
[redacted]

Fully incremental analysis results generated by the company model with ERG amendments R1 and R2 (list prices)

Treatment	Total Cost	Total QALYs	ICER per QALY gained
[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]	[redacted]	[redacted]

DMF=dimethyl fumarate; GA=glatiramer acetate; ICER=incremental cost effectiveness ratio; IFN=interferon; µg=microgram; QALY=quality adjusted life year;
Extended dominance= the incremental cost effectiveness ratio (ICER) for a given treatment alternative is higher than that of the next, more effective, alternative

The ERG highlights that the relative cost effectiveness of treatments changes when ICERs per QALY gained are estimated using Patient Access Scheme prices, instead of list prices, where applicable.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

As noted in the company's submission (CS, Section B1.3.1), approximately 85% of people with multiple sclerosis (MS) are first diagnosed with relapsing-remitting MS (RRMS). NHS England and the Association of British Neurologists (ABN) have developed a treatment algorithm for the current management of RRMS.[1] Information provided in this document[1] show that patients with RRMS can be classified as having:

- Active RRMS: (1) one relapse in the last 2 years and who also have radiological activity, or (2) two significant relapse in the last 2 years.
- Highly active (HA) RRMS: unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year despite treatment with at least one disease modifying therapy (DMT).
- Rapidly-evolving severe (RES) RRMS: two or more disabling relapses in 1 year, and one or more gadolinium-enhancing (Gd-E) T1 brain lesions on brain magnetic resonance imaging (MRI), or a significant increase in T2-weighted brain MRI lesion load compared with a previous MRI.

For the purpose of this ERG report, the use of the term 'active RRMS' excludes HA RRMS and RES RRMS.

In the final scope issued by NICE[2] for this appraisal, all three patient populations were included as being potentially eligible for consideration. However, it is stated in the CS (p13 and p18) that ozanimod is only expected to be used in NHS clinical practice as a first-line treatment for active RRMS, not HA RRMS or RES RRMS.

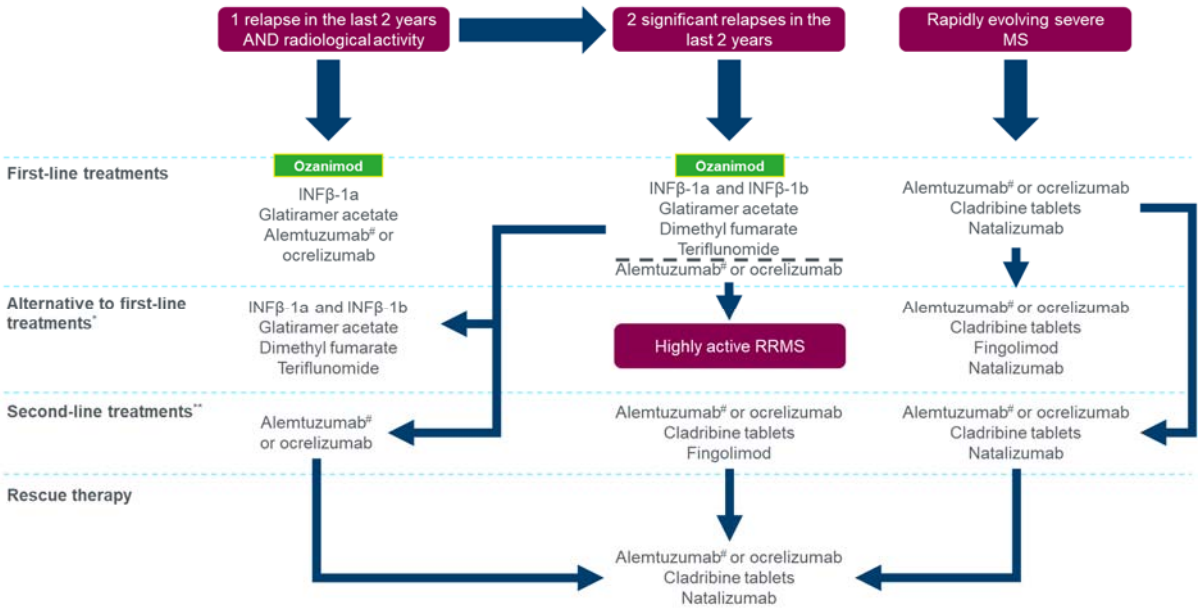
The company highlight (CS, p18) that in absence of treatment, approximately 50% of patients diagnosed with RRMS subsequently develop secondary progressive MS (SPMS) within 10 years and up to 90% develop SPMS after 20 to 25 years.[3,4] SPMS is a type of MS with a worse prognosis than RRMS, associated with irreversible disability.[3] In clinical practice, SPMS is hard to diagnose,[3,5] typically characterised by signs that the patient's MS has been getting steadily worse for six months.[5]

2.2 Company's overview of current service provision

In the CS summary document (Section A1), the company highlights:

> "There is no cure for MS and current pharmacological management of RRMS includes disease-modifying therapies (DMTs) to reduce the frequency and severity of and the rate of disease progression. Despite a number of recent NICE approvals there remains an unmet need for a highly effective and well-tolerated treatment particularly for patients who are newly diagnosed and wish to have a convenient, effective and well tolerated therapy."

The treatment algorithm for the current management of RRMS developed by NHS England and the ABN[1] includes treatment pathways for patients with various types of MS, including those with active RRMS, HA RRMS and RES RRMS. The company has depicted the pathway for these three populations in the (CS, Figure 1) and this is reproduced below (Figure 1). Current DMT options for patients with active RRMS, HA RRMS and RES RRMS are also summarised by the ERG in Table 1.



* Alternative first-line therapies due to intolerance

** For patients experiencing disease activity whilst on first-line treatment

#At the time that the ERG received the company's submission (5 November 2019), alemtuzumab was under review by the EMA due to safety concerns. The EMA advised that during the review, alemtuzumab use should only be started in adults with RRMS that is highly active despite treatment with at least two DMTs, or when other DMTs cannot be used. On 15 November 2019, the EMA advised that alemtuzumab should only be used if the disease is highly active despite treatment with at least one DMT or if the disease is worsening rapidly

Ocrelizumab is recommended by NICE in cases where alemtuzumab is contraindicated or unsuitable

Figure 1.Treatment algorithm for the current management of RRMS

DMTs=disease-modifying therapies; EMA=European Medicines Agency; IFN=interferon; MS=multiple sclerosis; RRMS=relapsing remitting multiple sclerosis

Source: CS, Figure 1, which is stated by the company to be based on NHS England 2019;[1] the notes to the figure presented in this ERG report have been edited by the ERG

As highlighted by the company (CS, Section B.1.3.3), in NHS clinical practice, the choice of DMT prescribed to treat RRMS is largely driven by an informed discussion and consensus between the prescribing clinician and the patient. Factors that are considered to be relevant include the level of disease activity, patient risk tolerance, patient preference and patient lifestyle considerations, such as family planning.

Clinical advice to the ERG is that for patients with two significant relapses in the last 2 years, treatment with dimethyl fumarate (DMF) tends to be the preferred first-line DMT for patients with active RRMS. Clinical advice to the ERG is that DMF is an oral treatment which is associated with few safety concerns. Clinical advice to the ERG is that DMF is perceived by many clinicians to be superior to most other treatment options. First-choice options for patients with one relapse in the last 2 years who also have radiological activity are interferon beta-1a (IFN β-1a; Avonex or Rebif) or glatiramer acetate (GA; Copaxone or generic). As can be seen from Figure 1 and Table 1, there are more first-choice first-line options for patients with active RRMS who have had two significant relapses in the last 2 years than for patients who have had one relapse in the last 2 years and who also have radiological activity. Information presented in Figure 1 shows that once patients who have had two significant relapses in the last 2 years require a second-line DMT, they are considered to have HA RRMS.

[redacted]

As noted in Table 1, peginterferon beta-1a (peg-IFN β-1a) does not currently feature in the treatment algorithm developed by NHS England and the ABN.[1] This is because the NICE appraisal of this DMT is ongoing (ID1521).[6] However, clinical advice to the ERG is that peg-IFN β-1a is currently used in NHS clinical practice [redacted].

Table 1 Current disease modifying treatment options for patients with active RRMS

Treatment	Type	NICE	Population*	Note
IFN β-1a (Avonex and Rebif)	Injection	TA527 (2018)[7]	Active RRMS (1) 1st-line (2) 1st-line	Avonex is injected weekly (30µg) Rebif is injected 3 times a week (22µg or 44µg per administration)
IFN β-1b (Extavia)	Injection	TA527 (2018)[7]	Active RRMS (1) 1st-line alternative (2) 1st-line	Injected every other day (250µg) Betaferon (another type of IFN β-1b) is not recommended by NICE
Glatiramer acetate (Copaxone and generic)	Injection	TA527 (2018)[7]	Active RRMS (1) 1st-line (2) 1st-line	Injected daily (20mg) or 3 times a week (40mg per administration)
Peg-IFN β-1a (Plegridy)	Injection	No guidance issued yet	Not included in the treatment algorithm developed by NHS England and the ABN[1]	The recommended dose is 125µg every 2 weeks Not included in the treatment algorithm[1] as the NICE appraisal[6] is still in progress (ID1521)[6]
Teriflunomide (Aubagio)	Oral	TA303 (2014)[8]	Active RRMS (1) 1st-line alternative (2) 1st-line	Taken daily (14mg)
Dimethyl fumarate (Tecfidera)	Oral	TA320 (2014)[9]	Active RRMS (1) 1st-line alternative (2) 1st-line	The recommended dose is 120mg twice daily in the first week of treatment and 240mg twice daily thereafter Clinical advice to the ERG is this is often the preferred 1st-line DMT for active RRMS in clinical practice
Alemtuzumab (Lemtrada)	Infusion	TA312 (2014)[10]	HA RRMS# RES RRMS#	#Alemtuzumab was previously available for patients with active RRMS when recommended by NICE. Following a review by the EMA, it is now restricted to HA RRMS despite treatment with at least one DMT or if the disease is worsening rapidly.[11] Thus, it is not a relevant comparator to ozanimod based on population
Ocrelizumab (Ocrevus)	Infusion	TA533 (2018)[12]	Active RRMS (1) 1st-line or 2nd-line (2) 1st-line HA RRMS RES RRMS	Recommended by NICE where alemtuzumab is contraindicated or otherwise unsuitable[12] The first dose is administered as 2×300mg infusions 2 weeks apart; subsequent doses are administered as a single 600mg infusion every 6 months
Cladribine (Mavenclad)	Oral	TA493 (2017)[13]	HA RRMS RES RRMS	Not a relevant comparator to ozanimod based on population
Fingolimod (Gilenya)	Oral	TA254 (2012)[14]	HA RRMS RES RRMS alternative	Similar class of drug as ozanimod but not a relevant comparator to ozanimod based on population
Natalizumab (Tysabri)	Infusion	TA127 (2007)[15]	RES RRMS 1st or 2nd-line	Not a relevant comparator to ozanimod based on population

DMT=disease modifying therapy; EMA=European Medicines Agency; HA=highly active; IFN β-1a=interferon beta-1a; IFN β-1b=interferon beta-1b; peg-IFN β-1a=peginterferon beta-1a; RES=rapidly evolving severe disease; RRMS=relapse-remitting multiple sclerosis; TA=technology assessment

* Key to RRMS populations (with the recommended line of treatment being based on the treatment algorithm developed by NHS England and the ABN[1]): (1): 1 relapse in last 2 years and radiological activity (2): 2 significant relapses in the last 2 years

Note: alternatives to 1st-line DMTs are alternatives that can be given as a result of intolerance to first-choice options

Note: All injectable DMTs are injected subcutaneously except for Avonex which is an intramuscular injection. Furthermore, it has been noted by NICE[7] that interferon beta-1b (Extavia) is supplied as a solvent and powder which must be mixed before being administered and therefore this may be more difficult for patients with RRMS to use than other injectable DMTs

As per its then European Medicines Agency (EMA) license, alemtuzumab was recommended by NICE (TA312[10]) for treating active RRMS, as well as for more severe RRMS (HA RRMS or RES RRMS) in 2014. However, as noted by the company (CS, Section B.1.3.3), at the time the company produced its submission, the alemtuzumab licence was being reviewed by the European Medicines Agency (EMA) and was only recommended for more severe cases of MS.[16] This review has now been completed and alemtuzumab is now restricted as a treatment option for HA RRMS and RES RRMS and only for patients without certain heart, circulation or bleeding disorders or autoimmune disorders other than MS.[11] Ocrelizumab has been recommended by NICE (TA533[12]) for the treatment of RRMS (i.e. patients with active RRMS, HA RRMS or RES RRMS) when alemtuzumab is contraindicated or otherwise unsuitable in 2018. Therefore, clinical advice to the ERG is that clinicians who would previously have considered alemtuzumab for active RRMS will now consider treatment with ocrelizumab in those instances instead. Clinical advice to the ERG is that most clinicians would probably only consider ocrelizumab for more severe cases of active RRMS, e.g. for patients who do not quite meet the criteria for HA RRMS or RES RRMS or who have had a very disabling relapse. [redacted].

2.3 Ozanimod

Ozanimod is a sphingosine-1-phosphate 1 receptor (S1P1R) modulator (CS, Table 2). As noted by the company (CS, p19), research suggests there is a key role for the S1P1R in the development and progression of MS as it mediates lymphocyte trafficking.[17] The ERG notes that fingolimod was the first S1P1R modulator to be used in clinical practice. Fingolimod is only used to treat HA RRMS and sometimes RES RRMS in NHS clinical practice in England and Wales.

Currently, ozanimod does not have a marketing authorisation in the UK. The EMA Committee for Medicinal Products for Human Use decision is expected in [redacted] and the marketing authorisation is expected in [redacted].

As noted in the CS (p13 and p18) and Section 2.1 of this ERG report, the company state that the anticipated use of ozanimod is to treat patients with active RRMS but not HA RRMS or RES RRMS. The company appear to have reached this view in part as a result of clinical feedback but also from ABN guidance which classifies DMTs as either Category 1 (moderate efficacy and established safety profiles) or Category 2 (high efficacy and more complex safety profiles).[18] The company considers that ozanimod belongs to Category 1 and will therefore used as a first-line treatment for active RRMS. The ERG has received clinical advice supporting this view and additional clinical advice suggesting that ozanimod may also be

suitable for patients with HA RRMS. The ERG also notes that fingolimod is classified as a Category 1 DMT but is used to treat HA RRMS.

Ozanimod is administered orally once daily. [redacted] The company in its submission (and therefore the ERG in this report) has focussed primarily on evidence for the 1mg dose of ozanimod. Ozanimod 1mg is titrated at a dose of 0.25mg on Days 1 to 4, 0.5mg on Days 5 to 7 and the full 1mg dose is first given on Day 8.

2.4 Number of patients eligible for treatment with ozanimod

The total number of patients with active RRMS eligible for treatment with a DMT in England and Wales was estimated by the company to be [redacted] (Table 2). The company states in its Budget Impact Assessment report (p8) that [redacted]. As the company also highlights, only a proportion of these patients would receive ozanimod; the company's estimates being [redacted] in the first year rising to [redacted] after 5 years (Budget Impact Assessment report, Table 9).

Table 2 Company estimate of number of patients potentially eligible for treatment with ozanimod in England and Wales in 2019

Population	Proportion	Number	Source
Total adult (>18 years) population		46,868,875	ONS 2019[19]
Prevalent patients with MS	0.20%	92,908	Mackenzie et al 2015[20]
Incident patients with MS	0.009%	4,228	Mackenzie et al 2015[20]
Patients with RRMS	42.00%	40,797	Hawton and Green 2016[21]
Patients with RRMS eligible for DMT*	31.00%	12,647	Zajiceck et al 2010[22]

ONS=Office for National Statistics
* The eligible population represents a population of patients with active RRMS eligible for DMT treatment with beta-interferons, glatiramer acetate, dimethyl fumarate or teriflunomide
Source: data extracted from company Budget Impact Assessment report, Table 3

2.5 Critique of company's definition of the decision problem

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[2] and that addressed within the CS is presented in Table 3.

Table 3 Comparison between NICE scope and company's decision problem

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Intervention	Ozanimod	Ozanimod 1mg daily oral	[redacted]
Population	People with relapsing-remitting multiple sclerosis (RRMS)	As per scope	~75% patients had active RRMS (the population the company consider ozanimod is suitable for) but ~23% had more severe RRMS and ~2% had SPMS
Comparator (s)	For patients with active RRMS: • Alemtuzumab* • Beta-interferon • Dimethyl fumarate • Glatiramer acetate • Teriflunomide • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • Peginterferon beta-1a (subject to ongoing NICE appraisal) For patients with highly active (HA) RRMS despite previous treatment: • Alemtuzumab* • Cladribine tablets • Fingolimod • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with rapidly-evolving severe (RES) RRMS: • Alemtuzumab* • Cladribine tablets • Natalizumab • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	For patients with active RRMS:* • Beta-interferons • Glatiramer acetate • Dimethyl fumarate • Teriflunomide • Ocrelizumab** (only if alemtuzumab is contraindicated or otherwise unsuitable) • Peginterferon beta-1a (subject to ongoing NICE appraisal) *Alemtuzumab is currently under review by the EMA due to safety concerns. As a result, the EMA committee advises that during the review alemtuzumab use should only be started in adults with RRMS that is highly active despite treatment with at least two disease-modifying therapies, or when other disease-modifying therapies cannot be used. Due to the expected use of ozanimod in UK clinical practice as a therapy to treat patients with active RRMS (and not highly active RRMS) alemtuzumab is not considered a relevant comparator to ozanimod Since ocrelizumab is only recommended by NICE to be used in patients where alemtuzumab is contraindicated or otherwise unsuitable, it is also not considered a relevant comparator to ozanimod Due to the expected use of ozanimod in UK clinical practice as a therapy to treat patients with active RRMS, this submission will not consider ozanimod for the treatment of patients with either HA or RES RRMS	The ERG considers that the comparators considered by the company are appropriate for patients with active RRMS (including peginterferon beta-1a which although being currently reviewed by NICE [ID1521], is currently used to treat patients in NHS clinical practice) The ERG also considers that ocrelizumab, which was excluded as a comparator by the company, should have been included as a comparator since it is recommended by NICE as a first-line treatment option for patients with active RRMS (TA533) and clinical advice to the ERG is that it is used to treat some of this patient population

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Outcomes	• Relapse rate • Severity of relapse • Disability (e.g. EDSS) • Symptoms of MS (e.g. fatigue, cognition and visual disturbance) • Freedom from disease activity (e.g. lesions on MRI scans) • Mortality • Adverse effects of treatment • Health-related quality of life	• Relapse rate • Disability • Freedom from disease activity • Mortality • Adverse effects of treatment • Health-related quality of life • Brain atrophy (brain volume) • Radiological (MRI) measurements of disease activity (T2 and Gd-E T1 brain lesion) RADIANCE and SUNBEAM [i.e. trials of ozanimod] did not explore severity of relapse, and symptoms in their trial design endpoints. Freedom from disease activity has been reported as no evidence of disease activity 3 (NEDA-3) and 4 (NEDA-4).	The ERG considers that the outcomes are relevant for measuring the clinical effectiveness of DMTs for patients with RRMS in phase III trials Clinical advice to the ERG is that severity of relapse is a clinically important outcome which is often not captured by clinical trials The ERG notes that in the RADIANCE Part B and SUNBEAM trials of ozanimod, disability is measured by confirmed disease progression (CDP) at 3 months (CDP-3M) and 6 months (CDP-6M), i.e. worsening of ≥1-point increase in Expanded Disability Status Scale (EDSS). Although EDSS and CDP are clinically relevant measures, limitations with both measures are widely recognised and highlighted by the company in the CS (Section B.1.3.2)
Subgroups	If the evidence allows the following subgroups will be considered: People who could not tolerate previous treatment	No subgroups will be considered	The ERG notes that whereas the RADIANCE Part B and SUNBEAM trials of ozanimod (and some trials of other DMTs) include analyses of some subgroups, evidence for the subgroup of people who could not tolerate previous treatment is lacking

Gd-E=gadolinium-enhancing; MRI=magnetic resonance imaging
Source: Final scope issued by NICE,[2] CS Table 1 and Section B.1.4

3 CLINICAL EFFECTIVENESS

3.1 Systematic review methods

Full details of the company's process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D to the CS. The ERG considered whether the review was conducted in accordance with key features of the systematic review process, as summarised in Table 4. Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence appear to be satisfactory.

Table 4 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Partially	Eligibility criteria in relation to outcomes should have been more explicit (see note for item "Were the eligibility criteria appropriate to the decision problem?" below)
Were appropriate sources searched?	Yes	Sources included MEDLINE, Embase, the Cochrane Library and searches of trial registries for ongoing trials. No searches of conference websites were conducted as an exclusion criterion was conference abstracts. The company also consulted the reference lists of two previously conducted NMAs of interventions in the treatment of RRMS.[13,23]
Was the timespan of the searches appropriate?	Yes	The search was originally run 10 October 2017 and updated 12 June 2019
Were appropriate search terms used?	Yes	No additional ERG comments
Were the eligibility criteria appropriate to the decision problem?	Partially	In relation to outcomes, it is stated studies which do not report outcomes of interest will be excluded, without stating what the outcomes of interest are (CS, Appendix D1.1.2, Table 3)
Was study selection applied by two or more reviewers independently?	Yes	This improves the accuracy of study selection and reduces study selection bias
Was data extracted by two or more reviewers independently?	Unclear	While the company has stated two investigators independently extracted data for the final list of selected eligible studies for the cost effectiveness review (CS, Appendix G, Section G1.1, p103), equivalent information is not reported for the clinical effectiveness review
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company conducted a quality assessment exercise using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal[24] (CS, Appendix D1.2.3,Table 11)
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Responsibility for quality assessment is not reported
Were attempts to synthesise evidence appropriate?	Yes	NMAs were required to compare ozanimod with all appropriate comparators. For full details of the NMAs, see Section 3.10 of this ERG report

NMA=network meta-analysis

3.2 Identified trials

A total of 47 randomised controlled trials (RCTs) from 46 publications[25-70] were "included for potential analysis" in the company's systematic review (CS, Appendix D1.1.3, Figure 1). This included three trials of ozanimod, 38 trials[25-28,30-45,47-52,54-62,64,67-70] with at least one comparator relevant to the company's decision problem and six trials[29,46,53,63,65,66] of DMTs which the company did not consider to be relevant to the decision problem (i.e., trials of cladribine,[46] natalizumab[63,66] and fingolimod[29,53,65] versus placebo).

The three ozanimod RCTs were a phase II trial (the RADIANCE Part A trial[32] in which the comparator was placebo) and two phase III trials (the RADIANCE Part B and SUNBEAM trials[35,40] in which the comparator was IFN β-1a [Avonex]).

In addition to data from the trials of ozanimod, the company's pooled analysis of safety and tolerability evidence incorporates data from the phase I RPC01-PK/PD study and the ongoing single-arm phase III DAYBREAK open label extension (OLE) study. The DAYBREAK OLE study includes patients who had been enrolled in the RPC01-1001PK/PD study, RADIANCE Part A trial, RADIANCE Part B and SUNBEAM trials.

3.3 Characteristics of the included ozanimod trials

Data presented for trials of ozanimod that are included in the CS include data extracted by the company from the CSRs.[71-73]

3.3.1 Trial characteristics

All three RCTs of ozanimod included two ozanimod arms: a 1mg dose arm and a 0.5mg dose arm. The company in its submission (and therefore the ERG in this report) has only presented evidence for the efficacy of ozanimod for the 1mg dose (ozanimod 0.5mg results can be found in the journal publications of the trials of ozanimod[32,35,40]). However, safety data are presented in the CS for both doses of ozanimod.

The RADIANCE Part A trial was a multi-centre, double-blind, placebo-controlled RCT. Randomisation was 1:1:1 and stratified by country. Patients were enrolled between 18 October 2012 and 13 April 2014 and the length of follow-up was 24 weeks. In total, the trial included 258 patients (ozanimod 1mg, n=83; ozanimod 0.5mg, n=87; placebo, n=88). The primary outcome was reduction in the cumulative number of Gd-E T1 brain MRI lesions from Week 12 to Week 24. Secondary outcomes included the number of Gd-E T1 brain MRI lesions at Week 24, the cumulative number of new or enlarging hyperintense T2-weighted brain MRI lesions at Weeks 12 to Week 24, ARR and safety and tolerability.

The RADIANCE Part A trial also included a blinded extension phase of 96 weeks, in which patients were enrolled between 1 May 2013 and 11 May 2016.[74] In the blinded extension phase, patients who had been receiving ozanimod remained on ozanimod at the same dose (ozanimod 1mg, n=81; ozanimod 0.5mg, n=85) whilst patients who had been in the placebo arm were randomised to ozanimod 1mg (n=42) or ozanimod 0.5mg (n=41). Outcomes included mean number of Gd-E T1 brain lesions, proportions of participants free of Gd-E T1 brain lesions, mean number of new or enlarging hyperintense T2-weighted brain MRI lesions on brain MRI, ARR and safety and tolerability.

The RADIANCE Part B and SUNBEAM trials were both double-blind, double-dummy, active-controlled parallel arm RCTs. In both trials, randomisation was 1:1:1 and stratified by baseline Expanded Disability Status Scale (EDSS) (≤3.5, >3.5) and country. In the RADIANCE Part B trial, the length of follow-up was 24 months (with patients enrolled between 27 December 2013 and 31 March 2015). In the SUNBEAM trial, patients were enrolled between 18 December 2014 and 12 November 2015 and followed up ≥12 months [redacted].

In both trials, the primary efficacy endpoint was ARR during the treatment period. Other outcomes relevant to the final scope issued by NICE[2] and the company's decision problem were also reported, namely MRI measurements of disease activity, brain atrophy (brain volume) including brain volume loss (BVL), CDP, health related quality of life (HRQoL), no evidence of disease activity (NEDA) and safety and tolerability. In total, the RADIANCE Part B and SUNBEAM trials included 2659 patients (RADIANCE Part B, N=1313; ozanimod 1mg, n=433; ozanimod 0.5mg n=439; IFN β-1a [Avonex], n=441; SUNBEAM, N=1346; ozanimod 1mg, n=447; ozanimod 0.5mg, n=451; IFN β-1a [Avonex], n=448).

The eligibility criteria for entry into all three RCTs are summarised in Table 5 of this ERG report. The ERG also notes that patients at higher risk of bradycardia have been excluded from the trials since patients with specific cardiovascular conditions at screening were excluded from the ozanimod trials. It is therefore unclear if ozanimod would be suitable for such patients within clinical practice.

The ERG highlights that concomitant medications with a known impact on the cardiac conduction system were not permitted in any of the trials, e.g. beta-blockers (CS, Section B.2.3.2). Clinical advice to the ERG is that, before treating patients with fingolimod, cardiology advice is required for patients who are receiving treatment with a beta-blocker. It is therefore unclear whether, if ozanimod were to be recommended by NICE, would similar advice be required before starting treatment.

Table 5 Eligibility criteria for patient entry into the RADIANCE Part A, RADIANCE Part B and SUNBEAM trials

Inclusion criteria	Exclusion criteria
• Adult subjects with RMS aged 18 to 55 years, inclusive • Meeting the revised McDonald 2010 criteria • EDSS (expanded disability status scale) score between 0 and 5.0 at baseline • At least 1 documented relapse within the last 12 months, or at least 1 documented relapse within the last 24 months plus at least 1 Gd-E T1 brain MRI lesion within the last 12 months, prior to randomization • No history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening through randomisation • Positive varicella zoster virus immunoglobulin G antibody status or varicella zoster virus vaccination at least 30 days before randomisation	• PPMS • Disease duration greater than 15 years and an EDSS of 2.0 or less • Previous inability to tolerate IFN-β • Specific cardiovascular conditions (e.g., recent myocardial infarction, stroke, or prolonged QTcF) • Resting heart rate less than 55 bpm at screening • Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers • Any active infection

bpm=beats per minute; EDSS=Expanded Disability Status Scale; Gd-E=gadolinium-enhancing; PPMS=primary progressive multiple sclerosis; QTcF=Fridericia-corrected QT interval; RMS=relapsing multiple sclerosis
Source: CS, Section B.2.2.2

3.3.2 Baseline characteristics of patients enrolled in the ozanimod trials

In the CS, baseline characteristics are only reported for the RADIANCE Part B and SUNBEAM trials (CS, Section B.2.3.4) and not the RADIANCE Part A trial. Baseline characteristics were well balanced between the ozanimod 1mg and placebo arms of each trial and also between these four arms across trials. In the RADIANCE Part B and SUNBEAM trials, the ERG observes from the data for these four arm presented in the CS (Table 6) that:

- The mean age of patients was 35 years.
- Two-thirds (67%) of patients were women and approximately 99% of patients were classified as being white.
- Most patients were from Eastern Europe (approximately 86% in the RADIANCE Part B trial and approximately 93% in the SUNBEAM trial, approximately 90% overall).
- The mean time since MS onset was just under 7 years and the mean time since MS diagnosis was approximately 4 years.
- The mean EDSS score was approximately 2.5 in the RADIANCE Part B trial and approximately 2.6 in the SUNBEAM trial.
- The mean number of relapses in the last 12 months was 1.3.

Clinical advice to the ERG is that these characteristics are not dissimilar to the characteristics of patients with active RRMS typically recruited to MS trials and are likely to be similar to patients seen in NHS clinical practice in England and Wales, the most notable exceptions being that the ozanimod trials included a much higher proportion of white and Eastern European patients than would be seen in England and Wales. It is unclear if results would therefore differ in a more diverse patient population as would be expected to be seen in NHS clinical practice.

Of note, the company highlights that, in both trials, approximately 70% of patients had received no prior DMT treatment for MS (CS, p38). The ERG notes that the company only considers ozanimod as a first-line treatment option (See Section 2.3 of this ERG report). However, it is unclear if patients had stopped treatment with their prior DMT due to poor efficacy (meaning the study drug could be considered to be a second-line treatment) or intolerability (in which case, the study drug may be considered an alternative first line therapy; see Section 2.2 [Table 1] of this ERG report). The ERG also notes that people who could not tolerate previous

treatment were a subgroup of interest specified in the final scope issued by NICE[2] (see Section 2.5 [Table 3] of this ERG report).

Furthermore, the company also highlights that in both trials, "Patients had a wide range of disease activity" (CS, p38). The ERG notes that it is also reported in the CS (Table 6) that approximately 23% of patients had "high disease activity". It is not specified in the CS what is meant by "high disease activity". However, this is defined in the company's pooled analysis statistical analysis plan (SAP)[75] as follows:

[redacted]

Clinical advice to the ERG is that the first part of this definition is broadly comparable to a RES RRMS population and the second part of the definition is broadly comparable to a HA RRMS population. Thus, approximately 23% of patients can be considered to have more severe RRMS than active RRMS.

Further information on prior treatment and disease activity is reported in the company's subgroup analysis report (which includes information for both trials pooled)[76] and summarised by the ERG in Table 6.

Table 6 Prior treatment and disease activity in the RADIANCE Part B and SUNBEAM trials (pooled data)

Characteristic	IFN β-1a 30µg (Avonex)	Ozanimod 1mg
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Celgene 2019c,[76] demographic information tables for Group 1 to Group 5

In addition, the company highlights (CS, p23) that the recruited population in these two trials also included a small proportion of patients with SPMS (1.8% of the pooled intention-to-treat [ITT] population). Hence the target population of the RADIANCE Part B and SUNBEAM trials is referred to by the company, more broadly, as relapsing MS (RMS).

Importantly, the ERG notes that the company does not consider ozanimod to be a treatment option for patients with HA RRMS or RES RRMS, nor for patients with SPMS (See Section 2.3 of this ERG report). Thus, while most patients had active RRMS (approximately 75% of patients in the four relevant arms of both trials), a relatively high proportion did not (approximately 25%).

While baseline characteristics are not presented in the CS for the RADIANCE Part A trial, the ERG observes from the published paper[32] that the characteristics were mostly well balanced between arms. Furthermore, the characteristics were broadly similar to those of the RADIANCE Part B and SUNBEAM trials, namely:

- The mean age of patients in the RADIANCE Part A trial was 38-39 years.
- 71% of patients in the ozanimod 1mg and placebo arms were women and 99% of patients were classified as being white.
- Most patients were from Eastern Europe (approximately 90% in all three arms).
- The mean time since MS onset was approximately 6 years in the ozanimod 1mg arm and 8 years in the placebo arm and the mean time since MS diagnosis was approximately 7 years in the placebo arm and approximately 6 years in the ozanimod 1mg arm.
- The mean EDSS score was approximately 2.9.
- The mean number of relapses in the last 12 months was 1.3 in the ozanimod 1mg and placebo arms.

Information on disease activity and prior treatment is not presented for the RADIANCE Part A trial in the published paper.[32]

3.4 Quality assessment for the trials of ozanimod

The company conducted a quality assessment of the RCTs of ozanimod using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[24] The company's assessments and ERG comments are presented in Table 7.

Overall, the ERG agrees with the company's assessments and considers that the trials of ozanimod were generally well designed and well conducted.

Table 7 Quality assessment for the trials of ozanimod

Quality assessment item	Company assessment			ERG comment
	RADIANCE Part A	RADIANCE Part B	SUNBEAM	
Was randomisation carried out appropriately?	Yes	Yes	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Agree
Were the arms similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Agree
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Agree
Were there any unexpected imbalances in drop-outs between arms?	No	No	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	The ERG generally agrees that the approach used to account for missing data was appropriate. However, the ERG has concerns with the LOCF method used to impute missing data (see Table 8 of this ERG report).

LOCF=last observation carried forward
Source: CS, extracted from Table 11, Appendix D.1.2.3 and ERG comment

3.5 Statistical approach adopted for the trials of ozanimod

Information relevant to the statistical approach taken by the company has been taken from the clinical study reports (CSRs), the trial statistical analysis plans (TSAPs),[77-79] the SAP of the pooled analysis of the RADIANCE Part B and the SUNBEAM trials,[75] and from the CS. A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the included trials is provided in Table 8.

Table 8 ERG assessment of statistical approaches used in the ozanimod trials

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations (ITT, PP and safety populations) are clearly defined and pre-defined in the TSAPs (Section 5.3) and the SAP of the pooled analysis of the RADIANCE Part B and SUNBEAM trials (Section 3.2). Clinical effectiveness results are presented for the ITT population (i.e. all randomised patients who are confirmed to have received at least one dose of study drug) within the CS (Section 2.6). Safety results are presented for the safety population (i.e. all patients who have received at least one dose of study drug) within the CS (Section 2.10).
Was an appropriate sample size calculation pre-specified?	Yes	The sample size calculations of the RADIANCE Part B and SUNBEAM trials are reported in the CS (Table 7). To control for potential type 1 error resulting from multiple treatment comparisons (two ozanimod doses and one IFN β-1a dose) and three key secondary outcomes, a sequential, closed, hierarchical procedure was employed for statistical testing in the RADIANCE Part B and SUNBEAM trials (CS, Table 7). The ERG is satisfied that the sample size calculations and approach to statistical testing within the ozanimod trials are appropriate and pre-specified in the TSAPs (Section 5).
Were all protocol amendments made prior to analysis?	Yes	A list of all amendments made from the original trial protocols and TSAPs and the rationale for these amendments are outlined within the CSRs (Section 9.8). The ERG is satisfied that all amendments to the trial protocols and TSAPs are reasonable and were made prior to final analysis.
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary and secondary efficacy outcomes of the trials described in the CS (Table 5) and the statistical analysis approach for primary and key secondary efficacy outcomes of the RADIANCE Part B and SUNBEAM trials are reported in the CS (Table 8). Statistical analysis approaches for all efficacy outcomes of the RADIANCE Part A, RADIANCE Part B and SUNBEAM trials are described in the TSAPs (Section 9). The statistical analysis approaches are described in the SAP of the pooled analysis of the RADIANCE Part B and SUNBEAM trials (Section 3.7 to 3.8). The ERG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-defined in the TSAPs (Section 9) and SAP of the pooled analysis (Section 3.7 to 3.8) and that the definitions and analysis approaches are appropriate.
Was the analysis approach for PROs appropriate and pre-specified?	Yes (For RADIANCE Part B and SUNBEAM trials)	The PRO outcome measured in the trials was change in MSQoL-54 score from baseline to month 24 (RADIANCE Part B) or month 12 (SUNBEAM), measured in the ITT population (CS, Table 5). The ERG is satisfied that the PRO outcome definitions and analysis approaches were pre-defined in the TSAPs (Section 9.3) and that the definitions and analysis approaches are appropriate. The ERG notes that MSQoL-54 is included within the schedule of assessments for the RADIANCE Part A trial (CSR, Table 9-3), but no results for the MSQoL-54 score are provided within the CSR.

Item	ERG assessment	Statistical approach with ERG comments
Was the analysis approach for AEs appropriate and pre-specified?	Yes	AEs were assessed using the MedDRA classification system. AEs are presented as listings for the safety population; no formal statistical analyses were conducted and only treatment-emergent AEs were presented within the CS (Section B.2.10). The ERG is satisfied that the approaches used to analyse AEs were pre-defined in the TSAPs (Section 10) and approaches are appropriate. The ERG is also satisfied that all summary tables of AEs are presented in the CSRs (Section 12.2 to 12.3); all AEs by system organ class or by preferred term, by relationship to investigational product, by severity, also AEs of special interest, AEs leading to treatment discontinuation, SAEs and deaths.
Were modelling assumptions (e.g. proportional hazards) assessed?	Yes	It was pre-specified in the TSAPs that ARR would be analysed for all trials using a Poisson regression model (Section 9.1.1). An assumption of Poisson regression is that the mean and variance of the number of events is equal. This assumption is explored in a sensitivity analysis by using a negative binomial assumption instead (TSAP, Section 9.1.2) and results of this sensitivity analysis demonstrate that the assumption of equal mean and variance is valid (Section 11.4.1.4 of the RADIANCE Part B and SUNBEAM CSRs and Section 11.4.1.2.2 of the RADIANCE Part A CSR). It was also pre-specified in the TSAPs that key secondary efficacy outcomes of the RADIANCE Part B and SUNBEAM trials CDP-3M and CDP-6M would be analysed using a Cox PH model (Section 9.2.1). As part of the clarification process, the company tested the PH assumption using the methodology of Grambsh and Therneau (a statistical test of Schoenfeld residuals against time).[80] Based on these investigations (response to question A4 of the clarification letter), there was no evidence that the PH assumption was violated for CDP-3M or CDP-6M in the RADIANCE Part B trial, the SUNBEAM trial or the pooled analysis. The ERG is satisfied that it is appropriate for the Cox PH model to be used and for HRs to be presented for CDP-3M and CDP-6M.
Was a suitable approach employed for handling missing data?	Yes	The approach to managing missing data is described in the TSAPs; the general approach outlined in Section 5.4.4 (plus Appendix A) and the approaches for each secondary efficacy outcome are outlined in Section 9.2 and Section 9.3. Missing data for secondary efficacy outcomes is generally handled by a range of sensitivity analyses including mean imputation, complete-case analysis, LOCF and mixed-effects regression. The ERG considers that most of the approaches used to handle missing data are appropriate but notes that the LOCF method ignores the uncertainty introduced by missing outcome data.[81] The ERG therefore prefers the alternative approaches used for handling missing data.
Were all subgroup and sensitivity analyses pre-specified?	Yes	The ERG is satisfied that all of the pre-planned subgroup analyses presented within the CS (Section B.2.7 and Appendix E) were pre-specified in the TSAPs (Section 5) and the SAP of the pooled analysis of the RADIANCE Part B and SUNBEAM trials (Section 4). No sensitivity analyses are presented within the CS. The ERG notes that sensitivity analyses for efficacy outcomes were pre-specified in the TSAPs (Section 9) and the SAP of the pooled analysis of the RADIANCE Part B and SUNBEAM trials (Section 3.7 to 3.8). Results of these sensitivity analyses are reported in the CSRs (Section 11.4.1.4 of the RADIANCE Part B and SUNBEAM CSRs and Section 11.4.1.2.2 of the RADIANCE Part A CSR) but results of sensitivity analyses for the pooled analysis of the RADIANCE Part B and SUNBEAM trials are not available.

AE=adverse event; ARR=annualised relapse rate; CDP-3M=time to onset of disability progression confirmed after 3 months; CDP-6M=time to onset of disability progression confirmed after 6 months; CSR=clinical study report; HR=hazard ratio; IFN=interferon; ITT=intention-to-treat; MedDRA=medical dictionary for regulatory activities; LOCF=last observation carried forward; MSQoL=multiple sclerosis quality of life; PH=proportional hazards; PP=per protocol; PRO=patient reported outcome; SAE=serious adverse event; SAP=statistical analysis plan; TSAP=trial statistical analysis plan
Source: extracted from the CS, CSRs of RADIANCE Part A,[71] RADIANCE Part B[72] and SUNBEAM;[73] TSAPs of RADIANCE Part A,[79] RADIANCE Part B[77] and SUNBEAM;[78] SAP of the pooled analysis of RADIANCE Part B and SUNBEAM;[75] the company's response to the clarification letter and ERG comment

Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company.

3.5.1 Pooled efficacy analysis of the RADIANCE Part B and SUNBEAM trials

A pre-specified integrated (pooled) efficacy analysis of the RADIANCE Part B and SUNBEAM trials at 12 months was conducted. In order to increase the power of the key efficacy outcome 'time to onset of disability progression' as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months (CDP-3M and CDP-6M respectively), formal statistical testing of this outcome within the pooled analysis was pre-specified within the sequential, hierarchical testing procedure of the RADIANCE Part B and SUNBEAM trials (see Section 5 of the RADIANCE Part B[77] and SUNBEAM TSAPs[78]). For other outcomes, the objective of the pooled efficacy analysis was treatment effect estimation rather than formal statistical testing. The ERG agrees with the company's assessment that the pooled analysis was appropriate due to similarities in study design, randomisation ratio, patient population and other design aspects (CS, Section 2.8). The ERG also considers the pre-specified statistical analysis approach of including study as a covariate within Poisson, Negative Binomial or Cox Proportional Hazards Regression models to adjust for study differences within the pooled analyses is appropriate.[75]

3.6 Efficacy results from the trials of ozanimod

Efficacy results presented within this section are based on the final analyses of the phase III RADIANCE Part B and SUNBEAM trials, in addition to the results of the pre-specified pooled analyses of the RADIANCE Part B and SUNBEAM trials and results of the phase II RADIANCE Part A trial (where measured). Results for the RADIANCE Part A blinded extension can be found within the CS (Table 22, Table 24, Table 26) and results for ozanimod 0.5mg can be found in the publications of the trials of ozanimod.[32,35,40]

3.6.1 Annualised relapse rate (ARR)

A summary of ARR results in the ITT population of the RCTs of ozanimod are provided in Table 9. The patient relapse rate and the relapse free rate (the latter was not measured in the RADIANCE Part A trial) are also provided in the CS (Table 7 and Table 23).

In both the RADIANCE Part B and SUNBEAM trials, as well as in the pooled analysis, ozanimod statistically significantly reduced ARR compared with IFN β-1a 30µg (Avonex); however, in the RADIANCE Part A trial, there was no statistically significant difference between ozanimod and placebo [redacted]

Table 9 Summary of ARR results in the ITT populations of the trials of ozanimod and the pooled analysis[a]

Results	RADIANCE Part A		RADIANCE Part B		SUNBEAM		Pooled analysis	
	24 weeks		24 months		≥12 months		up to 12 months	
	Placebo (n=88)	Ozanimod 1mg (n=83)	IFN β-1a 30µg (Avonex) (n=441)	Ozanimod 1mg (n=433)	IFN β-1a 30µg (Avonex) (n=448)	Ozanimod 1mg (n=447)	IFN β-1a 30µg (Avonex) (n=889)	Ozanimod 1mg (n=880)
Number of patients with relapses: n (%)								
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted ARR (95% CI)	[redacted]	[redacted]	0.28 (0.23 to 0.32)	0.17 (0.14 to 0.21)	0.35 (0.28 to 0.44)	0.18 (0.14 to 0.24)	[redacted]	[redacted]
Unadjusted ARR[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percent reduction in ARR (95% CI)[c]	[redacted]		[redacted]		[redacted]		[redacted]	
Rate ratio (95% CI)[c]	[redacted]		0.62 (0.51 to 0.77)		0.52 (0.41 to 0.66)		[redacted]	
p-value[d]	[redacted]		<0.0001		<0.0001		[redacted]	

[a] Percentages are reported to one decimal place, effect sizes and CIs (e.g. adjusted ARR and 95% CI) are reported to two decimal places, p-values are reported to 4 decimal places
[b] The unadjusted relapse rate for each treatment arm was calculated as the total number of relapses experienced in the arm divided by the total number of days in the study for the arm, and multiplied by 365.25
[c] Rate ratio and percent reduction in ARR are expressed as ozanimod / control (placebo or IFN β-1a 30µg [Avonex]). Rate ratio < 1 and percent reduction > 0 favours ozanimod over control
[d] Based on the Poisson regression model, adjusted for region (Eastern Europe vs Rest of the World), baseline age and number of Gd-E T1 brain MRI lesions, and included the natural log transformation of time on study as an offset term. Pooled analysis was adjusted for study effect differences. RADIANCE Part A also adjusted for the number of relapses within 24 months prior to the study
[e] Not reported within the CS; estimated by the ERG based on the reported rate ratio and 95% CI
ARR=annualised relapse rate; CI=confidence interval; Gd-E=gadolinium–enhanced; IFN=interferon; NR=not reported
Source: CS, extracted and adapted from Table 9 and Table 12

Subgroup analysis

Pre-planned subgroup analyses were performed for ARR in the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis based on demographic subgroups (baseline age and weight, sex, race and region) and disease characteristic subgroups (EDSS, number of relapses, prior MS treatment, prior DMT, Gd-E T1 brain MRI lesions, hyperintense T2-weighted brain MRI lesions, high disease activity, lymphocyte count). A reduction in ARR on ozanimod compared to IFN β-1a 30µg (Avonex) was consistently observed in all subgroups within the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis (CS, Section B.2.7).

3.6.2 Confirmed disability progression (CDP) at 3 months and at 6 months

Time to onset of disability as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months (CDP-3M and CDP-6M respectively) was the third ranked (within the hierarchy of statistical testing, see CS, Table 7) key secondary outcome in the RADIANCE Part B and SUNBEAM trials and the primary outcome of the pooled analysis of the RADIANCE Part B and SUNBEAM trials (see Section 3.5.1 of this ERG report). CDP was not measured within the RADIANCE Part A trial. CDP-3M and CDP-6M results in the ITT population of the trials of ozanimod are provided in Table 10.

There was no evidence of a difference in CDP between the ozanimod and IFN β-1a 30µg (Avonex) arms in either trial at 3 months or at 6 months (see Table 10 of this ERG report). The company argues that the number of CDP events at 3 months and at 6 months within the RADIANCE Part B and SUNBEAM trials was low, and the Kaplan-Meier estimates of CDP-3M and CDP-6M in the IFN β-1a 30µg (Avonex) arm were lower than anticipated (versus historical rates[33,53]) which reduced the ability to detect a difference between the treatment arms.

The ERG notes that, within the pooled analysis of the RADIANCE Part B and SUNBEAM trials, which was conducted with the aim of increasing the statistical power of the CDP-3M and CDP-6M outcome, no evidence of a difference in CDP between the ozanimod and IFN β-1a 30µg (Avonex) arms at either 3 or 6 months was found (p=0.7651 and p=0.1126 respectively).

Table 10 Confirmed disability progression at 3 months and at 6 months in the ITT populations of the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis[a]

Results	RADIANCE Part B		SUNBEAM		Pooled analysis	
	24 months		≥12 months		up to 12 months	
	IFN β-1a 30µg (Avonex) (n=441)	Ozanimod 1mg (n=433)	IFN β-1a 30µg (Avonex) (n=448)	Ozanimod 1mg (n=447)	IFN β-1a 30µg (Avonex) (n=889)	Ozanimod 1mg (n=880)
Confirmed disability progression at 3 months						
Number of patients with a confirmed progression: n (%)	50 (11.3)	54 (12.5)	[redacted]	[redacted]	69 (7.8)	67 (7.6)
Number of patients censored: n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)[b]	1.05 (0.71 to 1.54)[c]		[redacted]		0.95 (0.68 to 1.33)[c]	
Percent reduction (95% CI)[b]	[redacted]		[redacted]		[redacted]	
p-value[c]	0.8224[c]		[redacted]		0.7651[d]	
Confirmed disability progression at 6 months						
Number of patients with a confirmed progression: n (%)	29 (6.6)	42 (9.7)	[redacted]	[redacted]	36 (4.0)	51 (5.8)
Number of patients censored: n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)[b]	1.44 (0.89 to 2.31)[c]		[redacted]		1.41 (0.92 to 2.17)[d]	
Percent reduction (95% CI)[b]	[redacted]		[redacted]		[redacted]	
p-value	0.1353[c]		[redacted]		0.1126[d]	

[a] Percentages are reported to one decimal places, effect sizes and CIs (e.g. HR and 95% CI) are reported to two decimal places, p-values are reported to 4 decimal places
[b] HR and percent reduction of disability progression are expressed as ozanimod / IFN β-1a 30µg (Avonex). HR < 1 and percent reduction > 0 favours ozanimod over IFN β-1a 30µg (Avonex)
[c] Based on the Cox proportional hazard model with factors for treatment arm, adjusted for region (Eastern Europe vs Rest of the World), age at Baseline, and Baseline EDSS score
[d] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs. Rest of the World), age at baseline, and baseline number of Gd-E T1 brain MRI lesions. The natural log transformation of the number of available MRI scans was used as an offset term. Pooled analysis was adjusted for study effect differences
[e] Incorrect numbers reported in the CS; calculated by the ERG as n=total number of patients in the treatment arm – number of patients with a confirmed progression (and associated %)
CI=confidence interval; EDSS=expanded disability status scale; Gd-E=gadolinium–enhanced; HR=hazard ratio IFN=interferon; MRI=magnetic resonance imaging; NR=not reported
Source: CS, extracted and adapted from Table 15 and Table 16

3.6.3 Other outcomes

Other efficacy outcomes relating to brain MRI lesions, brain volume loss, multiple sclerosis functional composite (MSFC) and no evidence of disease activity (NEDA-3 and NEDA-4) in the trials of ozanimod are summarised in Appendix 1, Section 6.1 of this ERG report.

Statistically significant advantages for ozanimod compared with IFN β-1a 30 µg (Avonex) were observed for outcomes relating to brain MRI lesions, brain volume loss, NEDA-3 and NEDA-4.

3.7 Patient reported outcomes from the trials of ozanimod

HRQoL was a patient reported outcome (PRO) measured in the RADIANCE Part B and SUNBEAM trials.

3.7.1 HRQoL outcomes

HRQoL was measured using the multiple sclerosis quality of life-54 instrument (MSQoL-54),[82] which is described in the CSRs (Sections 9.5.1.1.6) as a multidimensional HRQoL measure that combines both generic and MS-specific items into a single instrument. As also highlighted in the CSRs (Sections 9.5.1.1.6), where patients with visual or upper extremity impairments were unable to complete the 54-item instrument themselves, a study nurse or study co-ordinator completed the MSQoL-54. No EuroQoL-5 dimension (EQ-5D) data were collected in either of the RADIANCE Part B or SUNBEAM trials.

Although it appears that MSQoL-54 data were collected in the phase II RADIANCE Part A trial, the results have not been presented in the CS. Since the comparator in this trial was placebo, the ERG considers that the evidence from the RADIANCE Part B and SUNBEAM trials is the most informative.

3.7.2 HRQoL results

HRQoL results are presented for the ozanimod 1mg and IFN β-1a 30µg (Avonex) arms in the CS (pp49-50). Results are presented as change over time, at 6-month intervals, until End of Treatment (EOT), i.e., 24 months in the RADIANCE part B trial and ≥12 months in the SUNBEAM trial. Data pooled from both trials are also reported after 12 months from the RADIANCE part B trial and EOT from the SUNBEAM trial. Comparisons of the change from baseline between arms were adjusted for region, EDSS category at baseline, and baseline summary score of interest. Missing data were imputed using a mixed-effects regression model (random slope and intercept).

HRQoL results, as measured by changes in summary MSQoL-54 scores (physical health composite score and mental health composite score) are reported in the CS (Table 18). The results can be summarised as follows:

- Physical health composite score: numerical improvements (indicating improved HRQoL) over time to EOT were observed in the ozanimod arm in both RADIANCE Part B and SUNBEAM trials and in the IFN β-1a 30µg (Avonex) arm of the SUNBEAM trial. Numerical improvements over time to ≥12 months were also observed from the pooled analysis. The only statistically significant difference between arms (in favour of ozanimod versus IFN β-1a 30µg [Avonex]) was observed in the SUNBEAM trial.

- Mental health composite score: there were no statistically significant differences between arms in either trial or in the pooled analysis. A higher mean score at EOT than at baseline (indicating improved HRQoL) was observed in the ozanimod arm of the SUNBEAM trial. The mean score was numerically lower than at baseline (indicating a worsening of HRQoL) in the IFN β-1a 30µg (Avonex) arm of the SUNBEAM trial. In the RADIANCE Part B trial and pooled analysis, the mean score at EOT and after ≥12 months was numerically lower in both arms (indicating a worsening of HRQoL).

3.7.3 ERG interpretation of HRQoL results

The data from the SUNBEAM trial suggest that ozanimod may improve HRQoL as measured by physical health composite summary scores when compared with IFN β-1a 30µg (Avonex). However, the results of the pooled analysis suggest there is no statistically significant difference between arms after 12 months. Similarly, no statistical difference was reported between arms after 24 months in the RADIANCE Part B trial.

There does not appear to be a statistically significant difference in HRQoL between arms as measured by mental health composite summary scores from the RADIANCE Part B trial, SUNBEAM trial or pooled analysis.

3.8 Safety and tolerability results from ozanimod studies

3.8.1 Summary of safety data presented

Safety data have been presented by the company for patients treated with ozanimod 1mg and ozanimod 0.5mg from the RADIANCE Part B and SUNBEAM trials. In addition, integrated safety analyses were performed on combined data from RADIANCE Part B and SUNBEAM comprising of six safety pools, of which two are presented in the CS:

- Pool A1: RADIANCE Part B and SUNBEAM (882 patients treated with ozanimod 1mg)
- Pool B: RPC01-1001 study, RADIANCE Part A trial, RADIANCE Part B, SUNBEAM and DAYBREAK OLE trials (2631 patients treated with ozanimod 1mg)

In summary, the data presented in the CS included information on the following safety outcomes, for ozanimod 1mg, ozanimod 0.5mg and IFN β-1a (Avonex):

- Summary of treatment-emergent AEs (TEAEs) in the RADIANCE Part B and SUNBEAM trials, including by severity, seriousness and AEs leading to permanent discontinuation, study withdrawal and death (CS, Table 28 and Table 30).
- Summary of TEAEs in Pool A1, including by severity, seriousness and AEs leading to temporary discontinuation, permanent discontinuation, study withdrawal and death (CS, Table 32).
- Incidence of most frequent AEs in the RADIANCE Part B trial, SUNBEAM trial and Pool A1 (CS, Table 29, Table 31 and Table 33).

In addition, the company present an overview of:

- Incidence and incidence rates of TEAEs observed with ozanimod 1mg and ozanimod 0.5mg in Pool A1 and Pool B (CS, Table 34)
- AEs observed with ozanimod 1mg and ozanimod 0.5mg in RADIANCE Part A (CS, Section B.2.10.5).

Importantly, the company also provide information in relation to AEs of special interest (AESIs), i.e. safety risks associated with administration of S1P1R modulators (such as ozanimod and fingolimod).[77] AESIs include infections, malignancies, bradycardia and heart conduction abnormalities, pulmonary function abnormalities, ophthalmic abnormalities, hepatic abnormalities and dermatological abnormalities.[77]

3.8.2 Summary of safety results

The ERG notes that generally, the incidence of all TEAEs (including by severity and seriousness) in all arms of the SUNBEAM trial was lower than in the equivalent arms of the RADIANCE Part B trial. The ERG considers this is likely due to the longer follow-up in the RADIANCE Part B trial than in the SUNBEAM trial. Thus, patients in all arms of the RADIANCE Part B trial were exposed to their study drugs for longer than patients in the SUNBEAM trial (approximately [redacted] months versus approximately [redacted] months).

Overall, the ERG observes from all of the safety data presented that there was very little difference in terms of frequency for ozanimod 1mg versus ozanimod 0.5mg. Therefore, [redacted] and as there appeared to be little difference in safety and tolerability results for patients treated with either ozanimod dose, the ERG has primarily focussed on results for ozanimod 1mg in the remainder of this section.

Overall, the company concludes that ozanimod demonstrated a favourable safety profile versus IFN β-1a 30µg (Avonex) as ozanimod had lower overall incidence of TEAEs compared with IFN β-1a 30µg (Avonex). The ERG concurs (as can be seen in Table 11). In addition, for most preferred terms of AEs, there was very little difference between arms, the most notable difference being that influenza like illness was much more common with IFN β-1a 30µg (Avonex) than ozanimod (Table 11).

Table 11. Incidence of the most frequently reported treatment-emergent adverse events with ozanimod (≥ 5% of patients in any treatment arm) in Pool A1 and Pool B

Preferred term	Pool A1		Pool B
	IFN β-1a 30µg (Avonex) (N=885) n (%)	Ozanimod 1mg (N=882) n (%)	Ozanimod 1mg (N=2631) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]
Lymphopenia*	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]

IFN = interferon; TEAE=treatment-emergent adverse event
Note: Preferred terms are listed in order of decreasing frequency in the ozanimod 1 mg treatment group
*Investigators in the phase III RMS studies comprising Pool A1 were blinded to lymphocyte count data (a key pharmacodynamic effect of ozanimod), therefore AEs related to lymphocyte counts were not reported
Source: data extracted from CS, Tables 32, 33 and 34 and Celgene 2019f,[83] Table 9

The ERG also notes that in terms of severe AEs, serious AEs (SAEs), AEs leading to temporary discontinuation, permanent discontinuation, study withdrawal and death, there was very little difference in incidence between arms. The incidence of all these types of AEs was

low [redacted] in both the ozanimod and IFN β-1a 30µg (Avonex) arms, [redacted].

[redacted]

It can also be seen from Table 11 of this ERG report that generally, TEAEs reported in phase III trials (Pool A1) were similar to reported from all studies of ozanimod (Pool B).

Other notable findings in relation to ozanimod that are described by the company (CS, pp64-65) include:

- Few patients permanently discontinued ozanimod because of AEs of increased alanine transaminase.
- No patients discontinued study drug due to pulmonary events.
- Patients treated with ozanimod did not show any significant occurrence of cardiac AEs (e.g. bradycardia) in clinical trials. However, the ERG highlights that patients at higher risk of bradycardia were excluded from the phase III trials (see Section 3.3.1 of this ERG report).
- No serious infections including progressive multifocal leukoencephalopathy (PML) were reported in patients with an absolute lymphocyte count in Pool A1 < 0.2 x 10^9/L. However, clinical advice to the ERG is that PML can be late or linked with previous drugs and so not adequately captured over the length of a phase III trial.
- There was no evidence of increased risk of macular oedema in patients without pre-existing risk-factors.
- The incidence of malignancies were “low” ([redacted] of all patients in Pool A1[83]).
- Suicidal ideation or behaviour was “low” (approximately [redacted] of all patients in Pool A1[83]).

3.9 Safety data for ozanimod versus other relevant comparators

A summary of the incidence of AEs (reported by their preferred terms) for other relevant comparators (excluding ocrelizumab) is presented in the cost effectiveness section of the CS (Section B.3.3.7.3, Table 45), derived from data extracted by Pharmerit International.[84] The incidence of each specific type of AE found from treatment with ozanimod compares favourably with all comparators; the frequency of each type of AE reported for patients treated with ozanimod was one of the lowest, if not the lowest, when compared with all other comparators. Noticeably, influenza-like illness and injection-site reactions were far more common with beta-interferons, GAs and peg-IFN β-1a than with ozanimod.

Clinical advice to the ERG is that given ozanimod is a S1P1R modulator like fingolimod, in addition to the collection of data on AESIs, a comparison of AEs for these two DMTs would be informative. The ERG has therefore presented the data in Table 12. With the exception of [redacted], the incidence of each specific type of AE was lower in the trials of ozanimod than in the trials of fingolimod.

Table 12. Incidence of adverse events in seven trials of ozanimod or fingolimod*

Adverse event	Ozanimod 1mg (%)	Fingolimod (%)
Nasopharyngitis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Alanine transaminase increased	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]

*The trials are RADIANCE Part A, RADIANCE Part B and SUNBEAM trials for ozanimod and Saida et al 2012,[65] FREEDOMS,[33] FREEDOMS II[29] and TRANSFORMS[53] trials for fingolimod. All data are reported as an average across the trials but for some adverse events, data were not always available from all trials. Only data for the ozanimod 1mg dose and licensed 0.5mg dose for fingolimod have been extracted
Source: Data extracted from CS, Table 45 and Pharmerit International 2018, Table 1a

Additional safety data for ozanimod in relation to all AEs (of any type) and all SAEs (of any type) versus all relevant comparators (including ocrelizumab) have also been presented in the CS in its sections reporting on network meta-analysis (NMA) results (CS, Sections B.2.9.1, Table 27 and appendices, D1.3.4). The ERG has therefore presented all AE and all SAE results derived from the NMAs in Section 3.10.4 of this ERG report.

3.10 ERG critique of the indirect evidence

The company performed a series of NMAs to establish the comparative efficacy and tolerability of ozanimod versus relevant comparator treatments relevant to the NICE scope. However, the company has not conducted NMAs to present evidence for HRQoL.

3.10.1 Critique of trials identified and included in the NMAs

The company conducted a systematic literature review (see Section 4.1 of this report for further details) and identified a total of 47 RCTs from 46 publications[25-70] which could be included in at least one of the NMAs conducted by the company (CS, Appendix D.1.1.4; Table 4).

The company considered that the 47 included RCTs were similar with respect to trial design characteristics, including eligibility criteria and criteria for diagnosing MS (CS, Appendix D.1.1.5; Table 7). The company also considered that the following patient characteristics were generally consistent across treatment arms and across trials (CS, Appendix D.1.1.5; Table 8), including:

- mean age (ranging from 27 to 41 years)
- majority females (ranging from 56% to 81%, with only one trial recruiting 33% of females to one treatment arm)
- mean disease duration (where reported, ranging from approximately 1 year to approximately 10 years)
- mean symptom duration (where reported, ranging from approximately 2 years to approximately 11 years)
- mean EDSS score (where reported, ranging from 1.9 to 3.5)
- mean prior relapses in the last 1 to 3 years (where reported, on average was ≤2 per year with only one trial reporting 2.2 and 2.4 relapses in two treatment arms)
- mean Gd-E T1 brain MRI lesions (where reported, ranging from 0.7 to 4.6).

The ERG agrees with the company assessment that trial design and patient characteristics were generally consistent across the included trials and treatments. However, the ERG has concerns about the variation in trial duration, which ranged from 12 weeks (3 months) to 108 weeks (27 months). The ERG notes that the main NMA outcomes (ARR, CDP-3M and CDP-6M) are all time-dependent and, as acknowledged by the company (CS, Section B.2.9.2, p63),

it was necessary to make statistical assumptions in order to synthesise data from different time points within the NMA. The ERG also notes that the trials were published over a wide range of years (1987 to 2019). Changes in trial methodology, reporting standards and MRI technology will have occurred over time. The ERG, therefore, considers that the large range of trial durations and the dates that trials were conducted should be carefully considered when drawing conclusions from NMA results.

The company states that "no evidence of treatment-effect modifying characteristics was noted in the clinical trials of the general MS literature with the exception of prior treatment exposure and disease severity" (CS, Appendix D.1.1.5). In response to question A10 of the clarification letter, the company provided an updated table of patient characteristics including the proportion of patients with prior treatment and with prior DMT treatment. Variable rates of patients with prior treatment and prior DMT treatment were reported across a limited number of the included trials; 13 of the 47 trials (28%) reported patients with prior treatment and 16 of the 47 trials (34%) reported patients with prior DMT treatment. Where reported, 17% to 100% of patients had received prior treatment and 0% to 42.6% of patients had received prior DMT treatment. The company concluded that "there was no evidence of clinically meaningful differences" in the proportion of patients with prior treatment and with prior DMT treatment. However, the ERG considers that these wide ranges of patient rates with prior treatment and prior DMT treatment may lead to statistical heterogeneity and therefore uncertainty in the NMAs.

In response to question A10 of the clarification letter, the company also explain that it was not possible to categorise patients within the included trials by disease severity (for example, "high disease activity" or "rapidly evolving severe"). The ERG agrees that categorisation of disease severity is not possible from the information within the majority of trial publications and notes that it is uncertain how any effect modification by level of disease severity might impact NMA results.

3.10.2 Quality assessment of the trials included in the NMAs

The company conducted a quality assessment using the minimum criteria set out in the NICE Guide to the Methods of Technology Appraisal[24] for all trials included in the NMAs (CS, Appendix D.1.2.3, Table 11).

Overall, the ERG agrees with the quality assessments made by the company and notes that the majority of trials included within at least one NMA were generally of good quality relating to balanced prognostic factors, appropriate use of an ITT analysis and reporting of all measured outcomes. However, information relating to methods of randomisation were omitted

from 12 trial publications (26%) and unexpected imbalances in drop-outs between arms were reported in 14 trial publications (30%). Furthermore, only 23 trial publications (49%) clearly reported that treatment allocation was concealed and 22 trial publications (47%) clearly reported that providers, patients and outcome assessors were blinded. The ERG considers that these uncertainties in the quality of the included trials should be considered when drawing conclusions from NMA results.

3.10.3 Methodological approach to the NMAs

All NMAs were conducted within a Bayesian analysis framework using WinBUGS Software according to the methods described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[85] Both fixed and random-effects NMA models were evaluated and model fit was determined according to deviance information criterion (DIC) statistics. A summary of the analysis approaches for each outcome can be found in Table 13 and further details of the analysis approach and the programming language used can be found in the CS (Appendix D.1.2.1 and Appendix D.1.2.2 respectively) and in the Pharmerit International 2019 report of the systematic review and NMAs of treatments for RRMS.[86,87]

Assessments of heterogeneity and inconsistency were conducted and trials which seemed to contribute to heterogeneity and inconsistency were removed within sensitivity analyses.[86,87] NMA results remained largely unchanged following sensitivity analyses. In response to question A10 of the clarification letter, the company provided estimates (with 95% credible intervals [CrIs]) of heterogeneity parameters for all evaluated NMA models. The ERG considers that these parameters suggest that heterogeneity present in the analyses appears to be very minimal. Therefore, the ERG considers that any heterogeneity or inconsistency present in NMAs has no important impact on the numerical results of the NMAs, but the ERG emphasises that areas of uncertainty and variability such as trial duration and the dates that trials were conducted, prior treatment and disease severity (Section 3.10.1 of this ERG report) should be taken into account when drawing conclusions from the NMAs.

The ERG notes that four approaches were taken within the NMAs of CDP-3M and CDP-6M (see Table 13 of this ERG report for further details) and that modelling of CDP-3M or CDP-6M has been one of the key issues highlighted within previous NICE Technology Appraisals.[9,12] CDP-6M is now the preferred definition of disability progression (confirmed progression should include two sequential examinations at least 6 months apart)[88] and was considered by the TA320 (DMF)[9] NICE Appraisal Committee to be a more robust measure of treatment effect than CDP-3M as CDP-3M may be more influenced by relapses.[9] As prior to CDP-6M being the EMA's preferred definition of disability progression, CDP-3M was the recommended definition of disability progression, older studies did not report CDP-6M data (CS, Appendix

D.1.2; Table 9). Therefore, to make best use of available data, recent appraisal submissions (cladribine [TA493][13] and ocrelizumab [TA533][12]) and the CS for this appraisal have included a combined analysis in which CDP-3M and CDP-6M are analysed within a single model. In this model, estimates of CDP-6M relative efficacy can be generated for treatments with no reported CDP-6M data (CS, Appendix D1.2.1, Table 10). A key assumption of this model is that the CDP-3M HR is proportional to the CDP-6M HR, i.e., a linear relationship between the CDP-3M and CDP-6M HRs is assumed.

Table 13 Summary of the methodological approach taken for outcomes considered within the NMAs

Outcome	Analysis approach	Measure	Appropriate approach?	ERG comment
ARR	Modelled as count (rate) data using a Poisson model	Annualised rate ratio and 95% CrI	Yes	An assumption of this modelling approach is that the relapse rate is constant across patients and over time. The company did not formally assess this assumption and although relapse rates have been shown to decrease over time,[89] clinical advice to the ERG is that for the short duration of the trials included within the NMA (i.e. ≤24 months), the assumption is reasonable.
CDP-3M and CDP-6M	Modelled as time-to event data using a Cox PH model	Annualised hazard ratio and 95% CrI	Yes	An assumption of this modelling approach is that the PH assumption holds within all trials included in the NMA. There was no evidence that the PH assumption was violated for the RADIANCE Part B or SUNBEAM trials (see Table 8 of this ERG report). The company did not formally assess this assumption for the other trials included within the NMAs. Four approaches were taken within the NMAs of CDP-3M and CDP-6M (CS, Appendix 1.2.1, Table 10): • Base-case; CDP-3M and CDP-6M modelled independently • Placebo adjusted risk; CDP-3M and CDP-6M modelled independently and adjusted for placebo response in placebo controlled trials • Treatment class-based model; CDP-3M and CDP-6M modelled independently with treatments grouped into classes with similar mechanism of action • Combined analysis: CPM-3M and CDP-6M analysed in a single model with the assumption that the HR of CDP-3M is proportional to the HR of CDP-6M (i.e. a linear relationship) Rationales supporting choice of all analysis approaches, and all NMA results for CDP-3M and CDP-6M, are provided in an Appendix to the Pharmerit International 2019 report.[86,87]
Discontinuation	Modelled as time-to event data using a Cox PH model	Annualised hazard ratio and 95% CrI	Yes	An assumption of this modelling approach is that the PH assumption holds. The company did not formally assess this assumption for any included trials, therefore it is unknown whether PH is valid for the NMAs
AEs and SAEs	Modelled as binomial data with logit link	Odds ratio and 95% CrI	Yes	No additional ERG comments
Gd-E T1 brain MRI lesions, hyperintense T2-weighted brain MRI lesions at 12 and 24 months	Modelled as continuous data with a normal likelihood	Mean difference and 95% CrI	Yes	No additional ERG comments

AE=adverse event; ARR=annualised relapse rate; CDP-3M=time to onset of disability progression confirmed after 3 months; CDP-6M=time to onset of disability progression confirmed after 6 months; CrI=credible interval; Gd-E=gadolinium–enhanced; MRI=magnetic resonance imaging; NMA=network meta-analysis; PH=proportional hazard; SAE=serious adverse event
Source: CS, extracted and adapted from Appendix D.1.2.1 and Appendix D.1.2.2 with additional information taken from Pharmerit International 2019 report[86] and appendix[87]

3.10.4 Results from the NMAs

Table 14 provides a summary of the number of trials and patients, the range of durations of the trials contributing to the NMAs and the locations of the network diagrams for each outcome. References for the trials contributing to the NMA for each outcome can be found in the CS (Table 9, Appendix D.1.2). In response to question A11 of the clarification letter, the company provided the data that was inputted into the NMAs for all outcomes (including also the source of the data such as trial publication, trial CSR or previous NMA[13,23]). The majority of trials reported ARR, treatment discontinuation and SAEs, while only around half of trials reported CDP-3M or CDP-6M, and less than 40% of trials reported outcomes associated with Gd-E T1 brain MRI lesions or hyperintense T2-weighted brain MRI lesions.

Table 14 Summary details of trials and patients contributing to NMAs

Outcome	Number of trials: n (%)	Number of patients	Range of trial durations	Network diagrams
ARR	46 (98%)	25,588	12 weeks to 36 months	CS, Figure 2, Appendix D.1.3.1
CDP-3M	23 (49%)	19,360	48 weeks to 36 months	CS, Figure 3, Appendix D.1.3.2
CDP-6M	23 (49%)	16,902	48 weeks to 36 months	CS, Figure 4, Appendix D.1.3.2
Treatment discontinuation	41 (87%)	24,930	12 weeks to 36 months	CS, Figure 7, Appendix D.1.3.3
AEs	28 (60%)	20,152	24 weeks to 36 months	CS, Figure 8, Appendix D.1.3.4
SAEs	36 (77%)	21,480	24 weeks to 36 months	Figure 6.14, Pharmerit International 2019 report[86,87]
Gd-E T1 brain MRI lesions	18 (38%)	13,962	24 weeks to 108 weeks	Figure 6.16, Pharmerit International 2019 report[86,87]
Hyperintense T2-weighted brain MRI lesions (12 months)	9 (19%)	7,454	48 weeks to 24 months	Figure 6.17, Pharmerit International 2019 report[86,87]
Hyperintense T2-weighted brain MRI lesions (24 months)	11 (23%)	9,795	96 weeks to 24 months	Figure 6.18, Pharmerit International 2019 report[86,87]

AE=adverse event; ARR=annualised relapse rate; CDP-3M=time to onset of disability progression confirmed after 3 months; CDP-6M=time to onset of disability progression confirmed after 6 months; Gd-E=gadolinium–enhanced; MRI= magnetic resonance imaging; SAE=serious adverse event.
Source: CS, extracted and adapted from Table 9 (Appendix D.1.2), Appendix D.1.3 and Pharmerit International 2019 report[86,87]

Results from fixed-effects NMAs for key efficacy and safety outcomes can be found in Table 15. As highlighted in Section 2.2 and Table 3 of this ERG report, ocrelizumab should have been included as a comparator since it is recommended by NICE as a first-line treatment option for patients with active RRMS (TA533)[12] and clinical advice to the ERG is that it is used to treat some of this patient population. Therefore, the ERG has included results for the

comparison of ozanimod versus ocrelizumab (which were reported in Appendix D1.3 of the CS). The ERG agrees with the company assessment that the fixed and random-effects models provided a very similar model fit (according to the DIC statistic) and that fixed and random-effects NMA results were very similar for all outcomes. The ERG, therefore, considers that it is appropriate to present results from fixed-effects NMAs for all outcomes.

Results for Gd-E T1 brain MRI lesions and hyperintense T2-weighted brain MRI lesions (at 12 and 24 months), results of NMAs conducted with random-effects and results for all outcomes for other treatments for RRMS which were included in the networks but not considered by the company to be relevant to the decision problem can be found in the CS (Appendix D.1.3) and the Pharmerit International 2019 report.[86,87] With the exception of ocrelizumab, the ERG agrees that the other treatments for RRMS presented in Appendix D.1.3 to the CS are not relevant first-line treatment options for patients with active RRMS.

Table 15 Summary of key efficacy and safety outcomes of ozanimod 1mg vs comparator (fixed-effects NMA)[a]

Comparator	ARR, Rate ratio (95% CrI)	CDP-3M, Annualized HR (95% CrI)	CDP-6M, Annualized HR (95% CrI)	CDP-6M combined Annualized HR (95% CrI)	Discontinuation Annualized HR (95% CrI)	AEs, OR (95% CrI)	SAEs OR (95% CrI)
Placebo	**0.48 (0.40 to 0.57)**	[redacted]	[redacted]	[redacted]	[redacted]	0.98 (0.74 to 1.32)	0.84 (0.49 to 1.44)
IFN β-1a 22µg (Rebif)	**0.68 (0.54 to 0.85)**	[redacted]	[redacted]	[redacted]	[redacted]	--	--
IFN β-1a 30µg (Avonex)	**0.57 (0.48 to 0.66)**	[redacted]	[redacted]	[redacted]	[redacted]	**0.53 (0.43 to 0.65)**	1.07 (0.68 to 1.69)
IFN β-1a 44µg (Rebif)	**0.72 (0.60 to 0.87)**	[redacted]	[redacted]	[redacted]	[redacted]	0.66 (0.34 to 1.25)	0.95 (0.47 to 1.90)
IFN β-1b (Betaferon)[b]	**0.70 (0.58 to 0.85)**	[redacted]	[redacted]	[redacted]	[redacted]	2.08 (0.89 to 4.89)	1.38 (0.72 to 2.65)
GA 20mg (Copaxone or generic)	**0.72 (0.58 to 0.89)**	[redacted]	[redacted]	[redacted]	[redacted]	1.20 (0.79 to 1.83)	1.15 (0.65 to 2.02)
GA 40mg (Copaxone or generic)	**0.72 (0.60 to 0.87)**	[redacted]	[redacted]	[redacted]	[redacted]	**0.61 (0.42 to 0.89)**	0.75 (0.36 to 1.54)
Peg-IFN β-1a	0.74 (0.55 to 1.01)	[redacted]	[redacted]	[redacted]	[redacted]	**0.32 (0.19 to 0.53)**	1.26 (0.66 to 2.42)
Teriflunomide	**0.72 (0.56 to 0.93)**	[redacted]	[redacted]	[redacted]	[redacted]	0.77 (0.51 to 1.16)	0.77 (0.42 to 1.42)
DMF	0.88 (0.70 to 1.10)	[redacted]	[redacted]	[redacted]	[redacted]	**0.58 (0.36 to 0.91)**	1.07 (0.60 to 1.90)
Ocrelizumab	**1.32 (1.03 to 1.68)**	[redacted]	[redacted]	[redacted]	[redacted]	0.67 (0.35 to 1.25)	1.24 (0.57 to 2.68)

[a] Rate ratios, HRs and ORs<1 indicate an advantage to ozanimod over the comparator. Green highlighted cells represent statistically significant results in favour of ozanimod 1mg over the comparator and red highlighted cells represent statistically significant results in favour of the comparator over ozanimod 1mg

[b] Extavia rather than Betaferon is used in NHS clinical practice. However, data for IFN β-1b are only available from studies of Betaferon

AEs=adverse events; ARR=Annualised Relapse Rate; CDP-3M=time to onset of disability progression confirmed after 3 months; CDP-6M=time to onset of disability progression confirmed after 6 months; CrI=Credible Interval; DMF=dimethyl fumarate; GA=glatiramer acetate; HR=Hazard ratio; IFN=interferon; NMA=network meta-analysis OR=odds ratio; SAEs=serious adverse events

Source: CS, extracted and adapted from Table 27 and Appendix D.1.3 (Table 12) and Pharmerit International 2019 report[86,87] (where discrepancies were present in the CS).

CDP-3M and CDP-6M

When considered separately (i.e., base case analysis approach, see Table 13 of this ERG report), NMA results indicate that ocrelizumab was associated with a statistically significant later time to CDP-3M and CDP-6M compared to ozanimod 1mg and that IFN β-1b (Betaferon) was also associated with a statistically significant later time to CDP-6M compared to ozanimod 1mg. There was a statistically significant advantage for ocrelizumab compared to ozanimod 1mg in the combined analysis of CDP-3M and CDP-6M (CDP-6M combined). There was no statistically significant evidence of a difference in CDP-3M, CDP-6M or CDP-6M combined between ozanimod 1mg and any of the other treatments.

Sensitivity analyses were performed including using both tentative and confirmed disability progression results and using disability progressions confirmed during the open-label extension of the RADIANCE Part B and SUNBEAM trials. The company state that within these sensitivity analyses, the HRs of CDP-3M and CDP-6M for ozanimod 1mg compared to placebo "improve";[86,87] however, the ERG notes that CrIs for these HRs (ozanimod 1mg versus placebo) and HRs for ozanimod 1mg versus other treatments have not been provided by the company.

Sensitivity analyses imputing missing values for CDP-3M and CDP-6M were also performed, with results similar to those from the base case analysis.[86,87] The company highlight that results for CDP-3M and CDP-6M were largely similar across the four analysis approaches (see Table 15 of this ERG report for further details). Numerical results for the four approaches are provided in the Pharmerit International 2019 report and appendix.[86,87]

As described in Section 3.10.3 of this ERG report, an assumption of the combined analysis of CDP-3M and CDP-6M was that the CDP-3M HR was proportional to the CDP-6M HR (i.e., a linear relationship was assumed to exist between the CDP-3M and CDP-6M HRs). This assumption appears to hold for all trials, except for the trials of ozanimod (Pharmerit International 2019 appendix,[87] Figure 17) and it is noted within the Pharmerit International 2019 report that this may "adversely affect the ozanimod NMA CDP-6M outcomes".[86] The ERG agrees this key assumption of the combined analysis does appear to have been violated for the trials of ozanimod and, therefore, that caution should be taken when drawing conclusions from ozanimod CDP-6M combined outcomes.

ARR

NMA results indicate that ozanimod 1mg is associated with a statistically significant reduction in ARR compared to placebo, Avonex, IFN β-1a 22µg (Rebif), IFN β-1a 44µg (Rebif), IFN β-1b (Betaferon), GA 20mg (Copaxone or generic), GA 40mg (Copaxone or generic) and

teriflunomide. Results also indicate that ocrelizumab is associated with a statistically significant reduction in ARR compared to ozanimod 1mg and that there is no statistically significant evidence of a difference in ARR between ozanimod 1mg and peg-IFN β-1a or DMF.

Treatment discontinuation, AEs and SAEs

NMA results indicated that ozanimod 1mg is associated with a statistically significant later time to treatment discontinuation compared to IFN β-1a 30µg (Avonex), IFN β-1a 22µg (Rebif), IFN β-1a 44µg (Rebif), GA 40mg (Copaxone or generic) and peg-IFN β-1a. Results also indicated that ozanimod 1mg is associated with statistically significantly fewer AEs than IFN β-1a 30µg (Avonex), GA 40mg (Copaxone or generic) and peg-IFN β-1a and DMF. There was no statistically significant evidence of a difference in the number of SAEs between ozanimod 1mg and any of the other treatments.

The ERG notes that limited information has been provided by the company regarding the definitions and/or recording of the treatment discontinuation and AE outcomes; for example, the ERG assumes that reasons for treatment discontinuation, severity of AEs or specific types of AEs have not been taken into account within the company NMAs. The ERG considers that the NMA of SAEs is likely to be a more clinically useful analysis of the safety of treatments for RRMS than the NMA of AEs. However, the ERG also acknowledges that as only a small number of SAEs occurred during the follow-up periods of the trials, results from these NMAs are uncertain as CrIs are wide.

3.11 Conclusions of the clinical effectiveness section

The company consider ozanimod would only be a first-line treatment option for patients with active RRMS. The company has presented direct evidence for the efficacy and safety of ozanimod versus one of the comparators of interest to this appraisal, IFN β-1a 30μg (Avonex) from the RADIANCE Part B and SUNBEAM trials. Both trials are well-designed and good quality trials with an appropriate and pre-defined statistical approach to the analysis of efficacy, safety and patient reported outcomes. Most patients in these two trials had active RRMS (approximately 75%) but a proportion also had more severe RRMS (approximately 23%) and even SPMS (approximately 2%). The ozanimod trials also included a much higher proportion of white and Eastern European patients than would be seen in England and Wales. It is unclear if results would differ in a more diverse patient population as would be expected to be seen in NHS clinical practice.

Evidence for the efficacy and safety of ozanimod versus all the other relevant comparators is derived from NMAs of CDP, ARR, discontinuation of study drug, AEs and SAEs. The NMAs include up to 47 trials (including the RADIANCE Part B and SUNBEAM trials) and include trials of all relevant comparators. The ERG considers that the most relevant comparators for patients with active RRMS and one relapse in the last two years and who also have radiological activity are IFN β-1a (Avonex or Rebif) or GA (Copaxone or generic). For patients with active RRMS and two significant relapses in the last two years, the ERG considers DMF to be the most relevant comparator. While the company did not consider ocrelizumab to be a relevant comparator to the current appraisal, it has presented results from the NMAs for ozanimod versus ocrelizumab in appendices to the CS. The ERG considers that ocrelizumab should have been included as a comparator since it is recommended by NICE as a first-line treatment option for patients with active RRMS (TA533) and clinical advice to the ERG is that it is used to treat some of this patient population.

With the exception of CDP-3M and CDP-6M, direct evidence from the RADIANCE Part B and SUNBEAM trials shows ozanimod to be superior to IFN β-1a (Avonex) for efficacy outcomes, including ARR. Indirect evidence from the NMAs also shows ozanimod to statistically significantly improve ARR versus most relevant comparators, the exceptions being peg-IFN β-1a and DMF where there is no statistically significant difference and ocrelizumab which results in statistically significantly superior ARR to ozanimod. Ocrelizumab also resulted in statistically significantly improved CDP-6M to ozanimod. There were no other statistically significant differences in the CDP-6M combined outcome between ozanimod and the other relevant comparators (IFN β-1a 22μg [Rebif], IFN β-1a 30μg [Avonex], IFN β-1a 44μg [Rebif],

IFN β-1b [Extavia] based on data from studies of IFN β-1b [Betaferon], peg-IFN β-1a, GA 20mg [Copaxone or generic], GA 40mg [Copaxone or generic], DMF and teriflunomide).

In terms of safety, the incidence of each specific type of AE found from treatment with ozanimod compared favourably with all comparators. The NMA of SAEs also showed there were no statistically significant differences between ozanimod and any other comparator.

As ozanimod is a S1P1R modulator, information on AESIs associated with administration of S1PR modulators was also collected in the trials of ozanimod. There appeared to be no particular safety concerns relating to AESIs. However, the ERG notes that patients at higher risk of bradycardia were excluded from the trials given exclusion criteria included patients with specific cardiovascular conditions at screening. It is therefore unclear if ozanimod would be suitable for such patients within clinical practice.

An important area of uncertainty in the evidence base relates to HRQoL. Analysis of pooled HRQoL data from the RADIANCE Part B and SUNBEAM trials showed no statistically significant difference between ozanimod and IFN β-1a 30µg (Avonex). The company has not presented evidence for HRQoL versus other relevant comparators and so it is unclear how ozanimod compares with any of the other relevant comparators in terms of HRQoL.

Another important area of uncertainty base relates to potential heterogeneity in the NMAs. Heterogeneity may occur from the types of RRMS and line of treatment patients had (which were not consistently reported in the trials but where they were reported, appear to vary). Heterogeneity may also occur from the differing follow-up durations of the trials (varying from 3 to 27 months) and dates trials were conducted (published 1987 to 2019).

A final area of uncertainty relates to the modelling of CDP-3M and CDP-6M within a combined analysis for the NMA which enables CDP-6M outcomes to be generated when CDP-6M data are not reported in trials. This requires the assumption that the CDP-3M HR is proportional to the CDP-6M HR i.e. a linear relationship. However, the assumption of linear relationship between the CDP-3M and CDP-6M HRs for ozanimod appears to have been violated.

The uncertainties highlighted above with the NMAs should be taken into account when drawing conclusions from the NMAs. Nonetheless, the ERG considers that despite these uncertainties, the results of the NMAs are adequate to aid decision making.

4 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of ozanimod for treating RRMS. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 Published cost effectiveness evidence

4.1.1 Objective of the company's literature searches

The company undertook systematic and targeted searches to identify economic evaluations of treatments for RRMS. The same search strategies were used to identify studies containing resource use and costs of treatment with DMTs.

4.1.2 Search strategy

The search strategies for the review of economic evaluations were developed by the company and run in July 2019.

The search strategies were comprehensive and included relevant databases: EMBASE, MEDLINE, CENTRAL, and EconLit. Searches were undertaken to identify abstracts for research presented at the following 2017 and 2018 conferences: European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-EU. The company also searched the NICE website. No data limits were applied.

4.1.3 Eligibility criteria used in study selection

The population eligibility criterion matched the population specified in the final scope issued by NICE[2] and comprised patients with RRMS (including patients with HA RRMS and RES RRMS). The search also included patients with SPMS as the company model includes patients progressing to SPMS health states. Studies were restricted to those published in English.

4.1.4 Findings from the company's cost effectiveness review

The company's cost effectiveness searches did not identify any relevant economic evaluations that included treatment with ozanimod for RRMS.

4.2 ERG critique of the company's literature review

A summary of the ERG's critique of the company's literature review methods (provided in Appendix G of the CS) is presented in Table 16.

Table 16 ERG appraisal of systematic review methods (cost effectiveness)

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	N/A
Were appropriate criteria used to assess the quality of the primary studies?	N/A
Was the quality assessment conducted by two or more reviewers independently?	N/A
Were any relevant studies identified?	No

ERG=Evidence Review Group; N/A=not applicable

The ERG undertook its own scoping searches and is confident that no relevant economic evaluations of treatment with ozanimod for RRMS have been missed by the company's searches.

4.3 ERG summary of the company's submitted economic evaluation

4.3.1 NICE reference case checklist

Table 17 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE: people with RRMS	Yes
Comparator(s)	As listed in the scope developed by NICE	In the base case, the company presents cost effectiveness results for treatments for active RRMS Ocrelizumab is also included as a treatment for active RRMS in the final scope issued by NICE.[2] Cost effectiveness results for the comparison of ozanimod versus ocrelizumab are provided in Appendix L (and also versus fingolimod, alemtuzumab, natalizumab and cladribine)
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form 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
Synthesis of evidence on outcomes	Based on systematic review	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year; RRMS=Relapsing-remitting multiple sclerosis
Source: NICE Reference Case[24]

4.3.2 Model structure

The company model structure (a Markov cohort model, built in Microsoft Excel) is shown in Figure 2 and comprises 21 mutually exclusive health states. These health states include 10 RRMS EDSS states and 10 SPMS EDSS states, and death. On-treatment and off-treatment

health states are not included in Figure 2; when included, the number of health states in the model increases to 41. At the end of each annual cycle, patients can progress to the next (higher or lower) EDSS health state or remain in their current health state. Reversal of progression (i.e., SPMS to RMSS) cannot occur in the company model. This model structure has been used in previous NICE technology appraisals of drugs (e.g., TA320 [DMF][9] and TA493 [cladribine][13]) to treat MS and the outputs were validated against the model reported by Palace et al (2019)[90] that was designed to support the risk-sharing scheme for DMTs in the NHS.

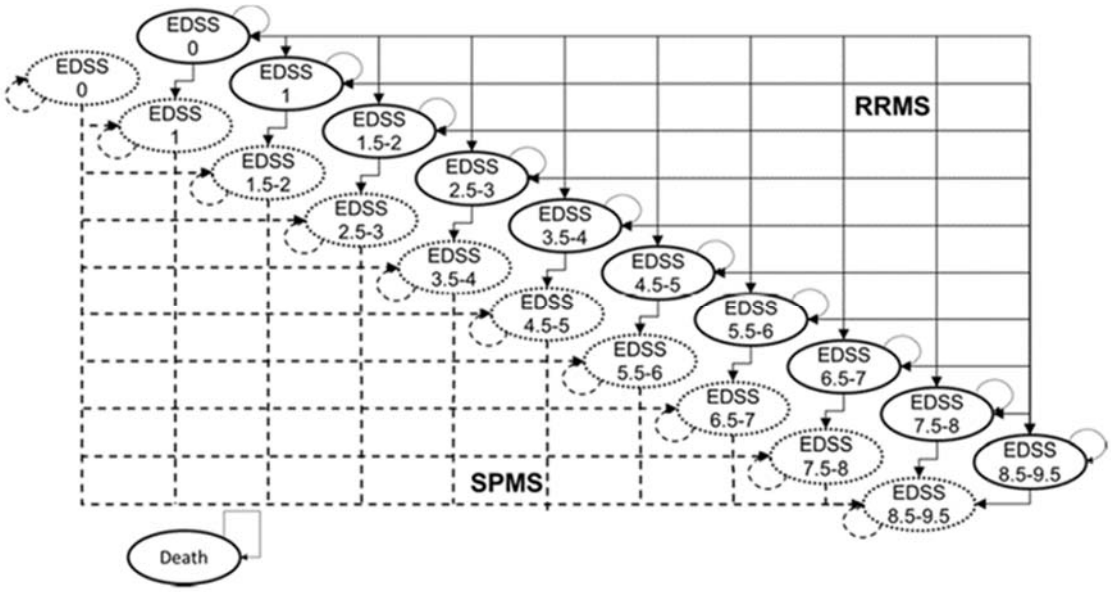


Figure 2 Structure of the company model

EDSS=Expanded Disability Status Scale; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis
Source: CS, Section B 3.2.2.1 Figure 8, which is stated by the company to be from NICE guidance in development for daclizumab;[91] the ERG notes that the guidance was published in 2017 but has now been withdrawn

4.3.3 Interventions and comparators

The company base case analysis compared the cost effectiveness of treatment with ozanimod versus IFN β-1a 22µg (Rebif), IFN β-1a 30µg (Avonex), IFN β-1a 44µg (Rebif), IFN β-1b (Extavia), GA 20mg (Copaxone), GA 40mg (Copaxone), peg-IFN β-1a (the latter is subject to an ongoing NICE appraisal[6]), teriflunomide and DMF. The company presents cost effectiveness results for ozanimod versus alemtuzumab, ocrelizumab, fingolimod, natalizumab and cladribine in Appendix L of the CS.

4.3.4 Population

The population considered in the company model is people with active RRMS. This population is narrower than the population specified in the final scope issued by NICE.[2] However,

approximately a quarter of patients in the RADIANCE Part B and SUNBEAM phase III trials had more severe RRMS and 30% of patients had prior DMT treatment, although whether ozanimod was used as an alternative first-line therapy or a second-line treatment in these patients is unclear. The baseline characteristics of the modelled population were derived from pooled baseline characteristics data from the RADIANCE Part B and SUNBEAM phase III trials. Approximately two-thirds (66.8%) of the modelled population were female and, at baseline, the mean age was 36 years and 95.4% of patients had an EDSS of between 1 and 4.

The outcome data used to populate the model are based on the trials included in the company's NMAs. In general, the ERG considers the patient characteristics to be consistent across the trials included in the networks, however prior treatment and disease severity remains an uncertainty within the NMAs (see Section 3.10 of this report).

4.3.5 Perspective, time horizon and discounting

The company states that costs are considered from the perspective of the NHS and Personal Social Services. The model cycle length is 1 year (a half-cycle correction is applied) and the model time horizon is set to 50 years. Costs and outcomes were discounted at 3.5% per annum.

4.3.6 Treatment effectiveness and extrapolation in the base case

Natural history model

The natural history, or best supportive care (BSC), reference case arm is used to estimate the long-term disability progression and OS of patients with RRMS. A previously published transition matrix (Palace 2019[90]) based upon data from the British Columbia Multiple Sclerosis (BCMS) registry (Palace 2014[92]) is used to model disease progression (CS, Table 37). The BCMS registry contains data from patients with RRMS (84.3%) and patients with SPMS (15.7%). As the company model estimates both the mortality of the general population and MS-related standardised mortality, EDSS 10 has been excluded from the published matrix to prevent double-counting of mortality.

Progression from RRMS to SPMS in the company model (CS, Table 38) is based on EDSS-transition probabilities used in previous NICE submissions TA127 (natalizumab)[15] and TA320 (DMF)[9] and in a study published by Mauskopf (2016)[93] in the USA.

Treatment adjusted model

The treatment adjusted model has been developed by populating the natural history model with efficacy results (confirmed disability progression [CDP-6M combined] and ARR) from the

company's fixed effects NMAs for each DMT versus placebo, and AEs from each of the individual trials (CS, Section B.2.8).

A treatment-specific HR was applied to **disability progression** in the natural history arm. This can either increase or decrease the rate of progression through the EDSS states. Due to lack of data, and for simplicity reasons, the same constant HR was applied to all EDSS states. The company considered that, for the comparison of the effectiveness of ozanimod versus placebo, the disability progression HR generated by the company's NMA was implausibly high (see CS, Section B.2.6) and, therefore, in the base case, this HR was set equal to the company NMA HR estimate for the comparison of ozanimod versus IFN β-1a 30µg (Avonex).

In the base case, the effectiveness of all treatments was set to 100% for the first 2 years and then decreased over time from 3 years onwards. This approach is consistent with previous NICE appraisals of drugs to treat MS (TA493 [cladribine],[13] TA527 [IFN β and GA][7] and TA533 [ocrelizumab][12]).

The **relapse rate** corresponding to each EDSS state was applied to the number of patients occupying that state in each model cycle. The company highlights that this method may lead to double-counting in cases where the drug is modelled to act independently on EDSS and relapse rate. A rate ratio for each DMT was applied to the natural history EDSS-specific ARRs, (rates reported by Patzold and Pockington [1982],[94] CS, Table 39) based on NMA results (CS, Table 44).

Background **mortality rates** have been estimated using gender and age-specific UK life tables (ONS 2018[95]) and EDSS-specific mortality multipliers (CS, Table 40) have then been applied to these rates. The EDSS-specific rates used are those published by Sadovnick et al (1992)[96] which have been used in previous NICE appraisals of drugs to treat MS (TA254 [fingolimod],[14] TA303 [teriflunomide][8] and TA312 [alemtuzumab][10]).

The order in which calculations and transitions between health states occur in the model is shown in Figure 3.

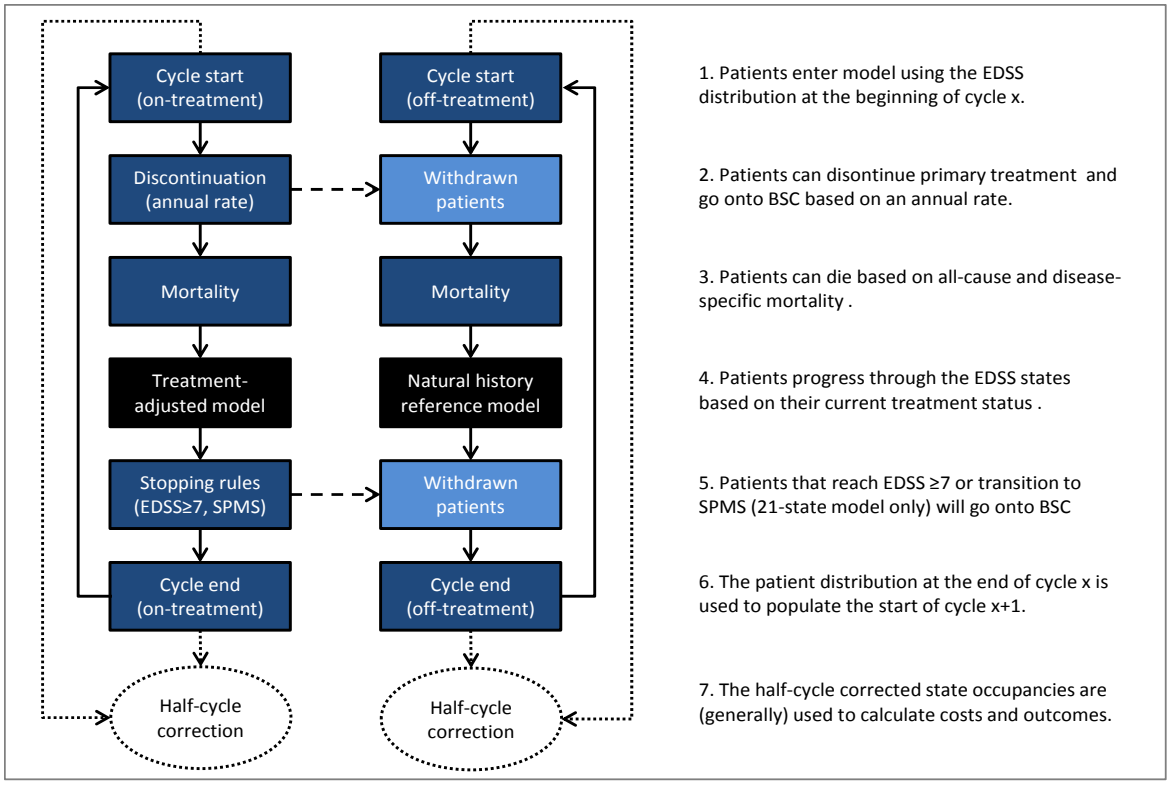


Figure 3 Transition flow and calculation process for patients on primary treatment in the model

BSC=best supportive care; EDSS=expanded disability status scale; SPMS=secondary progressive multiple sclerosis
Source: CS, Figure 9

In the company base case, there are four factors that can initiate primary **treatment stopping**: (i) progression to SPMS, (ii) EDSS >7, which is assumed to equate to patients being unable to walk, and (iii) treatment-specific annual discontinuation rates that reflect a lack of tolerability or efficacy of the primary treatment and (iv) death. Further details about treatment stopping rules are provided in the CS (Table 41). Annual discontinuation rates were generated using results from the company random-effects NMA (CS, Table 46).

In the company model, patients who have withdrawn from primary treatment continue in a BSC health state until death, where estimates of disease progression are based on the natural history parameters set out in the model.

4.3.7 Health-related quality of life

EuroQoL-5 dimension (EQ-5D)[97] data were not collected as part of either the RADIANCE Part B or SUNBEAM trials. The company's literature search for health state utility values identified three sources (papers by Hawton et al [2016a],[98] Orme et al [2007][99] and the NICE submission for ocrelizumab [TA533][12]).

The utility values used in TA533 (ocrelizumab)[12] were values derived from the OPERA trials[48,52] which were supplemented with information from the paper by Orme et al (2007)[99] for patients with EDSS states 7 to 9, where robust OPERA trial[48,52] data were lacking. Utility values for patients with SPMS were estimated by applying a utility decrement (-0.045) which had been calculated by Orme et al (2007),[99] to the RRMS utility values. The company used the TA533 (ocrelizumab)[12] utility values in the base case (see Table 18). However, the company used a different value from that used in TA533 (ocrelizumab)[12] to model the disutility associated with relapse; the value used by the company was that estimated by Hawton et al (2016a).[98] The same carer disutility values used in TA533 (ocrelizumab)[12] were also included in the company base case (details are not provided in the CS). The company also presents a scenario analysis that does not include carer disutilities (CS, Table 76).

Table 18 Utility values used in the company model

Health state			Source
EDSS state	RRMS	SPMS	
0	0.881*	0.836	OPERA trial[48] and Orme et al (2007)[99] (and used in TA533 [ocrelizumab][12])
1	0.843	0.798	
2	0.770	0.725	
3	0.705	0.660	
4	0.644	0.599	
5	0.601	0.556	
6	0.493	0.448	
7	0.309	0.263	
8	-0.038	-0.083	
9	-0.184	-0.229	
Disutility associated with relapse		0.076	Hawton et al (2016a)[98]

*In the CS (Table 48), the value is 0.811 but the value used in the company model is 0.881 which is the OPERA trial[48] value
EDSS=Expanded Disability Status Scale; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis
Source: CS, Table 48; CS, Section B.3.4.4; and company model

4.3.8 Adverse events

The company model includes disutilities associated with AEs. The disutility parameter values used in the model (details provided in the CS, Table 47) were either assumptions or values used in previous NICE appraisals of treatments for RRMS (TA493 [cladribine],[13] TA533 [ocrelizumab],[12] and TA312 [alemtuzumab][10]).

Adverse event incidence rates were applied as one-off events at the start of the simulation, except for injection site reactions which were relevant for the time horizon a patient was on treatment. Incidence rates were obtained from the Pharmerit International report (Pharmerit International 2018[84]). The AE rates used in the company model for each DMT are shown in the CS, Table 45.

4.3.9 Resources and costs

Summary details of level of resource use and associated costs used in the company model are provided in Table 19.

Table 19 Resource use and costs

Cost	Details	Location in company submission
Drug acquisition	List prices (BNF 2019[100]) PAS exist for DMF, fingolimod, GA (Copaxone), IFN β-1a (Avonex and Rebif), IFN β-1b (Extavia), ocrelizumab and teriflunomide	Table 49
Drug administration	The company assumed that prescription of IFN β-1a (Avonex and Rebif), IFN β-1b (Extavia), GA (Copaxone), and peg-IFN β-1a would be associated with a cost of 3 hours of nurse (band 7) time as patients would need to be taught how to self-administer their treatment (£159, PSSRU 2018[101])	Table 51
Drug monitoring	Monitoring included neurology visits, MS nurse visits, complete blood counts, liver and renal function tests, urinalyses, tuberculin skin tests and MRIs, in different combinations for each primary treatment. Most drugs were assumed to require higher levels of monitoring during the first year of treatment compared with subsequent years of treatment. Drug monitoring costs were obtained from NHS Reference Costs 2017-18,[102] Midmeds (2017)[103] and NICE TA312 (alemtuzumab)[10]	Assumptions: Table 52 Costs: Table 53
Relapse	Direct cost per relapse not leading to a hospitalisation: £630 Direct cost per relapse leading to a hospitalisation: £4,116 These costs are those reported by Hawton et al (2016b)[21] adjusted for inflation to 2019 prices using the PSSRU HCHS index[101]	B.5.2.1.2.
Direct costs	Separate estimates, by RRMS and SPMS, for each EDSS state were used in the model (Tyas 2007[104])	Table 54
Adverse events	Resource use data were extracted from TA533 (ocrelizumab)[12] and costed using NHS Reference Costs[102]	Table 56

BNF=British National Formulary; DMF=dimethyl fumarate; EDSS=Expanded Disability Status Scale; GA=glatiramer acetate; IFN β-1a=interferon beta-1a; HCHS=hospital and community health services; IFN β-1a =interferon beta-1b; MS=multiple sclerosis; MRI=magnetic resonance imaging; peg-IFN β-1a=peg interferon beta-1a; PAS=Patient Access Scheme; PSSRU=Personal Social Services Research Unit; RRMS=relapsing remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis

4.3.10 Cost effectiveness results

A summary of the base case settings for the company model is shown in the CS, Table 57. A summary of the key model base case structural assumptions is provided in the CS, Table 58.

The company base case cost effectiveness results are shown in Table 20 (pairwise analysis) and Table 21 (fully incremental). Absolute dominance occurs for alternatives which are more expensive but generate fewer QALYs. A treatment option is deemed to be extendedly dominated when, after the removal of treatment options that are subject to absolute dominance, there is an alternative that generates more QALYs than the next best alternative, at a lower cost per additional QALY (i.e., lower ICER).

Table 20 Base case results, pairwise results versus ozanimod including ocrelizumab

Model arm	Total			Incremental			ICER per QALY gained
	Costs	QALYs	LYG	Costs	QALYs	LYG	
Ozanimod 1mg	[redacted]	[redacted]	[redacted]				
IFN β-1a 30µg (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA 20mg (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMF 240mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250µg (Extavia)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
peg-IFN β-1a 125µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA, 40mg (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Extavia rather than Betaferon is used in NHS clinical practice. However, data for IFN β-1b are only available from studies of Betaferon

DMF=dimethyl fumarate; GA=glatiramer acetate; ICER=incremental cost effectiveness ratio; IFN β-1a=interferon beta-1a; IFN β-1a=interferon beta-1b; LYG=life years gained; peg-IFN β-1a=peg interferon beta-1a; LYG= life years gained; QALY=quality adjusted life years

Source: CS, Tables 59 and 60

Table 21 Base case results, fully incremental including ocrelizumab

Model arm	Total			ICER per QALY gained (£/QALY)
	Costs	QALYs	LYG	
peg-IFN β-1a 125µg	[redacted]	[redacted]	[redacted]	
GA 20mg (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b 250µg (Extavia)*	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]
GA, 40mg (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg	[redacted]	[redacted]	[redacted]	[redacted]
DMF 240mg	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1mg	[redacted]	[redacted]	[redacted]	[redacted]

* Extavia rather than Betaferon is used in NHS clinical practice. However, data for IFN β-1b are only available from studies of Betaferon

DMF=dimethyl fumarate; GA=glatiramer acetate; IFN β-1a=interferon beta-1a; IFN β-1a=interferon beta-1b; peg-IFN β-1a=peg interferon beta-1a; LYG= life years gained; QALY=quality adjusted life years

Source: Company model

4.3.11 Sensitivity analyses

Deterministic sensitivity analyses

The company identified model parameters that they considered were subject to uncertainty and ran the model using upper and lower bound values (within plausible ranges) for each of those parameters. The company presents the results for the comparison of ozanimod versus IFN β-1a 30µg (Avonex) in the CS (Figure 10) and these are reproduced in

[redacted]

Figure 4. The parameters which, when adjusted, have more than a 20% effect on the ICER per QALY gained

[redacted]

Figure 4 Tornado diagram: ozanimod versus IFN β-1a 30µg (Avonex)

DSA=deterministic sensitivity analysis; ICER=incremental cost-effectiveness ratio; RRMS=elapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis; QALY=quality adjusted life year
If both bars for a parameter are in the same direction (both positive or both negative), at least one of the ICERs is dominant
Source: CS, Figure 10

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA). Model parameters were randomly sampled within the bounds that the company deemed plausible and the model was run 5,000 times. The scatter plot is shown in Figure 5 and the cost effectiveness acceptability curve is shown in Figure 6. Results from this analysis show that [redacted]

Figure 5 Cost effectiveness scatterplot (ozanimod versus all comparators)

WTP=willingness to pay
Source: CS, Figure 11

Figure 6 Cost effectiveness acceptability curve (ozanimod versus all comparators)

WTP=willingness to pay
Source=CS, Figure 11

4.3.12 Scenario analyses

The company conducted 14 scenario analyses; these involved using different sources to model natural history and CDP. Scenarios exploring the effect of changes to mortality estimates, relapse costs, direct non-medical costs and carer disutilities were also undertaken. The remaining scenarios used parameter values from the Palace et al (2019)[90] risk-sharing scheme model.

Results showed that:

-

4.3.13 Subgroup analyses

The company did not carry out any subgroup analyses.

4.3.14 Model validation and face validity check

To validate the model, the company compared whole cohort mean EDSS and utility progression values generated by the company model with those generated by the model built by Palace et al (2019)[90] to support the risk-sharing scheme for disease-modifying therapies in the NHS.

4.4 ERG detailed critique of company economic model

4.4.1 Drummond checklist

Table 22 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	No	Increased effectiveness of ozanimod versus the other DMTs considered by the company in the base case analysis was not established
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ARR=annualised relapse rates; ERG=Evidence Review Group

4.4.2 Overview

The company submitted a cost effectiveness model, built in MS Excel, that has a 21 health state structure. The company highlight (CS, p84) that this structure has been used in models to inform several NICE TA company submissions and is based on a previously published model.[105] The model structure only allows patients to receive one DMT over their lifetime; as there are now a number of treatments available to treat RRMS this is unrealistic. A model that can simulate treatment switching or treatment sequencing would be complex to construct. Furthermore, it is unlikely that there are sufficiently robust data to populate such a model. Nevertheless, and recognising that all models are simplifications of clinical reality, given the range of treatments available to treat RMMS, a model that only simulates the effect of one treatment over a patient's disease course may be of limited use to decision makers.

Many complex algorithms, with individual formulae, often linked to a large number of cells, have been used to build the company model. Whilst undertaking standard formula checks (e.g., checking the precedents and dependents of values in cells), the Excel model frequently crashes. This complexity has made it impossible for the ERG to fully check that all algorithms have been correctly implemented. The checks that the ERG has been able to perform suggest that the model results are generated by accurate algorithms.

In the absence of treatment with DMTs, the parameter values used to model EDSS progression were derived from the BCMS registry data[92] and allow for improvement and deterioration in EDSS. The BCMS registry data included in the company base case analysis have been obtained from patients who had not received DMTs and, as such, are appropriately included in a model that only considers one DMT.

As utility data were not collected as part of the RADIANCE Part B and SUNBEAM trials, model utility values for EDSS states were based on values derived from data collected as part of the OPERA I and II trials of ocrelizumab;[48] these values were used in the NICE appraisal of ocrelizumab appraisal (TA533).[12] The mean age of patients participating in the OPERA trials[48] (37 years) and RADIANCE Part B and SUNBEAM trials (36 years) is similar; in addition, results from the company NMAs show that rates of SAEs and treatment discontinuation were not statistically significantly different between the four trials.[48] The ERG, therefore, considers that it is acceptable to use the utility values estimated from the OPERA trials[48] in the company base case model.

In line with the NICE Reference Case,[24] carer disutility has been included in the company base case analysis.

The company base case EDSS state costs included 'non-medical direct costs' which are not defined by the company and so may not be relevant to the NICE reference case perspective of NHS and Personal Social Services. However, the company performed a scenario analysis removing non-medical direct costs and results from this analysis showed that inclusion of non-medical costs made no difference to the relative cost effectiveness of all treatments.

The ERG considers that, for each health state, the company baseline ARR values, relapse costs and the utility decrements associated with a relapse are appropriate.

The company has assumed that the effect of treatment wanes and has applied a treatment waning effect to CDP-6M combined. The application of a waning effect is arbitrary and not supported by robust evidence. However, the ERG highlights that, currently, there is no robust published evidence that could be used to inform the modelling of treating waning.

The ERG has amended the company model to produce ERG preferred cost effectiveness results by:

- modelling a difference in treatment effect only when the clinical outcomes used to compare the relative efficacy of different treatments are shown to be statistically significantly different
- including ocrelizumab as a comparator
- using a more plausible approach to modelling treatment discontinuation rates within the confines of the current model structure (i.e., within a model that only allows patients to receive one line of treatment).

4.4.3 Modelling of only statistically significant evidence

In the company base case, treatment with ozanimod is dominated by six of the nine comparators considered by the company (CS, Table 60). However, the ERG considers that the company has potentially produced overly pessimistic relative cost effectiveness results for treatment with ozanimod by modelling differences in effectiveness (namely, CDP-6M combined, ARR, treatment discontinuation rates and SAE rates) between treatments which were shown by results from the company's NMAs not to be statistically significant. The ERG considers that when generating base case cost effectiveness results, if clinical effectiveness results are not statistically significantly different, then a difference in effect should not be modelled. Relevant results from the company's NMAs are provided in Table 23.

Table 23 Summary of efficacy and safety outcomes and treatment discontinuation rates from the company NMAs of ozanimod versus comparators for active RRMS

Treatment	CDP-6M combined annualised HR (95% CrI)	ARR, rate ratio (95% CrI)	SAE odds ratio (95% CrI)	Discontinuation, annualised HR (95% CrI)
Placebo	[redacted]	0.48 (0.4 to 0.57)	0.84 (0.49 to 1.44)	[redacted]
IFN β-1a 22µg (Rebif)	[redacted]	0.68 (0.54 to 0.85)	--	[redacted]
IFN β-1a 30µg (Avonex)	[redacted]	0.57 (0.48 to 0.66)	1.07 (0.68 to 1.69)	[redacted]
IFN β-1a 44µg (Rebif)	[redacted]	0.72 (0.6 to 0.87)	0.95 (0.47 to 1.9)	[redacted]
IFN β-1b (Betaferon)*	[redacted]	0.7 (0.58 to 0.85)	1.38 (0.72 to 2.65)	[redacted]
GA 20mg (Copaxone)	[redacted]	0.72 (0.58 to 0.89)	1.15 (0.65 to 2.02)	[redacted]
GA 40mg (Copaxone)	[redacted]	0.72 (0.6 to 0.87)	0.75 (0.36 to 1.54)	[redacted]
Peg IFN β-1a	[redacted]	0.74 (0.55 to 1.01)	1.26 (0.66 to 2.42)	[redacted]
Teriflunomide	[redacted]	0.72 (0.56 to 0.93)	0.77 (0.42 to 1.42)	[redacted]
DMF	[redacted]	0.88 (0.70 to 1.1)	1.07 (0.60 to 1.9)	[redacted]

NB Red shaded cells means that treatment outcomes are not statistically significantly different for treatment versus ozanimod
ARR=annualised relapse rate; CDP-6M=confirmed disease progression at 6 months; CrI=credible interval; DMF=dimethyl fumarate; GA=glatiramer acetate; HR=hazard ratio; IFN=interferon; µg=microgram; mg=milligram; SAE=serious adverse events
* Extavia rather than Betaferon is used in NHS clinical practice. However, data for IFN β-1b are only available from studies of Betaferon

Source: CS, extracted and adapted from Table 27

CPD-6M combined

The data presented in Table 23 show that, when comparing the effectiveness of ozanimod versus any of the company base case comparators, [redacted]

Annualised relapse rates

Results from the company's ARR NMA were [redacted]

Adverse events

Event rates for specific AEs, extracted from papers reporting results from clinical trials of each treatment, were included in the company model. This approach was inappropriate as any differences between trials in terms of specific events recorded and AE definitions were not accounted for by the company. [redacted].

Treatment discontinuation rates

Results from the company's treatment discontinuation rate NMA [redacted]

4.4.4 Inclusion of ocrelizumab as a comparator

The ERG considers that ocrelizumab is an appropriate comparator to ozanimod (see 2.5, Table 3 for the ERG's rationale). Results from the company NMAs (fixed effects models) showed that treatment with ocrelizumab was [redacted].

For the comparison of treatment with ozanimod versus ocrelizumab, when taking into account the [redacted] as a consequence of treatment with ocrelizumab, ozanimod is [redacted] and generates [redacted] QALYs than ocrelizumab. [redacted]

4.4.5 A more plausible approach to treatment discontinuation rates

The company has assumed that the annual rate of treatment discontinuation remains the same for each treatment over the lifetime of the model. In the company model, where there is only one line of treatment, clinical advice to the ERG is that treatment would only stop when the patient was perceived to be receiving no further clinical benefit, even if the patient was still experiencing relapses. The ERG, therefore, considers that a more realistic approach to modelling discontinuation is to use trial treatment discontinuation rates where available (i.e., during the first year), then, from year 2 onwards, assume that treatment continues whilst the patient receives benefit, which, in the company model, is up until a patient reaches EDSS state 7 or enters the SPMS state. Using this approach results in costs increasing for all treatments, with ozanimod remaining the most expensive treatment option and remaining dominated by six comparators.

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

The ERG has made the following revisions to the company base case:

1. modelling a difference in treatment effect only when the clinical outcomes used to compare relative efficacy of different treatments are shown, by results from the company NMAs, to be statistically significantly different and removing AE rates from the model (R1)

2. after one year, treatment is assumed to continue until progression to EDSS 7, or conversion to SPMS state (R2).

Rather than showing results of the changes against all comparators, the ERG's revised ICERs per QALY gained are shown, using list prices only, for three comparisons:

- treatment with ozanimod versus the reference case, i.e., the comparator with the most favourable ICER per QALY gained compared to ozanimod in the company base case, which, for analyses, undertaken using list prices, is [redacted] (see Table 24)
- the comparison of treatment with ozanimod versus DMF; clinical advice to the ERG, [redacted] is that DMF is the most widely used DMT for active RRMS in the NHS (see Table 25)
- the comparison of treatment with ozanimod versus ocrelizumab; the ERG considers that treatment with ocrelizumab is a valid comparator (see Table 26).

Fully incremental analysis results for all treatments included in the company base case analysis, including ocrelizumab, with both R1 and R2 implemented, are shown in Table 27.

Details of all Microsoft Excel revisions carried out by the ERG to the company model are provided in Appendix 2, Section **Error! Reference source not found.** of this ERG report. A confidential appendix which includes results from the analyses presented in Table 24, Table 25, Table 26, and Table 27 generated using Patient Access Scheme prices is also available in a separate document.

Table 24 ERG adjustments to company base case analysis: ozanimod versus reference case for ERG preferred scenario (list prices)

Scenario/ERG amendment	Ozanimod			Reference case*			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]										
R1) Modelling only statistically significant differences in outcomes where appropriate and removing AEs											
R2) Treatment discontinuation for first year only											
B. ERG preferred scenario (R1+ R2)											

* For this analysis, the reference case is [redacted]
AE=adverse event; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Table 25 ERG adjustments to company base case analysis: ozanimod versus dimethyl fumarate (list prices)

Scenario/ERG amendment	Ozanimod			Dimethyl fumarate			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Modelling only statistically significant differences in outcomes where appropriate and removing AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Treatment discontinuation for first year only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. ERG preferred scenario (R1+ R2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Table 26 ERG adjustments to company base case analysis: ozanimod versus ocrelizumab (list prices)

Scenario/ERG amendment	Ozanimod			Ocrelizumab			Incremental			*ICER*	
	Cost	**QALYs**	**Life Years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change from base case**
A. Company base case model assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Modelling only statistically significant differences in outcomes where appropriate and removing AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Treatment discontinuation for first year only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. ERG preferred scenario (R1, R2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

[redacted]

Table 27 Fully incremental analysis results generated by the company model with ERG amendments R1 and R2 (list prices)

Treatment	Cost	QALYs	Incremental costs	Incremental QALYs	ICER
GA 20mg (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA 40mg (Copaxone)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1b (Extavia)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peg IFN β-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 30µg (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN β-1a 44 µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DMF=dimethyl fumarate; GA=glatiramer acetate; ICER=incremental cost effectiveness ratio; IFN=interferon; µg=microgram; QALY=quality adjusted life year
Extended dominance= the incremental cost effectiveness ratio (ICER) for a given treatment alternative is higher than that of the next, more effective, alternative

4.6 Conclusions of the cost effectiveness section

The company model structure only allows treatment with one DMT over a patient's lifetime with no treatment switching. This is an oversimplification of clinical practice where at least ten comparator treatments for active RMSS are currently available and so renders all model results to be of limited relevance to decision makers.

In the company base case, within the limitations of the model structure and using list prices for the intervention and all comparators, treatment with ozanimod was dominated by six comparator treatments (CS, Table 60). However, these results were generated by modelling differences in the clinical effectiveness of treatments that were not statistically significantly different, [redacted]. In addition, treatment discontinuation rates were inappropriately modelled by the company.

When only evidence of statistically significant differences in treatment effect are included in the model and treatment discontinuation rates are modelled more appropriately, ozanimod is no longer [redacted] by any comparator, but has an ICER of [redacted] For the comparison of treatment with ozanimod versus DMF (the treatment that clinical advice to the ERG stated was the most commonly used in the NHS), [redacted].

The ERG considers that ocrelizumab is an appropriate comparator and should have been included in the company's base case analysis. When included in the analysis, and when only evidence of statistically significant differences in treatment effect are included, and treatment discontinuation rates are modelled appropriately, [redacted].

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6 APPENDICES

6.1 Appendix 1: other efficacy results from the trials of ozanimod

6.1.1 Outcomes associated with MRI lesions

Number of new or enlarging hyperintense T2-weighted brain MRI lesions

The mean number of new or enlarging hyperintense T2-weighted brain MRI lesions was the first ranked key secondary outcome in the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis. A summary of results for this outcome is provided in Table 28.

Table 28 Summary of new or enlarging hyperintense T2-weighted brain MRI lesions results in the ITT populations of the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis[a]

Results	RADIANCE Part B		SUNBEAM		Pooled analysis	
	24 months		≥12 months		up to 12 months	
	IFN β-1a 30µg (Avonex) (n=441)	Ozanimod 1mg (n=433)	IFN β-1a 30µg (Avonex) (n=448)	Ozanimod 1mg (n=447)	IFN β-1a 30µg (Avonex) (n=889)	Ozanimod 1mg (n=880)
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of available MRI scans	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (95% CI) per scan	3.18 (2.64 to 3.84)	1.85 (1.53 to 2.23)	2.84 (2.33 to 3.45)	1.47 (1.20 to 1.78)	[redacted]	[redacted]
Percent reduction (95% CI)[b]	[redacted]		[redacted]		[redacted]	
Rate ratio (95% CI)[b]	0.58 (0.47 to 0.72)		0.52 (0.43 to 0.63)		[redacted]	
p-value[c]	<0.0001		<0.0001		[redacted]	

[a] Means are reported to one decimal place, SDs, SEs, effect sizes and CIs (e.g. rate ratio and 95% CI) are reported to two decimal places, p-values are reported to 4 decimal places

[b] Rate ratio and percent reduction of brain MRI lesions are expressed as ozanimod / IFN β-1a 30µg (Avonex). Rate ratio < 1 and percent reduction > 0 favours ozanimod over IFN β-1a 30µg (Avonex)

[c] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs Rest of the World), age at Baseline, and Baseline number of Gd-E T1 brain MRI lesions. The natural log transformation of the number of available MRI scans over 24 months is used as an offset term

[d] Not reported in the CS; calculated from the ERG based on the reported results from the RADIANCE Part B and SUNBEAM trials

[e] Not reported in the CS; estimated by the ERG based on the reported percentage reduction of new or enlarging hyperintense T2-weighted brain MRI lesions and 95% CI. The ERG assumes that [redacted] reported as the rate ratio in Table 10 of the CS is actually the percentage reduction.

CI=confidence interval; Gd-E=gadolinium–enhanced; IFN=interferon; Max=maximum; Min=minimum; MRI=magnetic resonance imaging; NR=not reported; SD=standard deviation; SE=standard error

Source: CS, extracted and adapted from Table 10

In both the RADIANCE Part B and SUNBEAM trials as well as in the pooled analysis, ozanimod significantly reduced the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan compared with IFN β-1a 30 µg (Avonex).

The rate ratio of new or enlarging hyperintense T2-weighted brain MRI lesions on ozanimod compared to IFN β-1a 30µg (Avonex) was generally consistent across all subgroups within the RADIANCE Part B trial (CSR, Figure 7) and the SUNBEAM trial (CSR, Figure 9).

In the RADIANCE Part A trial, the number of new or enlarging hyperintense T2-weighted brain MRI lesions between weeks 12 and 24 was a secondary outcome. The number of new or enlarging hyperintense T2-weighted brain MRI lesions between weeks 12 to weeks 24 (CS, Table 25) was statistically significantly lower in the ozanimod treatment arm than in the placebo arm ([redacted]).

Number of Gd-E T1 brain MRI lesions

The mean number of Gd-E T1 brain MRI lesions was the second ranked key secondary outcome in the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis. A summary of results for this outcome is provided in Table 29.

In both the RADIANCE Part B and SUNBEAM trials as well as in the pooled analysis, ozanimod significantly reduced the total adjusted mean number Gd-E T1 brain MRI lesions per scan compared with IFN β-1a 30µg (Avonex).

The rate ratio of Gd-E T1 brain MRI lesions on ozanimod compared to IFN β-1a 30µg (Avonex) was generally consistent across all subgroups within the RADIANCE Part B trial (CSR, Figure 6) and the SUNBEAM trial (CSR, Figure 8).

In the RADIANCE Part A trial, the cumulative number of Gd-E T1 brain MRI lesions between weeks 12 and 24 was the primary outcome and the number of Gd-E T1 brain MRI lesions at week 24 was a secondary outcome. The total number of Gd-E T1 brain MRI lesions from Week 12 to Week 24 (CS, Table 21) and the number of Gd-E T1 brain MRI lesions at week 24 (CS, Table 25) were statistically significantly lower in the ozanimod treatment arm than in the placebo arm ([redacted]).

Table 29 Summary of Gd-E T1 brain MRI lesions results in the ITT populations the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis[a]

Results	RADIANCE Part B		SUNBEAM		Pooled analysis	
	24 months		≥12 months		up to 12 months	
	IFN β-1a 30µg (Avonex) (n=441)	Ozanimod 1mg (n=433)	IFN β-1a 30µg (Avonex) (n=448)	Ozanimod 1mg (n=447)	IFN β-1a 30µg (Avonex) (n=889)	Ozanimod 1mg (n=880)
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (95% CI) per scan	0.37 (0.26 to 0.54)	0.18 (0.12 to 0.27)	0.43 (0.30 to 0.64)	0.16 (0.11 to 0.24)	[redacted]	[redacted]
Percent reduction (95% CI)[b]	[redacted]		[redacted]		[redacted]	
Rate ratio (95% CI)[b]	0.47 (0.31 to 0.72)		0.37 (0.24 to 0.54)		[redacted]	
p-value[c]	0.0006		<0.0001		[redacted]	

[a] Means are reported to one decimal place, SDs, SEs, effect sizes and CIs (e.g. rate ratio and 95% CI) are reported to two decimal places, p-values are reported to 4 decimal places
[b] Rate ratio and percent reduction of brain MRI lesions are expressed as ozanimod / IFN β-1a 30µg (Avonex). Rate ratio < 1 and percent reduction > 0 favours ozanimod over IFN β-1a 30µg (Avonex)
[c] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe vs Rest of the World), age at Baseline, and Baseline number of Gd-E T1 brain MRI lesions. The natural log transformation of the number of available MRI scans over 24 months is used as an offset term
[d] Not reported in the CS; calculated from the ERG based on the reported results from the RADIANCE Part B and SUNBEAM trials
[e] Not reported in the CS; estimated by the ERG based on the reported percentage reduction of Gd-E T1 brain MRI lesions and 95% CI
CI=confidence interval; Gd-E=gadolinium–enhanced; IFN=interferon; Max=maximum; Min=minimum; MRI=magnetic resonance imaging; NR=not reported; SD=standard deviation; SE=standard error
Source: CS, extracted and adapted from Table 11.

6.1.2 Other outcomes

Exploratory outcomes in the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis included MRI assessment of percentage change from baseline (cm^3) in total brain volume, cortical grey volume and thalamic volume, MSFC and MSFC low-contrast letter acuity (LCLA) composite z-scores and MSFC component (Timed 25-foot Walk, 9-hole Peg Test, Symbol Digit Modalities Test / Paced Auditory Serial Addition Test) scores and z-scores and no evidence of disease activity (NEDA-3, a composite outcome comprised of ARR, CDP and MRI and NEDA-4, a composite outcome comprised of ARR, CDP, MRI and annualised BVL <0.4%).

Multiple Sclerosis Quality of Life-54 (MSQoL-54) scores were also measured as an exploratory efficacy outcome in the RADIANCE Part B trial, the SUNBEAM trial and the pooled analysis. MSQoL-54 is summarised in Section 3.7 of this ERG report.

These outcomes were not formally statistically tested; all p-values provided within the CS are for exploratory purposes.

Percentage change from baseline in brain volume loss (BVL, cm^3)

In both the RADIANCE Part B and SUNBEAM trials as well as in the pooled analysis, ozanimod resulted in a larger, and nominally statistically significant, mean percentage change from baseline compared with IFN β-1a 30µg (Avonex) in total brain volume loss (CS, Table 12), cortical grey matter volume loss (CS, Table 13) and thalamic volume loss (CS, Table 14).

Multiple sclerosis functional composite score

Across the RADIANCE Part B and SUNBEAM trials and within the pooled analysis, numerically favourable treatment effects in MSFC and MSFC (LCLA) z-scores in the ozanimod arm compared to the IFN β-1a 30µg (Avonex) arm were not statistically significant. Numerical results for MSFC and MSFC (LCLA) z-scores and MSFC component scores can be found in the CS (Table 17).

The company notes that more ozanimod-treated patients had clinically meaningful improvements in processing speed compared to those treated with IFN β-1a 30µg (Avonex) and that these findings are consistent with BVL findings, which are thought to play an important role in the loss of cognition and increase in disability progression in MS. Clinical advice to the ERG is that processing speed and BVL findings may play an important role, but that many other factors may also contribute to loss of cognition and increase in disability progression in MS.

NEDA-3 and NEDA-4

Numerical results for NEDA-3 and NEDA-4 can be found in the CS (Table 19 and Table 20) and in response to question A6 and A7 of the clarification letter. There was a statistically significant increase in in the ozanimod arm in the proportion of patients with NEDA-3 at 24 months in the RADIANCE B trial and in the pooled analysis at 24 months. There was also a statistically significant increase in the ozanimod arm in the proportion of patients with NEDA-4 in the pooled analysis at 24 months.

There were no statistically significant differences between arms in NEDA-3 or NEDA-4 in the SUNBEAM trial at ≥12 months or in the pooled analysis at 12 months and no statistically significant differences between arms in NEDA-4 in the RADIANCE Part B trial at 24 months

6.2 Appendix 2: Microsoft Excel revisions made by the ERG to the company's model

All revisions are activated by the company's switch and the ERG's logic switch.

Instructions for modifying the updated company model

Note: It may be necessary to force a full calculation in the model to update array formulas after making amendments: CTRL+ALT+F9

1. Paste the following table into a new sheet named 'ERG switches', and name the switches R1 and R2 with the modification names

TMenu of ERG revisions and switches for revisions

Revision #	Name cell	Switch	Description	Instructions
R1	StatSigOnly	Yes	Include statistically significant data only	0 for company base case, 1 for ERG revision
R2	TTDOneyearonly	Yes	Stop treatment discontinuation after year one unless reaching EDSS 7	0 for company base case, 1 for ERG revision
R3	-	No	Add ocrelizumab as a comparator	On Sheet "Controls" set value J14=Yes

2. In Workbook "ERG amendments for ozanimod" in worksheet "Data"
    - Copy range A1:B33
    - In company model in worksheet "Default_data" paste values in range M275:N307
3. In Workbook "ERG amendments for ozanimod" in worksheet "Data"
    - Copy range C1:C16
    - In company model in worksheet "Default_data" paste values in range N439:N454
4. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

Log for implementing ERG revisions

ERG revision number and description	Sheet	Cells	Modified formulae
R1 Use statistically significant data only	Defaul_data	C275 (copy modified formula to range C276:C307	=IF(StatSigOnly=0,N275,M275)
		C439 (copy modified formula to range C440:C454	=IF(StatSigOnly=1,N439,M439)
		C600 (Copy modified formula to range C601:C983	=IF(StatSigOnly=1,0,IF(INDEX($H600:$AA600,((country_no-1)*AD1)+(MATCH(C14,list_subgroups,0)))="","",INDEX($H600:$AA600,((country_no-1)*AD1)+(MATCH(C14,list_subgroups,0)))))
R2 Stop treatment discontinuation after year one unless reaching EDSS 7	Default_data	C455	=IF(TTDoneyearonly=1,0,C$439)
		C456	=IF(TTDoneyearonly=1,0,C$440)
		C457	=IF(TTDoneyearonly=1,0,C$441)
		C458	=IF(TTDoneyearonly=1,0,C$442)
		C459	=IF(TTDoneyearonly=1,0,C$443)
		C460	=IF(TTDoneyearonly=1,0,C$444)
		C461	=IF(TTDoneyearonly=1,0,C$445)
		C462	=IF(TTDoneyearonly=1,0,C$446)
		C463	=IF(TTDoneyearonly=1,0,C$447)
		C464	=IF(TTDoneyearonly=1,0,C$448)
		C465	=IF(TTDoneyearonly=1,0,C$449)
		C466	=IF(TTDoneyearonly=1,0,C$450)
		C467	=IF(TTDoneyearonly=1,0,C$451)
		C468	=IF(TTDoneyearonly=1,0,C$452)
		C469	=IF(TTDoneyearonly=1,0,C$453)
		C470	=IF(TTDoneyearonly=1,0,C$454)

5. In the sheet “Default_data”:
    - copy range C455:C470
    - paste formulae into cells C471:C486; C487:C502; C503:C518; C519:C534; C535:C550; C551:C566; C567:C582; C583:C598

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding. 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.]	**Celgene** - no funding **Bayer** - no funding **Biogen** - £31,752.55 - exhibitor at MS Trust annual conference for health professionals and honorarium **Genzyme** - £89,075.00 - exhibitor at MS Trust annual conference for health professionals; funding for specialist nurse programme **Merck** - £29,715.90 - exhibitor at MS Trust annual conference for health professionals; training course attendance; advisory board **Novartis** - £92,450.00 - exhibitor at MS Trust annual conference for health professionals; funding of HP bursaries; funding for specialist nurse programme **Teva** - £8,810.00 - exhibitor at MS Trust annual conference for health professionals

If so, please state the name of manufacturer, amount, and purpose of funding.	**Roche** - £29,286.10 - exhibitor at MS Trust annual conference for health professionals; advisory board
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.
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 relapsing remitting MS: • 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. People with MS rely heavily on their MS specialist team to provide information and guidance to help with treatment choices. MS teams are skilled and experienced in helping an individual make the choice that is the best match for their level of disease activity, their personal circumstances, their attitude to risk and their treatment goals.
8. Is there an unmet need for patients with this condition?	Clearly, the most significant unmet need for people with MS is a cure. In the absence of a cure, people with MS want to live a life free from the impact of their disease. For many people, the ultimate goal of taking one of the DMDs is to reduce their risk of disease progression and future disability. Inevitably, the frequency and severity of relapses rank highly for those with RRMS, not just for the disruption and distress that relapses cause, but also because of the risk of residual disability and increased chances of conversion to secondary progressive MS. Ranking the impact of individual symptoms is difficult and ultimately inadequate as the condition varies so widely between individuals. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to DMDs. For those people with very active relapsing MS - either rapidly evolving severe or highly active despite treatment - the side effects associated with the current, more effective DMDs 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 ozanimod compared to beta interferon: • More effective at reducing the risk of relapses • More effective at reducing invisible MS activity (lesions on MRI scans) • More effective at reducing brain volume loss • More effective at preserving cognitive function, an important factor for remaining in employment • Equivalent effectiveness in time to three month or six month confirmed disability progression • Low level of side effects – resulting in minimal requirements for routine blood and urine tests • Convenient dosing schedule – single tablet taken daily which has minimal impact on lifestyle, resulting in high level of adherence Ozanimod belongs to the same class of drugs as fingolimod (Gilenya) which has been used as a treatment for relapsing remitting MS since 2012. Experience gained with fingolimod will mean that clinicians will be prepared for and monitor for potential problems associated with ozanimod, and this will provide reassurance for patients who are more risk averse. Ozanimod has not been compared directly with fingolimod n a clinical trial, but a comparison of results from studies comparing ozanimod and fingolimod with beta interferon suggests that the two treatments have similar efficacy. Ozanimod is more selective than fingolimod for the target subtype 1 of sphingosine 1-phosphate receptors which are expressed on lymphocytes and lead to sequestration of lymphocytes in lymph nodes. As a result, ozanimod might be expected to cause fewer side effects compared to fingolimod. In ozanimod clinical trials, first-dose monitoring showed no slowing of heart rate, liver enzyme levels increases were transient, generally resolved and did not lead to treatment discontinuation, and risk of macular oedema appears to be very low.

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 ozanimod clinical trials, side effects caused by ozanimod were mild to moderate. Those which occurred more frequently in people taking ozanimod included nasopharyngitis, increased liver enzyme levels, hypertension and urinary tract infections.
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	None.

considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Once daily oral route of administration means that ozanimod can be taken at home, eliminating potential delays in starting treatment which has occurred with other DMDs which require access to outpatient infusion clinics. Overall, this route of administration minimises demands on NHS services. 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.
Key messages	

15. 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 ozanimod
- Ozanimod shows efficacy comparable to fingolimod, a treatment in the same drug class, but has fewer serious side effects
- Once daily oral route of administration, aiding adherence and minimising service usage
- Improved quality of life, reduced steroid administration and few hospital admissions (resulting from lower relapse rate)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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

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

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

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

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles.
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.]	**n/a**

If so, please state the name of 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 aim is to reduce relapses, disease progression and MS related disability
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	There is no widely accepted definition of this for MS. I consider the results reported in the Radiance and Sunbeam trials of reductions in relapse rate, lesions and brain volume vs Avonex to be of clinical significance

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Range of licenced and NICE approved MS disease modifying treatments with varying efficacy and safety profiles
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England treatment algorithm
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes, the pathway well defined and constrained by NICE/Blueteq and NHSE treatment algorithm. There is variability in prescribing habits between units (range of choices available with limited comparative data).

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	This treatment would be add to the current care pathway. The low rate of side effects and greater efficacy makes this appealing as a first and second line drug (the other available S1P modulator (Fingolimod) is approved as second line treatment currently).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Fingolimod - first dose cardiac monitoring and 3 month ophthalmological examination required, these may not be necessary with Ozanimod
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Should be used in specialist clinics, as with other MS disease modifying treatments
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – more effective and similar rate of side effects than first line comparator treatment
• Do you expect the technology to increase length of life more than current care?	Potentially
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This group of drugs is not suitable for use during pregnancy
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	May be significantly easier if cardiac monitoring for first dose and 3 month ophthalmological examination not required, low rate of side effects and serious adverse events may make monitoring less onerous. Oral treatment usually more acceptable to patients than current injectables (comparator drug in trials) and less resource-intensive than the infusion treatemnts (Ocrelizumab, Natalizumab, Alemtuzumab), low monitoring burden
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard stopping rules for MS disease modifying treatments are suggested in NHS England treatment algorithm
15. Do you consider that the use of the technology will result in any substantial health-	No

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
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 improve the way that current need is met?	Yes
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Yes, need for effective drugs with improved safety profiles, ease of administration and monitoring

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?	Trials suggest very low rate of side effects, whilst being significantly more effective than the first-line comparator
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes - relapse rate, enhancing and T2 lesions, brain volume loss, patient reported outcomes, disability progression, safety and tolerability
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	N/A
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

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

- More effective than active comparator drug
- Good safety and side effect profile
- Ease of administration
- Has a role in the current treatment algorithm

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Ozanimod for treating relapsing-remitting multiple sclerosis

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Eli Silber**
2. Name of organisation	**Kings College Hospital NHS Trust** (Nominated by MS trust)

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? **YES** 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 **YES** ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes I did not write it

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce MS relapses and the risk of long term disability as a result of relapses and progression.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in relapses of >40%. Reduction in relapses by at least 50% vs platform 1st line therapies.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are current disease modifying therapies with a range of efficacies. The current SIP inhibitor is only available as a second line therapy for patients with breakthrough disease. Furthermore it requires a day case hospital admission for monitoring for bradyarrythmias which adds to patient inconvenience and healthcare costs.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	There are a range of disease modifying therapies. These range from the injectable therapies (beta interferon and glatyrimer acetate) reducing relapses by approximately 30% to dimethyl fumarate (40+%), fingolimod 50% and monoclonal antibodies (alemtuzimab, nataluzimab and ocriluzimab) which reduce relapses by over 60%. This is intended as a first line therapy reducing relapses by approximately 50%.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE MS guidelines. NICE Guidelines for each of the MS disease modifying therapies. NHS MS treatment algorythm
• 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.)	Yes, there is an accepted MS therapy algorithm. There are currently two SIP inhibitors available. Fingolimod is used as a second line therapy for patients with breakthrough relapsing disease. Siponimod is licensed in secondary progressive MS.
• What impact would the technology have on the current pathway of care?	It will offer another option of a first line oral therapy with greater efficacy to dimethyl fumarate (DMF) (approximately 40% reduction in relapses) and teriflunomide (approximately 30% reduction in relapses). It will potentially reduce admissions for cardiac monitoring.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it is likely to slot into existing therapy algorithms and is likely to be used similarly to DMF and teriflunomide as first line oral therapies.

• How does healthcare resource use differ between the technology and current care?	The current SIP inhibitors are either 1. Second line following relapses and requires cardiac monitoring. 2. For secondary progressive MS
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Usually in MS centres (tertiary and potentially secondary care with appropriate resourcing)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil, likely to slot into existing pathways and treatment protocols.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Reduction in admissions for cardiac monitoring. On average more effective in reducing relapses that existing first line oral therapies. Safety profile better that existing established SIP inhibitor, in particular no severe lymphopenia/ liver dysfunction, fewer cases of macular oedema reported.
• Do you expect the technology to increase length of life more than current care?	Potentially small reduction in cardiac events. If more effective that existing first line oral therapies may reduce relapses and costs of managing these and long term disability.

• Do you expect the technology to increase health-related quality of life more than current care?	Compared to interferon drug improvement in screening cognitive test thus potentially beneficial effect on maintaining employment/ independent functioning.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with cardiac disease. Patients intolerant of DMF/ teriflunomide but wanting an oral therapy.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Easier, not requiring admissions for cardiac monitoring. No genetic testing for SIP metabolism. Dose escalation thus potentially easier for patients to self-manage initiation.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We will use existing NHS guidelines for escalation and therapy failure including stopping criteria. .
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Reduced cardiac events and admissions.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Reduced cardiac monitoring and admissions for initiation. Better blood safety profiles compared to existing SIP inhibitor.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No, valuable additional therapy that bridges the gap between first and second line therapies, easier to use with reduced admissions and better safety profile.
• Does the use of the technology address any particular unmet need of the patient population?	Patients with cardiac disease. Patients intolerant of DMF/ Teriflunomide .
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Potential risk of immune suppression=- appears to be safer that existing therapy. Will be managed as for existing therapies.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes- we actively manage patients with relapsing remitting MS. They are offered a range of therapies and most choose to be on a first line oral therapy.
• If not, how could the results be extrapolated to the UK setting?	There are existing guidelines. Likely to be placed similarly to existing 1st line oral therapies.
• What, in your view, are the most important outcomes, and were they measured in the trials?	50% reduction in relapses compared to platform injectable interferon drug.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, reduction in MRI activity is a good marker of reduction in relapses. In the studies approximately 50% less that platform therapy at 1 year and 38% at 2 years.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Nil to my knowledge
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA127, TA254, TA303, TA312, TA320, TA493, TA527, TA533?	No. Results of the risk sharing scheme are broadly in keeping with expected outcomes.
22. How do data on real-world experience compare with the trial data?	I am not aware of recent real life data.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, may be better for older patients with cardiac disease.

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is alemtuzumab considered to be established clinical practice in the NHS for treating relapsing-remitting multiple sclerosis? How is this expected to change given it has been restricted by the EMA to people with RRMS that is highly active despite treatment with at least two other disease-modifying therapies, or when other disease-modifying therapies cannot be used?	Alemtuzumab is an established therapy that should be treatment option for patients with aggressive disease. It has a place but patients should be offered a range of effective therapies as appropriate. They should be aware of risks and benefits and should make an educated decision, particularly in comparison with drugs of similar efficacy, such as Natalizumab and Ocriluzimab.

25. Who receives ocrelizumab in clinical practice and is its considered to be established clinical practice in the NHS for treating relapsing-remitting multiple sclerosis?	Ocrilizumab is an established therapy and is now widely used both as first and second line therapy for patients with relapsing remitting MS.
26. What is your opinion on the likely duration of treatment effect of ozanimod and the possibility of a treatment waning effect?	Extrapolating from fingolimod the treatment effects are likely to last for the majority (>70%) of patients. In our series of >150 patients the majority of patients remain on therapy because of efficacy (lack of relapses or new MRI activity) and tolerability/ safety.
Key messages	

27. In up to 5 bullet points, please summarise the key messages of your statement.

- This is an advance on the existing SIP inhibitor licensed in RR MS as it does not require cardiac monitoring for the majority of patients.
- This is intended as a first line therapy offering a potentially more effective oral therapy to patients with earlier RR disease.
- It can potentially be used with limited changes to existing therapy protocols and there are existing treatment and monitoring pathways established.
- The overall safety profile appears to be very favourable.
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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

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

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Lorraine Hazlehurst**
2. Are you (please tick all that apply):	☐ a patient with the condition ☐ a patient organisation employee or volunteer

3. Name of your nominating organisation	MS Society
4. Did your nominating organisation submit a submission?	☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hearing the news that I had MS was devastating. Living with a progressive, chronic and life changing condition has been impactful in all aspects of my life, from the ability to remain employed to having the energy and capability to live a full and integrated life with friends and family. For me, the major challenges include the fluctuating nature of the symptoms from good days where I can live well to bad days where I am unable to function. The uncertain progression pathway and what your future looks like is hard to reconcile or imagine. For the carers, who are often our friends and family, they too are impacted by this disease. We need help with daily tasks, which changes depending on what day it is and what phase our illness is. We need their emotional support, to help us deal with life today and future we may face. We may end up being reliant on them to bear the financial aspects of living. We may impact their opportunities as we find we cannot be as active or energetic as we once were. This is an illness that affects all those we are close to.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	As the condition is very individual, it is essential that there is a suite of medicines and treatments available to cater to the changing phases and individual nature for all patients. The current medicines may work for some patients but not others and many of them handle symptoms rather than prevent progression or repair damage. The older, often first prescribed medicines offered to me handled symptoms only rather than prevented progression. It is essential to me that I can access medicines and treatments as they are discovered that allow me to stabilise my health and live a long and full life.
10. Is there an unmet need for patients with this condition?	Yes. MS progression is not currently stopped. Damage is not currently being repaired or reversed. Primary progressive patients have limited medicine options.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	From my review of the published data for this medicine, it has several positives for the patient. It is a daily tablet. In my experience, this means it is an easy regime to be compliant with rather than alternatives such as injecting. It has shown reduction in lesion progression during clinical trials The side effects do not look onerous. Other medicines available have serious side effects that have meant I have chosen not to receive them or been unable to tolerate them. Do not underestimate the tough decision patients have to make when weighing up the risk profile of some of the medicines for MS.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	No obvious disadvantages from me
Patient population	
13. 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.	This is a medicine for relapsing remitting MS, does this mean that the primary or secondary progressive patients will not benefit ?
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**none**

Other issues	
15. Are there any other issues that you would like the committee to consider?	It is essential that there is a suite of medicines for MS patients. The condition has an uncertain and individual impact on each person affected and therefore as many options need to be available as one size does not fit all. New medicines need to be available to the patient as opposed to the older, potentially less targeted treatments.

Key messages

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

- MS is an uncertain, impactful chronic condition that affects all aspects of the lives of the patient and their friends and family
- Availability of treatments that allow people to live productive lives is key to the patient and benefits society
- A suite of medicines and treatment is essential as this illness impacts patients differently
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Tracy Nicholson**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I first presented with symptoms of MS in 1998 but did not receive a definitive diagnosis until 2000. Following a number of relapses affecting both sensory and motor function I commenced on my first DMD, (Rebif), in 2005. This was a period during which I felt both isolated and fearful; the uncertainty of both the type and frequency of relapse I may experience scarred me. I was under the care of a general neurologist with very limited experience of DMDs. I only saw the neurologist when I presented with new symptoms. My local MS services were practically non-existent and there was no network or support systems that I was able to reach out to. When I was prescribed Rebif I was transferred to the local prescribing centre at Addenbrookes and this was where life with MS began to improve. I was supported through the process of starting on an injectable therapy, the management of side effects, provided with contact details of the MS team who were on hand

	to provide help and support as required and regular visits to see either the Neurologist or the MS Specialist nurse. I remained relapse free for the next 14 years which gave me the confidence that a good quality of life was possible with MS. It also provided the opportunity to address one of my biggest issues; learning to live with the unknown. The experience of going to bed feeling ok and waking up the next morning to find that I was unable to get out of bed, was very traumatic. It took several years before I was able to attend or prepare for important events without feeling anxious that a relapse may occur before or during them. Eventually I developed the confidence to relax and understand that if a relapse were to happen, I would deal with it there and then. Throughout this period, every dose of Rebif was followed by side effects. These would vary from mild to moderate flu like symptoms, hot flushes, headaches, an inability to control my temperature (I would go from feeling cold to my bones to overheating), all of which resulted in 3 disturbed night's sleep a week. There were may discussions with the Health Care Professionals throughout this time about switching to another DMD or stopping treatment. Looking at the pros and cons of the limited other options available, I always came back to the thought process of if I hadn't experienced any further relapses on treatment, then I was prepared to deal with the side effects and disturbed sleep. In other words, if it isn't broken then why fix it. At the beginning of 2019 I started to experience new symptoms and with an MRI scan which showed evidence of active disease, my neurologist strongly advised a change of medication - especially in light of the more effective treatments options now available. We discussed the pros and cons of Tecfidera and Fingolimod and although the neurologist was steering me towards Fingolimod based on his experience of patients like me on both treatments, I opted for Tecfidera on the basis that the potential cardiac effects scared me. Having felt very lucky to be as well as I was at this point, I did not want to compromise myself in any other way. Unfortunately, I did not have a good experience with Tecfidera, despite heeding all the advice from the MS Nurses in regards to dosing. I constantly suffered from flushing which spread very quickly, making my skin feel prickled and like it was burning, along with abdominal discomfort and gastrointestinal upset. Added to which my white cell count dropped to a point where I had no choice but to stop treatment. This was then followed by 4-month treatment break whilst my white cell count returned to normal.

	I then, with a degree of caution, agreed to start on Fingolimod. At my first dosing I watched my heart rate drop to 44bpm and my BP go the same way. Ten hours later I was discharged from the assessment unit with a heart rate that was gradually working its way back to normal. Despite reassurances from the Neurologist and MS Nurse and the written information I was given, it was with great levels of anxiety I took my second dose the following morning. Three months on and I have settled on the drug and have not had any relapses or experienced any obvious side effects. What I was not prepared for over this time was the psychological impact. With the development of new symptoms came a big reminder that I have a progressive neurological disease that I can't control and a lot of the emotions I had experienced at diagnosis came back. My positive attitude and outlook were severely diminished and life became a bit of a struggle. My fatigue returned, the summer was long and hard, a time of year historically I had always felt my best physically. Decision making around drug choice was definitely impaired and fear for what the future may hold returned. The care, patience and understanding of the team at Addenbrookes has been amazing and now that I am settled on a new DMD things are looking up. It is very reassuring to know going forward that if my MS takes another unexpected turn there are still other treatment options out there.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	With regards to drug choice, efficacy is always the first thing to be discussed but from a patient's perspective it is definitely not the only criteria to be considered. The route of administration, the dose frequency, the side effect profile, can all impact on quality of life and need to be seriously considered. Each time you take a tablet, have an injection or infusion it is a reminder that you have MS. Each patient is different as is their disease course and these elements will have different levels of importance. The MS team plays a really important role here in helping and guiding pwms to make the right choice for them. The team at Addenbrookes have been amazing throughout my journey to date but I am acutely aware from talking to other people with MS that this same level of service is not always provided.

10. Is there an unmet need for patients with this condition?	Cure or something to reverse the effect of MS are the obvious unmet need but in the interim it has to be the availability of any intervention that can minimise the effect of the condition on daily life and enable the pwms to be the best they can be.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	As I have no personal experience of this technology this is difficult to answer; however having experienced the cardiac side effects of Fingolimod at first dosing, the fact that this technology is more specific and does not appear to have the same cardiac side effects has to be an advantage.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I have no experience of the drug so am unable to comment.
Patient population	
13. 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 I am aware of.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that I am aware of.
Other issues	
15. Are there any other issues that you would like the committee to consider?	The flexible once-daily dosing fits easily into day to day life and therefore will lead to much better compliance.

Key messages

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

- It is important to remember that living with MS is different for everyone affected by the disease and that one treatment option doesn't fit all. Consideration has to be given to all aspects of any intervention on the impact of the individuals quality of life, as this will ultimately result in better compliance.
- Ideally any decisions that are made in regards to care and treatment are done in conjunction with the relevant healthcare professionals, with risks and benefits appropriately explained and consideration given to any psychological impact.
- There should always be choice, an option to change your mind and confidence in alternative treatments should your disease course change.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Malcolm Qualie**
2. Name of organisation	**NHS England/NHS 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?	Yes, NICE have published NICE Guidelines - Multiple sclerosis in adults: management (CG186). NICE have also published several TA's relating to treatments for relapsing remitting MS (RRMS) and one for a treatment for primary progressive MS (PPMS). NHS England has issued an algorithm relating to the treatment of RRMS which can be found here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/
6. 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	NHS England has published a service specification for neuroscience centres (which in part includes MS services) which can be found here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/ Clinicians in England who treat patients with RRMS differ in their 1st line treatment options. Some prefer to use the more highly active directly acting treatments (DMTs) eg cladribine and, before its more restrictive licence, alemtuzumab. Some prefer the more traditional therapies such as beta interferon and glatiramer

experience is from outside England.)	acetate whereas others use dimethyl fumarate the latter being the most widely used first line treatment currently.
7. What impact would the technology have on the current pathway of care?	Ozanimod would represent a further oral option for people with RRMS. It is given once daily so may have an advantage over dimethyl fumarate which needs to be administered twice a day.
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 currently not being used outside any Pharma sponsored clinical trials.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently used DMTs are commissioned by NHS England from acute provider trusts. More complex therapies, such as alemtuzumab and ocrelizumab, are provided by specialist neuroscience centres, or as part of an agreed provider network. Whilst MDT involvement is required for more complex treatments, based on existing experience with fingolimod used in the treatment of RRMS, it is not expected that routine MDT involvement in initiation of ozanimod would be required.
• How does healthcare resource use differ between the technology and current care?	The direct cost of medicine will have the greatest impact on healthcare resource depending on its price vs current therapies for RRMS.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should only be prescribed in secondary care Trusts where there is an appropriately constructed MS service as described in the NHS England algorithm.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Ozanimod is expected to require a similar level of infrastructure to be in place as fingolimod, due to the similar pharmacology of these two agents. However, unlike fingolimod (which is used as a 2nd line agent for RRMS) in clinical trials ozanimod did not cause an initial temporary slowing of heart rate so dependent on the market authorisation granted, a patient should not require a day-case appointment for cardiac monitoring when treatment is initiated. Regular blood tests may also be less than those required for fingolimod.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Not known
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

Thank you for your time.

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

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Single technology appraisal

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Company addendum

July 2020

File name	Version	Contains confidential information	Date
		Yes	**10th July 2020**

Summary of Changes incorporated in the addendum document

Change	Original information			New information
	Document A	**Document B**	**Appendices**	**Addendum**
Decision problem (population and positioning)	A.2 (P4) A.5 (P7-10)	B1.1 (P13-17)		- Proposed position in the treatment pathway is narrower than the marketing authorisation
Patient access scheme discount	A.4 (P5)	B1.2 (P17)		-Updated discount in-line with updated price
Clinical effectiveness	A.7 (P14-17	B2 (P24-64)		-Representation of relevant results -Overview of MAIC of ozanimod versus teriflunomide and dimethyl fumarate

Innovation	A.16 (P29)	B2.12 (P78)		-Clarity added in regard to innovation versus the relevant comparators
Economic evaluation	A.10 - A.17 (P19-29)	B. 3.1. (P80-140)	-	-Type of economic evaluation -Comparators - Updated ozanimod PAS -Updated Ozanimod monitoring cost based on SmPC
Budget impact	A.18 (P29- 30)	-	-	-Updated market shares -Updated proportion of RRMS patients for oral therapy

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

1. Decision problem

1.1. Population and positioning

The marketing authorisation (MA) for ozanimod (Zeposia®) was granted on 20th May 2020 by the European Medicines Agency (EMA). Ozanimod is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features. The proposed position in the treatment pathway is narrower than the marketing authorisation. This submission focuses on part of the ozanimod MA for adult patients with RRMS with active disease as defined by clinical or imaging features, suitable for or requesting an oral treatment.

2. Patient access scheme discount

A revised simple discount Patient Access Scheme has been submitted to PASLU. The analysis has been provided with the new confidential PAS price of [redacted], as detailed in Table 1.

Table 1: Proposed patient access scheme discount

	List price (£)	PAS Price (£)
Initiation pack (4 x 0.25 mg & 3 x 0.5 mg)	£343.25	[redacted]
Maintenance pack (28 x 1 mg)	£1,373.00	[redacted]
Maintenance pack (98 x 1 mg)	£4,805.50	[redacted]
Annual cost (365.25 days)	£17,910.29	[redacted]

3. Clinical effectiveness

The clinical evidence for ozanimod is derived from the two pivotal Phase III RCTs (RADIANCE Part B and SUNBEAM), and a Phase II RCT (RADIANCE Part A). Ozanimod 1 mg demonstrated superior (pooled across RADIANCE Part B and SUNBEAM), dose dependent efficacy compared to IFN β-1a in reducing ARR, reducing the number of new or enlarging hyperintense T2-weighted brain MRI lesions, and reducing the number of Gd-E T1 lesions in patients with RRMS.

3.1. Annualised relapse rate in RADIANCE Part B and SUNBEAM

In both RADIANCE Part B and SUNBEAM, ozanimod significantly reduced ARR compared with IFN β-1a. The primary endpoint, ARR was statistically significantly lower for ozanimod compared to IFN- β-1a across both trials (Celgene 2017a, Celgene 2017b, Celgene 2019c).

In the RADIANCE Part B trial, treatment with ozanimod 1 mg resulted in statistically significant lower ARR compared with IFN β-1a (adjusted ARR 0.172 vs 0.276, respectively). The adjusted ARR was [redacted] lower with ozanimod 1 mg than with IFN β-1a ($p < 0.0001$), (Celgene 2017a).

In the SUNBEAM trial, treatment with ozanimod 1 mg resulted in statistically significantly lower ARR compared with IFN β-1a (adjusted ARR 0.181 vs. 0.350, respectively). The adjusted ARR was [redacted] lower with ozanimod 1 mg than with IFN β-1a ($p < 0.0001$), (Celgene 2017b).

In the pooled analysis, the percent reductions in the ARR for ozanimod 1 mg compared to IFN β-1a was [redacted]

3.2. New or enlarging hyperintense T2-weighted brain MRI lesions in RADIANCE Part B and SUNBEAM

T2 lesion formation, which is measured by MRI, mirrors a complex sequence of inflammatory, degenerative and reparative processes. The formation of T2 lesions is a marker of inflammatory activity and repair mechanisms, i.e. relapses and recovery (Mostert 2010, Rovira 2013). Whilst the appearance of T2 lesions can be transient in nature, the position of the lesion, or more importantly the number of T2 lesions at any given point in time, is an indicator of disease activity and disease severity.

Ozanimod demonstrated superiority to IFN β-1a in the reducing number of new or enlarging T2 and Gd-E lesions in patients with RMS. The mean number of new or enlarging T2 and Gd-E lesions was the 1st ranked key secondary endpoint in RADIANCE Part B and SUNBEAM, and it was met compared to IFN β-1a (Celgene 2019b).

In the RADIANCE Part B trial, a statistically significant reduction in the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg ($p < 0.0001$) compared to IFN β-1a (1.848 and 3.183 lesions, respectively), corresponding to a [redacted] reduction over 24 months (Celgene 2017a).

In the SUNBEAM trial, there was also a statistically significant reduction in the total adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan with ozanimod 1 mg ($p < 0.0001$) compared to IFN β-1a (1.465 and 2.836 lesions, respectively), corresponding to a [redacted] reduction over 12 months (Celgene 2017b).

In the pooled analysis over 12 months, a greater reduction in the adjusted mean number of new or enlarging hyperintense T2-weighted brain MRI lesions per scan was demonstrated with ozanimod 1 mg ($p < 0.0001$) compared to IFN β-1a ([redacted] and [redacted] lesions, respectively), corresponding to a [redacted] reduction (Celgene 2019b).

3.3. Gd-E brain MRI lesions in RADIANCE Part B and SUNBEAM

Gd-E is a marker for blood brain barrier (BBB) breakdown and histologically correlates with the inflammatory phase of lesion development, therefore an increase in Gd-E lesions relates to disease progression (Pitteri 2016). The second rank-ordered key secondary efficacy endpoint, the number of Gd-E T1 brain MRI lesions, was met for ozanimod 1 mg compared to IFN β-1a, in both controlled Phase III clinical studies and in the pooled analysis.

In RADIANCE Part B, a statistically significant reduction in the adjusted mean number of Gd-E brain MRI lesions was demonstrated with ozanimod 1 mg ($p = 0.0006$) compared to IFN β-1a (0.176 and 0.373 lesions, respectively), corresponding to a [redacted] reduction at Month 24 (Celgene 2017a).

In SUNBEAM, a statistically significant reduction in the adjusted mean number of Gd-E brain MRI lesions was demonstrated with ozanimod 1 mg ($p < 0.0001$), compared to IFN β-1a (0.160 and 0.433 lesions, respectively), corresponding to a [redacted] reduction at Month 12 (Celgene 2017b).

In the pooled analysis at Month 12, the adjusted mean number of Gd-E T1 brain MRI lesions was demonstrated with ozanimod 1 mg (p<0.0001) compared to IFN β-1a ([redacted] and [redacted] lesions, respectively), corresponding to a [redacted] reduction.

3.4. MRI measures of disease activity

Measures of brain atrophy included MRI assessment of total brain volume, cortical grey volume and thalamic volume. These were exploratory endpoints in RADIANCE Part B and SUNBEAM.

Treatment with ozanimod 1 mg resulted in nominally significant reductions in mean percentage whole brain volume loss compared to IFN β-1a in the two controlled Phase III clinical studies.(Celgene 2017a, Celgene 2017b, Celgene 2019b).

The difference in mean percent change from baseline in whole brain volume loss for ozanimod 1 mg vs IFN β-1a 30 µg was 0.24, 0.19 and 0.17 in RADIANCE Part B, SUNBEAM and in the pooled analysis, respectively.

Treatment with ozanimod 1 mg nominally significantly reduced mean percentage in cortical grey matter volume loss compared with IFN β-1a in the two controlled Phase III clinical studies and in the pooled analysis. The difference in mean percent change from baseline in cortical grey matter volume loss was 0.67, 0.84 and 0.74 in RADIANCE Part B, SUNBEAM and the pooled analysis, respectively (Celgene 2017a, Celgene 2017b, Celgene 2019b).

Treatment with ozanimod 1 mg reduced mean percentage thalamic volume loss compared to IFN β-1a in the two controlled Phase III clinical studies and in the pooled analysis. The difference in mean percent change from baseline in thalamic volume loss was 0.49, 0.55 and 0.38 in RADIANCE Part B, SUNBEAM and the pooled results respectively (Celgene 2017a, Celgene 2017b, Celgene 2019b).

3.5. Symbol Digit Modalities Test (SDMT)

Notably, in both the SUNBEAM trial and the pooled analysis, there were significantly greater increases in cognitive processing speed as measured by the SDMT/PASAT score in ozanimod-treated patients versus those receiving IFN β-1a at month 12. The PASAT was used as a cognitive component in RADIANCE Part B but was replaced with the SDMT in SUNBEAM as the SDMT is increasingly considered a superior (more sensitive and more reliable) measure of processing speed relative to the PASAT, and has greater physician and patient acceptance (Benedict 2017, Strober 2019); SDMT/PASAT-3 were combined in the pooled analysis. In addition, significantly more ozanimod-treated patients had clinically meaningful improvements in processing speed versus those receiving IFN β-1a. These results are consistent with BVL findings from SUNBEAM and pooled analyses which showed preservation of thalamic patient volume as well as cortical grey matter volume in ozanimod-treated patients at 12 and 24 months. BVL is thought to play an important role in the loss of cognition and increase in disability progression in MS.

3.6. No evidence of disease activity (NEDA)

No evidence of disease activity (NEDA) is a comprehensive measure of treatment response in patients with RRMS. NEDA-3 is a composite endpoint comprised of three outcomes: ARR, CDP and MRI.

There was a statistically significant increase in the proportion of patients in RADIANCE Part B with NEDA-3 at month 24 in the ozanimod 1 mg group compared with the IFN β-1a group (p=0.0309) (Celgene 2017a).

In SUNBEAM, there was no statistically significant difference in the proportion of patients with NEDA-3 at month 12 for the ozanimod 1 mg group compared with the IFN β-1a group ([redacted] vs [redacted] respectively; p=0.1732) (Celgene 2017b).

3.7. CDP in SUNBEAM and RADIANCE Part B

In the Phase III SUNBEAM and RADIANCE Part B clinical trials, as well as the prespecified pooled analysis, rates of confirmed disability progression after 3 months and after 6 months (CDP-3M and CDP-6M, respectively) were not significantly different for ozanimod compared to IFN β-1a. SUNBEAM and RADIANCE Part B were similarly designed multicenter, randomized, parallel-group trials with a long-term open-label extension. RADIANCE Part B was a 2-year trial, whereas SUNBEAM was a 1-year trial, in which patients continued treatment until the last participant was treated for 12 months. In both trials, rates of CDP, defined as a sustained worsening in EDSS of ≥1 point confirmed at 3 or 6 months, were low in each treatment group. However, rates were especially low in SUNBEAM, likely reflecting the shorter trial duration, which meant tentative disability progression would have had to develop within 6 months, with confirmation at 12 months. This likely contributed to low rates of CDP in the pooled dataset and reduced the ability to detect a meaningful difference between treatments.

The impact of low CDP event rates is further evident when examining the powering assumptions for the pooled analysis. Expected CDP rates for ozanimod were estimated based on rates of CDP-3M observed in the 1-year TRANSFORMS study that compared fingolimod 0.5mg (6% progression rate) to IFN β-1a (8% progression rate). The power analysis assumed a 6% treatment difference between ozanimod and IFN β-1a; however, only a 2% difference in CDP rates between groups was observed . Based on this 2% observed difference in CDP rates, 2541 patients per arm and 356 total events would have been needed to achieve 80% power to detect a significant difference between ozanimod 1mg and IFN β-1a In contrast, only 136 total events were observed on CDP-3M in the IFNB-1a and ozanimod 1 mg pooled analysis, indicating insufficient statistical power on this endpoint and represented by wide confidence intervals.

Furthermore, the CDP-3M powering assumption was 12-24% for IFNβ-1a and 6-18% for ozanimod; the actual pooled estimates were 7.8% for IFNβ-1a and 7.6% for ozanimod, and so it would need to be considered with extreme caution. The advantages and disadvantages of the EDSS in assessing disability in MS are well-known, and thus there is a recognised need for the development of alternative sensitive scales that assess disability (Bosma 2013, Meyer-Moock 2014, van Munster 2017). To fully capture the impact of disease progression on patients, the ozanimod clinical trial programme also included other tools and endpoints for assessing disease impairment.

The CDP endpoint should be considered within the context of the robust improvement in annualised relapse rate and number of new or enlarging T2 lesions and gadolinium-enhancing lesions, the reductions in the loss of normalized brain volume and cortical and thalamic brain volume, the increased percentage of patients with no evidence of disease activity, the improvement in cognition, and the maintenance of quality of life with ozanimod compared with IFN β-1a.

3.8. CDP in the network meta-analysis

The NMA analysis conducted for the RRMS population indicated that ozanimod 1 mg was associated with a statistically significantly better efficacy profile in reducing ARR compared to teriflunomide 14 mg (HR: 0.72, [95% CrI:0.56, 0.93]) and no statistically significant difference compared to dimethyl fumarate (Pharmerit International 2019). The efficacy of ozanimod was comparable to dimethyl fumarate and teriflunomide when assessing CDP-3M and CDP-6M as the differences between treatment were not statistically significant (See Table 3 below).

When tolerability and safety were considered, the NMA results indicated that the odds of experiencing AEs were significantly lower for ozanimod compared to dimethyl fumarate 240mg (bid) (HR: 0.58 [95% CrI:0.36, 0.91]), and ozanimod thus has a more tolerable safety profile (Pharmerit International 2019).

Table 2: Summary of key efficacy and safety outcomes of ozanimod 1 mg vs selected comparators

	ARR Rate Ratio (95% CrI)	CDP-3 Annualized HR (95% CrI)	CDP-6 Annualized HR (95% CrI)	Discontinuation Annualized HR (95% CrI)	AE OR (95% CrI)	SAE OR (95% CrI)
Placebo	0.48 (0.4, 0.57)	[redacted]	[redacted]	[redacted]	0.98 (0.74, 1.32)	0.84 (0.49, 1.44)
Dimethyl fumarate, 240mg (bid)	0.88 (0.7, 1.1)	[redacted]	[redacted]	[redacted]	0.58 (0.36, 0.91)	1.07 (0.6, 1.9)
Teriflunomide, 14mg	0.72 (0.56, 0.93)	[redacted]	[redacted]	[redacted]	0.77 (0.51, 1.16)	0.77 (0.42, 1.42)

ARR: Annualised Relapse Rate; bid: twice a day; CDP-3: Confirmed Disease Progression at 3 months; CDP-6: Confirmed Disease Progression at 6 months; CrI: Credible Interval; HR: Hazard ratio; mg: milligram; OR: Odds ratio

The validity of an NMA is based on the underlying assumption that there is no imbalance in the distribution of effect modifiers across the different types of direct treatment comparisons, regardless of the structure of the evidence network. Therefore, a matching-adjusted indirect comparison (MAIC) of ozanimod versus teriflunomide and dimethyl fumarate in patients with MS was conducted to further investigate the comparative effectiveness of ozanimod compared to these oral drugs (results are in Table 3, Table 4, and Table 5). Similar to the NMA, the CDP-3M and CDP-6M results showed no statistically significant difference between ozanimod 1 mg and teriflunomide or dimethyl fumarate at 2 years. The MAIC further suggests that ozanimod is associated with significantly improved ARR, significantly reduced risk of overall AEs and SAEs, and significantly fewer discontinuations.

Table 3: Anchored teriflunomide 14mg vs ozanimod 1mg MAIC results

	Measure	Ozanimod 1mg	Teriflunomide 14mg	Ozanimod 1mg vs Teriflunomide 14mg
ARR	RR (95% CI)	332/1,987 PY (0.17)	35/132 PY (0.26)	**0.65 (0.53, 0.80)**
Proportion relapsed	OR (95% CI)	187/660 (28%)	26/111 (23%)	0.97 (0.47, 2.00)
SAEs	OR (95% CI)	31/660 (5%)	6/110 (5%)	0.89 (0.26, 3.04)
Overall AEs	OR (95% CI)	450/660 (68%)	102/111 (92%)	0.97 (0.28, 3.40)
Discontinuations	OR (95% CI)	18/660 (3%)	22/111 (20%)	0.67 (0.28, 1.62)

CDP: Confirmed disease progression; ARR: Annualized relapse rate; SAE: Serious adverse event; OR: Odds ratio; RR: Rate ratio; PY: Person years. Note: Results in bold indicate statistical significance; CDP-6m with 2-year studies only includes RADIANCE ozanimod 1.0 mg IPD

Table 4: Unanchored dimethyl fumarate 240mg vs ozanimod 1mg MAIC results

Outcome	Measure	Ozanimod 1mg	Dimethyl fumarate 240mg	Ozanimod 1mg vs Dimethyl fumarate 240mg
CDP 6M	RR (95% CI)	50/1,083 PY (0.05)	80/1,536 PY (0.05)	0.89 (0.62, 1.26)
CDP 6M: 2-year studies	OR (95% CI)	50/390 (11%)	80/768 (10%)	1.01 (0.68, 1.50)
CDP 3M	HR (95% CI)	74*/880 (8%)	104*/768 (14%)	**0.67 (0.53, 0.86)**
CDP 3M	RR (95% CI)	65/1,072 PY (0.06)	112/1,454 PY (0.08)	0.79 (0.58, 1.07)
CDP 3M: 2-year studies	OR (95% CI)	52/390 (13%)	112/768 (15%)	0.90 (0.63, 1.28)
ARR	RR (95% CI)	195/1,136 PY (0.17)	252/1,181 (0.21)	**0.80 (0.67, 0.97)**
Proportion relapsed	OR (95% CI)	151/743 (20%)	215/769 (28%)	**0.66 (0.52, 0.83)**
SAE	OR (95% CI)	40/743 (5%)	135/769 (18%)	**0.27 (0.19, 0.39)**
Overall AEs	OR (95% CI)	513/743 (69%)	733/769 (95%)	**0.11 (0.08, 0.16)**
Discontinuations	OR (95% CI)	23/743 (3%)	174/773 (23%)	**0.11 (0.07, 0.17)**

CDP: Confirmed disease progression; ARR: Annualized relapse rate; SAE: Serious adverse event; OR: Odds ratio; RR: Rate ratio; PY: Person years. Note: Results in bold indicate statistical significance; CDP outcomes with 2-year studies only includes RADIANCE ozanimod 1.0mg IPD; * number of events determined after weighting and application of the Cox PH model which may lead to differences in # events compared to other methods

Table 5: Unanchored teriflunomide 14mg vs ozanimod 1mg MAIC results

Outcome	Measure	Ozanimod 1mg	Teriflunomide 14mg	Ozanimod 1mg vs Teriflunomide 14mg
				MAIC
CDP 6M	HR (95% CI)	61*/880 (7%)	160*/1,498 (11%)	0.78 (0.60, 1.01)
CDP 6M	RR (95% CI)	49/1,034 PY (0.05)	263/4,452 PY (0.06)	0.80 (0.59, 1.08)
CDP 6M: 2-year studies	OR (95% CI)	42/365 (11%)	263/2,226 (12%)	0.96 (0.68, 1.36)
CDP 3M	HR (95% CI)	81*/880 (9%)	302*/2,226 (14%)	**0.78 (0.66, 0.92)**
CDP 3M	RR (95% CI)	64/1,031 PY (0.06)	344/4,452 PY (0.08)	0.80 (0.61, 1.05)
CDP 3M: 1-year studies	OR (95% CI)	62/733 (8%)	29/370 (16%)	1.08 (0.68, 1.71)
CDP 3M: 2-year studies	OR (95% CI)	54/365 (15%)	344/2,226 (15%)	0.94 (0.68, 1.28)
ARR	RR (95% CI)	194/1,010 PY (0.19)	1,274/4,793 PY (0.27)	**0.73 (0.62, 0.84)**
Proportion relapsed	OR (95% CI)	165/755 (22%)	244/785 (34%)	**0.56 (0.44, 0.70)**
SAEs	OR (95% CI)	35/634 (6%)	221/2,231 (10%)	**0.53 (0.37, 0.77)**
Overall AEs	OR (95% CI)	460/663 (69%)	1932/2,231 (87%)	**0.35 (0.29, 0.43)**
Discontinuations	OR (95% CI)	26/798 (3%)	258/1,297 (20%)	**0.14(0.09, 0.21)**

CDP: Confirmed disease progression; ARR: Annualized relapse rate; SAE: Serious adverse event; OR; Odds ratio; RR: Rate ratio; PY: Person years. Note: Results in bold indicate statistical significance; * number of events determined after weighting and application of the Cox PH model which may lead to differences in # events compared to other methods

4. Innovation

There are currently only two oral therapies recommended by NICE in the treatment of RRMS. Teriflunomide and dimethyl fumarate are both recommended oral treatments for active RRMS (only in those who do not have highly active or rapidly evolving severe RRMS), as outlined in NICE TA303 and TA320 respectively (NICE 2014f, NICE 2014c).

Ozanimod offers a different mode of action, it is a modulator of the S1P1R pathway. It is an immunomodulator that selectively targets sphingosine-1-phosphate receptor-1 (S1P1R) and receptor-5 (S1P5R) to mitigate autoimmune responses and promote neuronal protection. In comparison to existing S1P modulators (e.g. fingolimod), ozanimod does not demonstrate cardiac conduction abnormalities (primarily QT interval prolongation) (Scott 2016), nor does ozanimod induce hypertension through engagement of S1P3 receptors on vascular smooth muscle cells. Ozanimod has demonstrated a consistent safety profile demonstrating lower rates of AEs compared with IFN β-1a in phase III trials.

Ozanimod offers an alternative mode of action and would be a valuable addition to the treatment pathway for RRMS, providing similar overall health benefits to dimethyl fumarate, and improved effectiveness on the ARR when compared to teriflunomide.

5. Economic evaluation

5.1. Overview of analysis inputs and assumptions

As the results of the NMA comparing ozanimod to the other two oral treatments, teriflunomide and dimethyl fumarate, revealed that the efficacy (e.g. ARR and CDP) of the three treatments were similar in terms of efficacy, and ozanimod was at least as good in terms of safety, a cost-minimisation was considered the most appropriate form of economic evaluation to assess the cost-effectiveness of ozanimod in the treatment of adults with RRMS. It should be noted that this is a conservative approach as t ozanimod has a statistically significant benefit in regard to ARR (See Section 3.8).

Celgene considers that dimethyl fumarate and teriflunomide are the only relevant comparators as ozanimod should only be considered for patients suitable for or requesting an oral treatment for RRMS.

The characteristics of the comparator treatments are presented in Table 6 below.

Table 6: Characteristics of ozanimod and comparators

	Ozanimod		Teriflunomide	Dimethyl fumarate
Pharmaceutical formulation	0.23mg hard capsules 0.46mg hard capsules 0.92mg hard capsule		14mg film-coated tablets	120mg gastro-resistant hard capsules 240mg gastro-resistant hard capsules
Doses and frequency	Days 1 - 4	0.23mg once daily		The starting dose is 120mg twice a day. After

	Ozanimod		Teriflunomide	Dimethyl fumarate
	Days 5 - 7	0.46mg once daily	The recommended dose of teriflunomide is 14mg once daily.	7 days, the dose should be increased to the recommended maintenance dose of 240mg twice a day
	Days 8 and after	0.92mg once daily		
Method of administration	Oral			
Average length of a course of treatment	The length of treatment may vary because it is anticipated to be used continuously until a joint decision is made between the patient and clinician to stop treatment.			
(Anticipated) care setting	Secondary care			

5.2. Features of the cost-minimisation analysis

Costs are assessed over a one-year time horizon and are presented in a disaggregate form.

Costs are not discounted as the time horizon is only one year. In the base case all efficacy, safety and discontinuation rates are assumed to be equal for all three treatments and omitted from the analysis.

In the sensitivity analyses the following scenario is considered:

- Adverse events costs included.

5.3. *Input data used in the cost-minimisation*

Cost data

In the base case analysis, only acquisition costs and monitoring costs are considered. These costs are presented in Table 7 and Table 8 below. Adverse event costs are considered in a scenario analysis.

Table 7: Acquisition costs

Ozanimod	Teriflunomide	Dimethyl fumarate
Acquisition costs - list price (excluding VAT)		
£343.25 per 7 capsule initiation pack £1,373 per 28-capsule pack (Celgene UK Ltd)	£1,037.84 per 28-tablet pack (BNF 2019)	£343 per 14-capsule pack of 120mg capsules £1,373 per 56-capsule pack of 240mg capsule (BNF 2019)
Acquisition costs - PAS price		

Ozanimod	Teriflunomide	Dimethyl fumarate
[redacted] (Celgene UK Ltd)	Not available for Celgene	Not available for Celgene
Units per course of treatment, assuming 365.25 days in a year		
1x 7 capsule initiation pack 12.79 x 28-capsule pack (EMA 2020)	28 tablets 13.04 x 28-tablet pack (BNF 2019)	1x 14 capsule pack 12.79 x 56-capsule pack (BNF 2019)
Average cost of a course of treatment (acquisition costs only)		
£17,910 (with list price) [redacted] **– Used in analysis**	**£13,538 (with list price) – Used in analysis**	**£17,910 (with list price) – Used in analysis**

Table 8: Monitoring costs

Monitoring item	Ozanimod		Teriflunomide		Dimethyl fumarate	
	Year 1	Year 2 +	Year 1	Year 2 +	Year 1	Year 2 +
Complete blood count						
Unit Cost	£2.51					
Source reference	NHS Reference Costs 2017-18: Haematology, (DAPS05) (Health 2018)					
Number of units	3	1	3	2	5	4
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£7.52	£2.51	£7.52	£5.01	£12.53	£10.02
ECG						
Unit Cost	£131.93					
Source reference	NHS Reference Costs 2017-18: Electrocardiogram Monitoring or Stress Testing, (EY51Z, Outpatient) (Health 2018)					
Number of units	1	0	0	0	0	0
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£131.93	£0.00	£0.00	£0.00	£0.00	£0.00
Liver function test						

Monitoring item	Ozanimod		Teriflunomide		Dimethyl fumarate	
	Year 1	Year 2 +	Year 1	Year 2 +	Year 1	Year 2 +
Unit Cost	£1.11					
Source reference	NHS Reference Costs 2017-18: Clinical Biochemistry, (DAPS04) (Health 2018)					
Number of units	6	4	16	7	4	2
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£6.65	£4.44	£17.75	£7.76	£4.44	£2.22
Urinalysis						
Unit Cost	£0.35					
Source reference	(MidMeds 2017)					
Number of units	0	0	0	0	4	2
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£0.00	£0.00	£0.00	£0.00	£1.41	£0.71
Tuberculin skin test						
Unit cost	£19.08					
Source reference	TA312 (NICE 2014)					
Number of units	0	0	1	0	0	0
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£0.00	£0.00	£19.06	£0.00	£0.00	£0.00
MRI						
Unit cost	£140.60					
Source reference	NHS Reference Costs 2017-18: Imaging: Direct Access, (RD01A) (Health 2018)					
Number of units	0	0	0	0	1	0
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£0.00	£0.00	£0.00	£0.00	£140.60	£0.00
Neurology visit						
Unit cost	£148.01					

Monitoring item	Ozanimod		Teriflunomide		Dimethyl fumarate	
	Year 1	Year 2 +	Year 1	Year 2 +	Year 1	Year 2 +
Source reference	NHS Reference Costs 2017-18: Neurology, (WF01A) (Health 2018)					
Number of units	1	1	1	1	1	1
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£148.01	£148.01	£148.01	£148.01	£148.01	£148.01
MS Nurse visit						
Unit cost	£27.00					
Source reference	NHS Reference Costs 2017-18: Neurology, (WF01D) (Health 2018)					
Number of units	2	2	2	2	2	1
Source reference	(EMA 2020)		(NICE 2018)			
Total annual cost per patient	£54.00	£54.00	£54.00	£54.00	£54.00	£27.00
Total monitoring costs per patient	**£348.11**	**£208.95**	**£246.36**	**£214.79**	**£360.99**	**£187.96**

The costs associated with adverse events are based on those used in the ocrelizumab submission (TA533) for standard events (NICE 2018). The costs used were sourced from the most up-to-date PSSRU, eMIT, or NHS Reference Costs. Within the ocrelizumab submission, 6.9% of the events were considered serious.

Adverse event data were sourced from 45 RCTs identified for the NMA. The incidence rates were obtained by combining raw data related to specific adverse events of interest reported for each comparator (Pharmerit International 2018). Table 9 presents the adverse event incidence rates for ozanimod, teriflunomide, and dimethyl fumarate.

Table 9: Incidence of adverse events by treatment (%) from the NMA

Adverse event	Ozanimod	Teriflunomide 14mg	Dimethyl fumarate 240mg(bid)
ALT increased	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]

Adverse event	Ozanimod	Teriflunomide 14mg	Dimethyl fumarate 240mg(bid)
Fatigue	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]

Adverse events costs are presented in Table 10 below and are in line with the original STA submission document.

Table 10: Adverse events costs

Adverse event	Cost (£)	Resource use	Source
ALT increased	0.00	None	
Arthralgia	20.00	Non-serious: NSAIDs: 350 mg 3 x daily for 6 days Serious: 1 MS specialist visit; 1 Rheumatologist visit	eMIT 2016: Ibuprofen 400 mg tablets / Pack size 24 National Reference Cost 2017-18, WF01A, Neurology and Rheumatology (Health 2018)
Back pain	54.92	Non-serious: None Serious: 1 MS specialist visit; 12 physical therapy sessions	National Reference Cost 2017-18, WF01A, Neurology (Health 2018) PSSRU: "Physiotherapy", one-to-one. (Curtis 2018)
Bronchitis	75.05	Non-serious: 2 GP consultations, 1 course of amoxicillin Serios: 2 GP consultations, 1 course of amoxicillin	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50); (Curtis 2018) eMIT 2019: Amoxicillin 500 mg capsules / Pack size 21 (Health 2019)

Adverse event	Cost (£)	Resource use	Source
Depression	2,549.50	Non-serious: 4 GP consultations, Citalopram: 20 mg per day for 6 months, 12 psychotherapy sessions Serious: 9 GP consultations, Citalopram: 40 mg per day for 6 months; 52 Psychotherapy sessions	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50); (Curtis 2018) eMIT 2019: Citalopram 20 mg tablets / Pack size 10; National Reference Cost 2017-18, WF01A, Neurology (Health 2018)
Dizziness	0.00	None	
Fatigue	4.08	Non-serious: None Serious: 1 GP visit; Provigil 200 mg / day for 2 months	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50); (Curtis 2018) eMIT 2019: Modafinil 200 mg / Pack size 30 (Health 2019)
Headache	10.21	Non-serious: None Serious: 1 Neurology consultation	National Reference Cost 2017-18, WF01A, Neurology (Health 2018)
Hypoaesthesia	0.00	None	
Influenza	0.00	None	
Influenza like illness	0.00	None	Same assumption as in the ocrelizumab submission (NICE 2018)
Injection site reaction	2.28	Non-serious: None Serious: 1 GP consultation	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50) (Curtis 2018)
Nasopharyngitis	2.59	Non-serious: None Serious: 1 GP consultation	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50) (Curtis 2018)
Oral herpes	0.00	None	
Oropharyngeal pain	0.00	None	
Pharyngitis	0.00	None	
Pain in extremity	0.00	None	
Pyrexia	0.00	None	
Rash	0.00	None	
Upper respiratory tract infection	37.50	Non-serious: 1 GP consultation Serious: 1 GP consultation	PSSRU 2018: GP surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualifications (£37.50) (Curtis 2018)

Adverse event	Cost (£)	Resource use	Source
Urinary tract infection	64.94	Non-serious: Ciprofloxacin:100 mg twice daily for 3 days Serious: 1 Hospital visit	eMIT 2019: Ciprofloxacin 100mg tablets / Pack size 1 (Health 2019) National Reference Cost 2017-18. Sample weighted average of LA04H, J, K, L, M, N, P, Q, R, S (Health 2018)

5.4. *Results of the cost-minimisation analysis*

Base-case results

In this section per patient results are presented for year 1 and year 2+ by treatments in Table 11 and Table 12 below. The results are presented for year 1 (initiation year) and subsequent years (year 2+) as all treatments have different monitoring regimes and costs in the initiation year to the subsequent years.

Table 11: Base case results per patient for year 1, with ozanimod PAS and comparator list price

Technologies	Acquisition costs (£)	Monitoring costs (£)	Total costs (£)	Difference compared to ozanimod (£)
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	13,538	246	13,785	[redacted]
Dimethyl fumarate	17,910	361	18,271	[redacted]

Table 12: Base case results per patient for year 2+, with ozanimod PAS and comparator list price

Technologies	Acquisition costs (£)	Monitoring costs (£)	Total costs (£)	Difference compared to ozanimod (£)
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	13,538	215	13,753	[redacted]
Dimethyl fumarate	17,910	188	18,098	[redacted]

Ozanimod is the most cost-effective treatment with the lowest total cost in year 1 and year 2+, providing per patient savings of between [redacted] and [redacted] compared with teriflunomide and dimethyl fumarate.

Scenario analysis results

One scenario analysis was conducted where adverse event costs are considered. The NMA showed that ozanimod is associated with a significantly reduced risk of overall AEs and SAEs compared to dimethyl fumarate.

Summary results for the scenario including adverse event costs are presented in Table 13 below. As all AE's are assumed to occur in the initiation year, only year 1 is considered in this scenario analysis.

Table 13: Scenario with adverse events included, results per patient for year 1, with ozanimod PAS and comparator list price

Technologies	Acquisition costs (£)	Monitoring costs (£)	AE costs (£)	Total costs (£)	Difference compared to ozanimod (£)
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	13,538	246	260	14,045	[redacted]
Dimethyl fumarate	17,910	361	208	18,479	[redacted]

In the scenario analysis ozanimod continues to be the most cost-effective treatment. The addition of adverse event costs increases the savings with ozanimod over teriflunomide and dimethyl fumarate to [redacted].

5.5. Cost-minimisation Conclusion

The cost-minimisation analysis shows that ozanimod is cost-effective in RRMS patients suitable for or requesting oral treatment when compared to the other NICE approved oral treatments, teriflunomide and dimethyl fumarate.

6. Budget impact

6.1. Epidemiology and market share data

The budget impact is calculated for 5 years. The epidemiology data used to estimate eligible patient numbers is presented below in Table 14.

Table 14: Epidemiology

	2020	2021	2022	2023	2024
Total adult population	46,868,875				
Reference	(ONS 2019)				
Adult population growth		0.61%	0.54%	0.47%	0.47%
Reference	(ONS 2019)				
Total population with growth	46,868,875	47,153,127	47,406,586	47,630,968	47,855,704
Prevalence rate MS	0.20%	0.20%	0.20%	0.20%	0.20%
Reference	(Mackenzie 2015)				
Incident rate MS	0.009%	0.009%	0.009%	0.009%	0.009%
Reference	(Mackenzie 2015)				
Number of prevalent patients	92,908	93,472	93,974	94,419	94,865
Number of incident patients	4,228	4,253	4,276	4,297	4,317

	2020	2021	2022	2023	2024
Proportion of patients in RRMS	42.00%	42.00%	42.00%	42.00%	42.00%
Reference	(Hawton 2016)				
Number of patients in RRMS	40,797	41,045	41,265	41,461	41,656
Proportion of RRMS treated	31.00%	31.00%	31.00%	31.00%	31.00%
Reference	(Zajicek 2010)				
Number of patients in RRMS treated	12,647	12,724	12,792	12,853	12,913
Proportion of patients eligible for oral treatment	55%	57%	58%	59%	61%
Reference	Celgene assumption				
Number of patients used in the analysis	6,956	7,253	7,420	7,583	7,877

The current market share data for the comparators are based on IMS data and is assumed to be constant over the 5 years in the analysis (Celgene 2019a). In the analysis with ozanimod, the assumption was used that the ozanimod market share uptake is weighted according to the existing market share for the two comparators, i.e. ozanimod will take more market share from dimethyl fumarate than teriflunomide. Market share data for ozanimod are based on assumptions made by Celgene and presented in Table 15 below.

Table 15: Market share used in the budget impact analysis

Technology	2019	2020	2021	2022	2023
Without ozanimod					
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With ozanimod, weighted uptake					
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2. Results

6.2.1. Base case results

Table 16 and Table 17 respectively present the gross drug acquisition and monitoring costs for England and Wales without, and with ozanimod.

Table 16. Base case five-year budget impact results per population without ozanimod, using comparator list price

Technologies	Costs (£)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Ozanimod	0	0	0	0	0
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 17. Base case five-year budget impact results per population with ozanimod, using ozanimod PAS price and comparator list price

Technologies	Costs (£)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18: Base case five-year budget impact to the NHS after the introduction of ozanimod, using ozanimod PAS price and comparator list price

Costs (£)					Total budget impact (£)
Year 1	Year 2	Year 3	Year 4	Year 5	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18 presents the net budget impact of introducing ozanimod as a treatment option for adults with RRMS suitable for or requesting oral treatment. A [redacted] in year 1, increasing to [redacted] in year 5, providing a net five year [redacted].

6.2.2. Scenario results

Adverse events are included in Year 1 for both the prevalent and incident populations for all the treatments, and then only for the incident populations in Year 2+. Adverse event incidence rates and costs are the same as applied in the cost-minimisation analysis. Budget impact results for the scenario analysis are presented in Table 19 to Table 21 below.

Table 19: Scenario including adverse events, five-year budget impact results per population without ozanimod, using comparator list price

Technologies	Costs (£)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Ozanimod	0	0	0	0	0
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Costs (£)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Scenario including adverse events, five-year budget impact results per population with ozanimod, using ozanimod PAS price and comparator list price

Technologies	Costs (£)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: Scenario including adverse events, five-year budget impact to the NHS after the introduction of ozanimod, using ozanimod PAS price and comparator list price

Costs (£)					Total budget impact (£)
Year 1	Year 2	Year 3	Year 4	Year 5	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

When adverse event costs were included the savings associated with ozanimod increased. Net savings ranged from [redacted] in year 1 to [redacted], providing a 5 year net saving of [redacted].

6.3. Conclusion

The budget impact analysis shows that the introduction of ozanimod is cost saving for the NHS, supporting the case for its implementation as an alternative therapy option for adults with RRMS suitable for or requesting oral treatment.

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ADDENDUM TO ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ozanimod for treating relapsing–remitting multiple sclerosis

Addendum to ERG STA report

Confidential until published

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A MEMBER OF THE RUSSELL GROUP

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Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Rui Duarte	Critical appraisal of the clinical and economic evidence, editorial input
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Joanne McEntee	Critical appraisal of the company submission
Ian Pomeroy	Clinical advice and critical appraisal of the clinical sections of the company submission

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List of abbreviations

ACS	addendum to company submission
AE	adverse event
ARR	annualised relapse rate
CDP	confirmed disability progression
CFS	company fast track appraisal submission
CS	company submission
DMF	dimethyl fumarate
DMT	disease modifying therapy
ERG	Evidence Review Group
HA	highly active
HRQoL	health-related quality of life
IFN	interferon
ITT	intention-to-treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMAs	network meta-analyses
RES	rapidly-evolving severe
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event

1 BACKGROUND

In November 2019, the company, Celgene, provided evidence to the National Institute for Health and Care Excellence (NICE) to inform the appraisal of ozanimod for the treatment of relapsing-remitting multiple sclerosis (RRMS) as part of the Single Technology Appraisal (STA) process. The main body of the original company submission (CS) included the comparison of ozanimod versus a number of relevant disease modifying therapies (DMTs). The Evidence Review Group (ERG) report, which included a critique of the original CS, was submitted to NICE on 21 January 2020. A summary of key points relating to the original CS and the ERG critique of the original CS is provided in Appendix 1 to this ERG addendum (Section 6.1).

The STA process was then put on hold and on 31 January 2020, the company submitted evidence to NICE to support the appraisal of ozanimod via the NICE Fast Track Appraisal (FTA) process. One of the criteria that can be used to determine eligibility for the NICE FTA process is that:

> A cost-comparison case can be made that shows it is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication
>
> (NICE website)[1]

The company considered that, for the treatment of RRMS, ozanimod could be appraised using the NICE FTA process since:

> … ozanimod can be appropriately assessed against the relevant comparators via the means of a cost-comparison due to the similarity in terms of cost and outcomes (as determined in a robust network meta-analysis).
>
> (company FTA submission [CFS] Summary [Document A], Table 2, p11)

The ERG critique of the CFS focused on whether it was appropriate for NICE to appraise treatment with ozanimod via the NICE FTA process. A summary of key points relating to the CFS and the ERG critique of the CFS is provided in Appendix 2 to this ERG addendum (Section 6.2).

Following submission of the ERG critique of the CFS to NICE, the company was informed by NICE that consideration of ozanimod using the FTA process was not appropriate. NICE then invited the company to submit any additional evidence that demonstrated the clinical and cost effectiveness of ozanimod as an addendum to the original CS. On 17 July 2020, NICE provided the ERG with an addendum to the original CS (ACS). In the ACS, the company re-iterated their view that ozanimod, dimethyl fumarate (DMF) and teriflunomide were similar in

terms of efficacy and also stated that ozanimod was at least as safe as these other two drugs. The company therefore concluded that a cost minimisation analysis was the most appropriate form of economic evaluation to undertake to demonstrate the cost effectiveness of ozanimod.

1.1 Clarification of terminology used in this ERG addendum

The ERG considers that it is important to clarify three points:

- This ERG addendum focuses on the evidence presented in the ACS, but the ERG critique has also been informed by the evidence presented in the CFS as the CFS included data and explanation about the company cost comparison/minimisation analysis that were not presented in the ACS.

- In the CFS the company carried out a cost comparison. However, in the ACS the company uses the term cost minimisation analysis for a very similar economic evaluation. For FTAs, NICE uses the term cost comparison analysis; however, amongst economists, there is no generally agreed understanding of this term.

- Both the company's and the ERG's use of the term 'active RRMS' excludes highly active (HA) RRMS and rapidly-evolving severe (RES) RRMS.

2 ERG SUMMARY AND CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE

2.1 Population

The marketing authorisation for ozanimod (Zeposia®), which was granted on 20 May 2020 by the European Medicines Agency,[2] is for the treatment of adult patients with RRMS with active disease as defined by clinical or imaging features. This marketing authorisation is very similar to the anticipated marketing authorisations described in the original CS and the CFS.

Details of the populations addressed in different company submissions relating to the NICE appraisals of ozanimod for treating RRMS are provided in Table 1.

Table 1 Patient populations addressed in the different company submissions

Original company submission (CS)	Company fast track appraisal submission (CFS)	Addendum to company submission (ACS)
Company anticipated marketing authorisation: [redacted] Expected use: first-line therapeutic option (CS, p22) for patients with active RRMS (and not HA RRMS and/or RES RRMS) (CS, p13) As detailed in the CS (Figure 1), the NHS England treatment algorithm[3] currently considers this population to consist of 2 subsets: (1) Patients with 1 relapse in last 2 years and evidence of radiological activity (2) Patients with 2 significant relapses in the last 2 years	Company anticipated marketing authorisation: [redacted] Expected use: first-line therapeutic option (CFS, p21) for patients [redacted] (CFS, p10)	Actual marketing authorisation: adult patients with RRMS with active disease as defined by clinical or imaging features (ACS, p3) Expected use: patients with active RRMS who are suitable for or requesting an oral treatment (ACS, p3) For the 2 comparators included in the cost minimisation analysis, according to NICE guidance TA320[4] and TA303,[5] the population of patients with active RRMS is "normally defined [by NICE] as 2 clinically significant relapses in the previous 2 years."[4,5]

ACS=addendum to the company submission; CFS=company fast track appraisal submission; CS=original company submission; HA=highly active; RES=rapidly evolving severe; RRMS=relapsing remitting multiple sclerosis
Source: CS, CFS and ACS

The population addressed in the ACS is described as patients with active RRMS "suitable for or requesting an oral treatment" (ACS, pp3, 9, 17, 19 and 20). The ERG considers it is unclear what is meant by patients "suitable for or requesting an oral treatment". The ERG highlights that the population addressed in the ACS appears to be a subset of the population described in the final scope issued by NICE (adult patients with RRMS)[6] and also a subset of the patients covered by the marketing authorisation for ozanimod.[2]

2.2 Comparators

The current NHS England treatment algorithm[3] suggests that the comparators listed in Table 2 should be used to treat patients with active RRMS. The options differ depending on the number of relapses the patient has had within the past 2 years.

Table 2 Treatment options for patients with RRMS recommended by NICE

One relapse in the last 2 years AND evidence of radiological activity	Two significant relapses in the last 2 years
Injectable treatments:[7,8] • Interferon beta-1a 30µg (Avonex) • Interferon beta-1a 22µg (Rebif) • Interferon beta-1a 44µg (Rebif) • Glatiramer acetate 20mg • Glatiramer acetate 40mg • Peginterferon beta-1a* Treatments administered by infusion:[9] • Ocrelizumab	Injectable treatments:[7,8] • Interferon beta-1a 30µg (Avonex) • Interferon beta-1a 22µg (Rebif) • Interferon beta-1a 44µg (Rebif) • Interferon beta-1b (Extavia) • Glatiramer acetate 20mg • Glatiramer acetate 40mg • Peginterferon beta-1a* Oral treatments:[4,5] • Dimethyl fumarate (DMF) • Teriflunomide Treatments administered by infusion:[9] • Ocrelizumab

Source: NHS England treatment algorithm (Section 10),[3] with additional information provided by the ERG
* Peginterferon beta-1a was not included in the NHS England treatment algorithm[3] but has since been recommended by NICE for treating RRMS (TA624)[8]

In the ACS, the company has provided comparative clinical effectiveness evidence for three NICE recommended treatments (TA527,[7] TA320[4] and TA303[5] respectively):

- Interferon beta-1a (IFN β-1a) 30µg (Avonex), an injectable DMT that is the comparator to ozanimod in the RADIANCE Part B trial[10] and SUNBEAM trial[11]
- DMF, an oral DMT
- Teriflunomide, an oral DMT.

In the ACS, the company has only presented cost effectiveness evidence for ozanimod versus DMF and for ozanimod versus teriflunomide. Both treatments are only recommended in guidance issued by NICE as options for patients with active RRMS "normally defined [by NICE] as 2 clinically significant relapses in the previous 2 years."[4,5]

Given the marketing authorisation for ozanimod,[2] and the population identified by the company in the original CS (see Section 2.1, Table 1), the ERG considers that all the comparators listed in Table 2 are relevant to this appraisal. In the original CS (main body and appendices), the company provided comparative clinical and cost effectiveness data for all the DMTs listed in Table 2.

2.3 Clinical effectiveness evidence

2.3.1 Direct clinical evidence

The only direct comparative clinical effectiveness evidence available is from the comparison of ozanimod versus IFN β-1a 30µg (Avonex), informed by two Phase III trials (RADIANCE Part B[10] and SUNBEAM[11]), and the comparison of ozanimod with placebo, from a Phase II trial (RADIANCE Part A[12]). Direct clinical evidence was presented in Section B.2.6 of the original CS. No new direct evidence is presented in the ACS. An ERG critique of the direct evidence can be found in Section 3 of the original ERG report.

There is no direct evidence for the comparison of ozanimod versus DMF or for the comparison of ozanimod versus teriflunomide.

2.3.2 Indirect clinical evidence

The company has provided indirect evidence generated using the following approaches:

- original network meta-analyses (NMAs)
- reduced NMAs
- matching-adjusted indirect comparisons (MAICs).

The company's original NMAs were initially presented in the original CS and results were replicated in the CFS and also, for selected comparators, in the ACS. During the FTA process, in response to ERG clarification question A3, the company provided results from reduced NMAs. The reduced NMAs only included data from trials that provided effectiveness evidence relating to treatment with ozanimod, DMF and teriflunomide (and data relating to IFN β-1a 30µg [Avonex] and placebo as these data were needed to construct a connected network).

In response to a request by the ERG for additional scientific evidence to support the company claim that ozanimod was similar to DMF or teriflunomide (FTA clarification question A2), the company presented results from MAICs. The results from these MAICs were also presented in the ACS.

Table 3 includes a summary of the ERG critique of the three approaches used to generate indirect evidence.

Table 3 ERG critique of indirect clinical evidence

Approach	ERG critique of methods	ERG comment on use of indirect evidence
Original NMAs	The ERG considers that the methodological approach taken for the original NMAs was appropriate.	The ERG considers that the results from the original NMAs should be used to inform a comparison between ozanimod and all relevant comparators within a population of adult patients with active RRMS (i.e., the population and comparators [including ocrelizumab] addressed in the original CS (main body and appendices). The ERG considers that specific results from the original NMAs should not be used to inform a comparison between ozanimod and DMF and ozanimod and teriflunomide as the inclusion of additional data from comparators that the company has deemed irrelevant and are derived from a wider population of adults with RRMS introduces uncertainty into the original NMA results.
Reduced NMAs	The ERG considers that the methodological approach taken for the reduced NMAs was appropriate. In the company response to ERG FTA clarification question A3, the company highlighted that the CrIs generated by the reduced NMAs were wider than the original NMA CrIs. The company considered that this was due to "…removal of a large amount of data from the network, resulting in more uncertainty". The ERG acknowledges that it is expected that the reduced NMAs (which include fewer data) will generate results with wider CrIs than the larger original NMAs (which include more data).	The ERG notes that the company has not presented the results from the reduced NMAs within the ACS. Reduced NMA results were only provided in response to an ERG clarification question. The ERG considers that the reduced NMAs should be used to inform a comparison of ozanimod versus DMF and ozanimod versus teriflunomide.
MAIC	During the FTA, the company conducted MAICs to generate further evidence to support the results from the original NMAs; these results were also included in the ACS. The ERG considers that, as the company used different outcome definitions in the MAICs and in the original and reduced NMAs, the results of these analyses cannot be compared. Further, due to the lack of details provided regarding the MAIC methods, the ERG has concerns about the methods used to generate the results.	Due to limited details and concerns regarding the methods, the ERG considers that the company's MAICs should not be used for decision making. Full details of the ERG's critique of the additional analyses undertaken by the company are provided in the academic-in-confidence appendix that accompanies the ERG FTA report (Appendices, Section 8.6).

ACS=addendum to the company submission; CFS=company fast track appraisal submission; CrI=credible interval; DMF=dimethyl fumarate; FTA=fast track appraisal; MAIC=matching-adjusted indirect comparisons; NMA=network meta-analysis

Results from the company's original NMAs showed a statistically significant advantage at the 5% significance level for ozanimod over teriflunomide in terms of annualised response rate (ARR); this result was not reflected in the results from the reduced ARR NMA. There were no statistically significant differences at the 5% significance level between ozanimod and DMF or between ozanimod and teriflunomide in the original NMAs or in the reduced NMAs for the confirmed disease progression (CDP) outcomes (3 months [CDP-3M] or 6 months [CDP-6M]), treatment discontinuations or serious adverse events (SAEs).

The company stated that the efficacy of ozanimod was "comparable" to the efficacy of DMF and teriflunomide as results from the original NMAs of CDP-3M and CDP-6M showed that the differences between treatments were not statistically significant (ACS, Section 3.8). The ERG considers that the correct interpretation of the results from the company's original (or reduced) NMAs is that these results did not demonstrate at the 5% significance level that ozanimod was superior to DMF or teriflunomide in terms of CDP-3M and CDP-6M. The ERG emphasises that this is not the same as providing statistical evidence that there is no difference between the treatments, or that ozanimod is "comparable" to DMF or that ozanimod is "comparable" teriflunomide.

3 ERG CRITIQUE OF THE COMPANY'S COST MINIMISATION ANALYSIS

3.1 Patient Access Scheme

The Patient Access Scheme (PAS) Liaison Unit and the company are in the process of agreeing a Patient Access Scheme discounted price for ozanimod. The cost effectiveness results presented in the ACS have been generated using the company's proposed PAS price for ozanimod. DMF and teriflunomide are also available to the NHS at discounted prices; however, the discounted prices of DMF and teriflunomide are not known to the company. The ERG has, therefore, provided company ACS base case results generated using the latest available discounted prices of ozanimod, DMF and teriflunomide in confidential appendices to this ERG STA addendum, available as separate documents.

The ERG has also updated the company base case results from the original STA (ozanimod versus ten comparators including ocrelizumab) in the confidential appendices using the latest available discounted prices.

3.2 ERG critique of company cost minimisation analysis

The ERG considers that the company has not presented statistical, or pharmacological, evidence to demonstrate that ozanimod is sufficiently similar to DMF or to teriflunomide to allow the results from cost minimisation analyses to be used in decision making. The company ACS base case results are presented in Table 4 of this ERG addendum.

The clinical effectiveness evidence base does not support the conduct of a cost minimisation analysis. However, as part of the ERG's role is to critique the methods the company has used to generate cost effectiveness evidence, the ERG has critiqued the company's cost minimisation analysis methods.

The company's cost minimisation analysis was undertaken in a simple Microsoft Excel worksheet. The ERG can confirm that the values in the worksheet reflect the parameter values presented in the ACS and it has been possible to reproduce the cost minimisation analysis results presented in the ACS.

The ERG is satisfied that the following elements of the company's cost minimisation analysis were appropriate:

- **The time horizon**: A 1-year time horizon was chosen by the company although costs in years 2+ were also considered by the company. As equal efficacy and discontinuation rates were assumed, the only difference in costs that related to time

were monitoring costs and so the company approach to the time horizon was appropriate.

- **Drug list prices and monitoring costs:** The list price of ozanimod was provided by the company. List prices for DMF and teriflunomide were sourced from the British National Formulary.[13] Unit costs were sourced from NHS Reference Costs (2017-18)[14] or from previous company STA submissions for ocrelizumab (TA533),[9] alemtuzumab (TA312),[15] DMF (TA320)[4] and teriflunomide (TA303).[5] The ERG considers that the drug prices and resource use costs used in the company's analyses are appropriate.

- **Administration costs**: Ozanimod, DMF and teriflunomide are all oral treatments and so the company's assumption that the cost of administrating these drugs was equal (set to £0 by the company) is acceptable.

The ERG considers that the methods used by the company to carry out the cost minimisation analysis were appropriate.

3.3 Cost minimisation analysis results

The company ACS base case analysis is shown in Table 4. The scenario analysis undertaken by the company is not relevant as it includes the modelling of differential effects; such an approach is appropriate for cost utility analyses but is not appropriate for cost minimisation analyses.

In the company ACS base case (PAS price for ozanimod, list prices for DMF and teriflunomide), over a 5-year time horizon, treatment with ozanimod is estimated to cost [redacted] less per patient than DMF and [redacted] less per patient than teriflunomide.

Confidential appendices which includes results from the analyses presented in Table 4 generated using PAS prices are available as separate documents.

Table 4 Company base case results (per patient costs, PAS price for ozanimod)

Drug	Year 1 costs			Costs per subsequent year			Years 1 to 5 costs			Incremental total costs versus ozanimod (£)
	Acquisition Cost (£)	Monitoring Cost (£)	Total cost (£)	Acquisition cost (£)	Monitoring cost (£)	Total cost (£)	Acquisition cost (£)	Monitoring cost (£)	Total cost (£)	
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Teriflunomide	13,538	246	13,785	13,538	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMF	17,910	361	18,271	17,910	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DMF=dimethyl fumarate; PAS=Patient Access Scheme

4 ERG CONCLUSIONS

In the ACS, the company presented a cost minimisation analysis of ozanimod versus DMF and ozanimod versus teriflunomide. Whilst ozanimod, DMF and teriflunomide are all oral drugs they are not pharmacologically similar. Results from the reduced NMAs that were carried out at the request of the ERG during the FTA failed to demonstrate that ozanimod was superior to DMF or to teriflunomide for ARR, CDP-3M or CDP-6M. The ERG emphasises that not showing superiority is not the same as providing statistical evidence that there is no difference between the treatments, or concluding that ozanimod is "comparable" to DMF and teriflunomide. Furthermore, there is no pharmacological basis to conclude that ozanimod is sufficiently similar to DMF or to teriflunomide to undertake a cost minimisation analysis.

Ozanimod is licensed for patients with active RRMS. Patients with active RRMS include patients who (i) who have had one significant relapse in the last 2 years and who have evidence of radiological activity and (ii) have had two significant relapses in the last 2 years. However, DMF and teriflunomide are only recommended by NICE as treatment options for patients with active RRMS "normally defined [by NICE] as 2 clinically significant relapses in the previous 2 years."[4,5] Therefore, the ERG considers that all comparators included by the company in the original CS decision problem, as well as ocrelizumab, are relevant, and the comparators should not be limited to DMF and teriflunomide.

The ERG considers that the clinical effectiveness results and cost utility analysis results presented for ten comparators in the original CS and in the ERG STA report should be used as the basis for decision making.

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6 APPENDICES

6.1 Company STA submission: summary and key issues identified by the ERG

6.1.1 Decision problem

- The anticipated marketing authorisation, which is expected to be issued in May 2020, for ozanimod is [redacted]. The company anticipates that ozanimod will be a first-line treatment option for patients with active RRMS (not HA RRMS or RES RRMS)
- The company highlights that active RRMS can be defined as patients with two significant relapses in the last 2 years or patients who have had one relapse in the last 2 years and who also have radiological activity (which corresponds with the NHS England treatment algorithm for the current management of RRMS)
- The ERG considers that all of the comparators considered by the company are appropriate DMTs for patients with active RRMS. The ERG further considers that ocrelizumab (for which the company only presented comparative effectiveness results in appendices to CS) is an appropriate comparator for patients with active RRMS. However, clinical advice to the ERG is that for patients with two significant relapses in the last 2 years, treatment with DMF tends to be the preferred first-line DMT for patients with active RRMS

6.1.2 Clinical evidence

- Only the RADIANCE Part B and SUNBEAM trials provide direct clinical effectiveness evidence comparing treatment with ozanimod versus a relevant comparator (IFN β-1a 30µg [Avonex]). Of patients enrolled into the trials:
    - 75% of patients had active RRMS, 23% of patients had "high disease activity" (i.e. broadly comparable to HA RRMS and RES RRMS) and 2% of patients had secondary progressive multiple sclerosis (SPMS)
    - Patients with specific cardiovascular conditions at screening were excluded
    - The trials include a very high proportion (>90%) of white and Eastern European patients
- Key results from the RADIANCE Part B and SUNBEAM trials are:
    - With the exception of CDP-3M or CDP-6M, ozanimod was statistically significantly superior to IFN β-1a (Avonex) for all efficacy outcomes, including ARR
    - Ozanimod demonstrated a favourable safety profile versus IFN β-1a 30µg (Avonex)
- The company generated indirect evidence for the effectiveness of treatment with ozanimod versus other comparators listed in the final scope issued by NICE by carrying out NMAs. The outcomes generated by the company NMAs were ARR, CDP-3M, CDP-6M, CDP-6M combined, treatment discontinuation, AEs and SAEs
- Key results from the NMAs are as follows:
    - Ocrelizumab was statistically significantly superior to ozanimod in terms of CDP-3M, CDP-6M and CDP-6M combined. IFN β-1b (Betaferon) was also statistically significantly superior to ozanimod in terms of CDP-6M. There was

no statistically significant evidence of a difference in CDP-3M, CDP-6M or CDP-6M combined between ozanimod and any of the other DMTs.

- Treatment with ozanimod statistically significantly improved ARR versus most comparators (exceptions being peginterferon β-1a, DMF and ocrelizumab; ocrelizumab was statistically significantly superior to ozanimod)

- NMAs were not conducted for specific types of AEs or SAEs. However, the company has reported incidence rates of specific types of AEs from studies of DMTs and results show that AE incidence rates from treatment with ozanimod compare favourably with AE incidence rates in the trials of all comparators
- An important area of uncertainty in the evidence base relates to heath-related quality of life (HRQoL). Analysis of pooled HRQoL data from the RADIANCE Part B and SUNBEAM trials showed no statistically significant difference between ozanimod and IFN β-1a 30µg (Avonex). The company has not presented evidence for HRQoL versus other relevant comparators

6.1.3 Cost effectiveness evidence

Company model structure

- The structure of the company model means that patients only receive one DMT over their lifetime. As there are now a number of treatments available to treat active RRMS, this is unrealistic
- A model that can simulate treatment switching or treatment sequencing would be complex to construct, and it is unlikely that there are sufficiently robust data to populate such a model
- The ERG considered that the model over-simplified reality and, therefore, results might be of limited use to decision makers

Effectiveness

- The ERG considers that when generating base case cost effectiveness results, if clinical effectiveness results are not statistically significantly different, then a difference in effect should not be modelled
- ERG revision 1: modelling a difference in effectiveness only when results from the company NMAs demonstrate a statistically significant difference

Time on treatment

- Treatment discontinuation rates in the model remain the same for each treatment over the lifetime of the model
- ERG revision 2: after 1 year (the period for which trial data were available), treatment is assumed to continue whilst the patient receives benefit which, in the model, is until progression to Expanded Disability Status Scale 7 or entering the SPMS state

Other treatments

- The ERG considered that ocrelizumab was a relevant comparator and generated results to compare the cost effectiveness of ozanimod versus ocrelizumab

6.2 Company FTA submission: summary of key issues identified by the ERG

6.2.1 Decision problem

- The anticipated marketing authorisation, which is expected to be issued in May 2020, for ozanimod is [redacted]. The company anticipates that ozanimod will be a first-line treatment option for patients with active RRMS (not HA RRMS or RES RRMS)
- Previous NICE guidance described active RRMS as being "normally defined as 2 clinically significant relapses in the previous 2 years" (TA320 [DMF] and TA303 [teriflunomide])
- The company considers that DMF and teriflunomide are the relevant comparators to ozanimod. Ozanimod, DMF and teriflunomide are all oral DMTs; however, they are not pharmacologically similar

6.2.2 Clinical evidence

- There is no direct clinical evidence comparing the effectiveness of ozanimod versus DMF or teriflunomide
- The company generated indirect evidence by carrying out NMAs. The outcomes generated by the company NMAs were ARR, CDP-3M, CDP-6M treatment discontinuation, AEs and SAEs
- Results from the company's original NMA show that, at the 5% significance level, ozanimod was statistically significantly superior to teriflunomide in terms of ARR and statistically significantly superior to DMF in terms of AEs
- In response to an ERG clarification question, the company provided NMA results from reduced NMAs that only included randomised controlled trials that provided effectiveness evidence for ozanimod, DMF and teriflunomide. The ERG considered that it was more appropriate to use results from these reduced NMAs, rather than results from the original NMAs, to inform the FTA
- Results from the reduced NMAs showed that, at the 5% significance level, treatment with ozanimod was not statistically significantly superior to either DMF or teriflunomide for any outcome
- The ERG considered that the MAICs carried out by the company were unnecessary and results could not be compared with either the original NMAs or the reduced NMAs. Further, concerns relating to the lack of details provided regarding methods used to undertake the MAICs meant that the ERG considered that MAIC results should not be used to inform the FTA process

6.2.3 Strength of the case for undertaking a cost minimisation analysis

- Results of statistical testing to assess the non-inferiority of ozanimod versus DMF and the non-inferiority of ozanimod versus teriflunomide for ARR, CDP-6M and SAEs only provided statistically significant evidence that ozanimod was non-inferior to teriflunomide for ARR using the company's original NMA
- For ARR, CDP-6M and SAEs for ozanimod versus DMF and for CDP-6M and SAEs for ozanimod versus teriflunomide, there was insufficient evidence to demonstrate that ozanimod was non-inferior to DMF or to teriflunomide

- The ERG therefore concluded that the company's argument that ozanimod was similar in terms of outcomes and safety profile to DMF or to teriflunomide was not made and, therefore, that a cost minimisation analysis was not appropriate

Confidential appendix 2: PAS vs list prices

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ozanimod for treating relapsing–remitting multiple sclerosis [ID1294]

Confidential appendix including Patient Access Scheme (PAS) discount for ozanimod and list prices for comparators

This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR 17/156/08

Completed 17 August 2020

CONFIDENTIAL DATA HAS BEEN REDACTED

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The Evidence Review Group (ERG) has made the following changes to the company model:

- R1: modelling a difference in treatment effect only when the clinical outcomes used to compare relative efficacy of different treatments are shown, by results from the company network meta-analyses, to be statistically significantly different and removing AE rates from the model (ERG report, Section 4.1.3)

- R2: after one year, treatment is assumed to continue until progression to Expanded Disability Status Scale 7, or conversion to secondary progressive multiple sclerosis state (ERG report, Section 4.1.5)

- Inclusion of ocrelizumab as a comparator (ERG report, Section 2.1.4)

Rather than showing results of the changes against all comparators, the ERG's revised incremental cost effectiveness ratios (ICERs) per quality adjusted life years (QALYs) gained are shown, using the proposed Patient Access Scheme (PAS) price for ozanimod and list prices for comparators treatments, for three comparisons:

- treatment with ozanimod versus the reference case, i.e., the comparator with the most favourable ICER per QALY gained compared to ozanimod in the company base case, which, for analyses, undertaken using PAS prices, is interferon beta-1a 22µg (Rebif), which is different from the list price reference case comparator (Table 1)
- the comparison of treatment with ozanimod versus dimethyl fumarate (DMF); clinical advice to the ERG, [redacted] is that DMF is the most widely used DMT for active RRMS in the NHS (see Table 2)
- the comparison of treatment with ozanimod versus ocrelizumab; the ERG considers that the treatment with ocrelizumab is a valid comparator (see Table 3).

Fully incremental analysis results generated by the company model with ERG amendments R1 and R2 are provided in Table 4.

Table 1 ERG adjustments to company base case analysis: ozanimod versus interferon beta-1a 22µg (Rebif) (PAS price for ozanimod, list price for interferon beta-1a 22µg)

Scenario/ERG amendment	Ozanimod			Interferon beta-1a 22µg			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	***£357,779***	***9.280***	***20.473***	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Modelling only statistically significant differences in outcomes where appropriate and removing AEs	[redacted]	[redacted]	[redacted]	£353,316	9.474	20.502	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Treatment discontinuation for first year only	[redacted]	[redacted]	[redacted]	£375,166	9.397	20.492	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. ERG preferred scenario (R1+R2)	[redacted]	[redacted]	[redacted]	**£373,533**	**9.477**	**20.502**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 2 ERG adjustments to company base case analysis: ozanimod versus dimethyl fumarate (PAS price for ozanimod, list price for dimethyl fumarate)

Scenario/ERG amendment	Ozanimod			Dimethyl fumarate			Incremental			*ICER*	
	Cost	**QALYs**	**Life Years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change from base case**
A. Company base case	[redacted]	[redacted]	[redacted]	***£407,952***	***9.661***	***20.521***	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Modelling only statistically significant differences in outcomes where appropriate and removing AEs	[redacted]	[redacted]	[redacted]	£414,371	9.481	20.502	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Treatment discontinuation for first year only	[redacted]	[redacted]	[redacted]	£444,113	9.869	20.557	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. ERG preferred scenario (R1+R2)	[redacted]	[redacted]	[redacted]	**£445,440**	**9.485**	**20.502**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 3 ERG adjustments to company base case analysis: ozanimod versus ocrelizumab (PAS price for ozanimod, list price for ocrelizumab)

Scenario/ERG amendment	Ozanimod			Ocrelizumab			Incremental			*ICER*	
	Cost	**QALYs**	**Life Years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change from base case**
A. Company base case model assumptions	[redacted]	[redacted]	[redacted]	***£416,740***	***10.029***	***20.569***	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Modelling only statistically significant differences in outcomes where appropriate and removing AEs	[redacted]	[redacted]	[redacted]	£413,261	10.182	20.593	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Treatment discontinuation for first year only	[redacted]	[redacted]	[redacted]	£463,158	10.390	20.633	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. ERG preferred scenario (R1+R2)	[redacted]	[redacted]	[redacted]	**£462,232**	**10.434**	**20.638**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 4 Fully incremental analysis results generated by the company model with ERG amendments R1 and R2 (PAS prices)

Treatment	Cost	QALYs	Incremental costs	Incremental QALYs	ICER/QALY gained
[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]
[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; PAS=Patient Access Scheme; QALY=quality adjusted life year
[redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

You are asked to check the ERG report and ERG addendum to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 27 August** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 3.2 of the Addendum to the ERG STA report the ERG incorrectly states that a 5-year time horizon was selected by the company	A 1-year time horizon was applied for year 1 (initiation) and year 2 (maintenance).	It is factually incorrect	Thank you for highlighting this error. The 5-year time horizon was selected for the budget impact assessment described in the FTA report. Text amended.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 28 of the STA ERG report, paragraph 2 it states "Importantly, the ERG notes that the company does not consider ozanimod to be a treatment option for patients with HA RRMS or RRMS, nor for patients with SPMS (See Section 2.3 of this ERG report). Thus, while most patients had active RRMS (approximately 75% of patients in the four relevant arms of both trials), a relatively high proportion did not (approximately 25%)."	"…ozanimod to be a treatment option for patients with HA or RES RRMS…"	Ozanimod is not to be considered as a treatment option for the HA or RES RRMS subtypes	Thank you for highlighting this important typographical error. Text amended.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 of the STA ERG report, paragraph 1, "When considered separately (i.e., base case analysis approach, see Table 13 of this ERG report), NMA results indicate that ocrelizumab was associated with a statistically significant later time to CDP-3M and CDP-6M compared to ozanimod 1mg and that IFN β-1b (Betaferon) was also associated with a statistically significant later time to CDP-6M compared to ozanimod 1mg."	"…statistically significant fewer progression events to CDP-3M and CDP-6M compared to ozanimod 1mg and that IFN β-1b (Betaferon) was also associated with a statistically significant fewer progression events to CDP-6M compared to ozanimod 1mg…"	The terminology 'fewer progression events' is a more clear and accurate description for this sentence	The ERG notes that hazard ratios are presented for the outcomes CDP-3M and CDP-6M, thus indicating that these outcomes have been analysed as 'time to CDP-3M' and 'time to CDP-6M.' Therefore, the ERG interpretation is accurate. No changes made to ERG STA report.

Table 15 of ERG STA report (error highlighted by the ERG)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect shading two columns in Table 15 (page 51 of the STA ERG report); i.e. Green highlighted cells represent statistically significant results in favour of ozanimod 1mg over the comparator and red highlighted cells represent statistically significant results in favour of the comparator over ozanimod 1mg The column presenting ARR and CDP-6M combined were incorrectly shaded	Correct the shading of these two columns	The shading of the two columns, with respect to statistically significant results of these two outcomes is factually incorrect	The ERG has amended the shading for the columns presenting results of ARR and CDP-6M combined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Ozanimod for treating relapsing–remitting multiple sclerosis

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Background

- November 2019: The company submitted evidence for ozanimod through the Single Technology Appraisal (STA) process
- January 2020: The ERG submitted its critique of the company STA submission
- January 2020: Company switched to the Fast Track Appraisal (FTA) process (cost-comparison case) and re-submitted evidence according to the FTA requirements
- February 2020: Company FTA submission received
- March 2020: ERG critique of FTA submission received
- March 2020: CHMP positive opinion received
- April 2020: 'Scrutiny' meeting in which the NICE team and selected committee representatives met to discuss the appropriateness of the topic proceeding as an FTA submission. To be eligible for FTA, companies must demonstrate that that the technology is "likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication". Please see section 2.4.31 to 2.4.36 of the NICE process guide for more information on eligibility criteria
    - NICE was not satisfied that the FTA process was suitable for ozanimod because, based on the evidence presented in the FTA submission, there was too much uncertainty about whether ozanimod is likely to provide similar or greater health benefits compared with the company's chosen comparators (dimethyl fumarate [DMF] and teriflunomide). The topic was therefore routed back to the STA process for a greater level of scrutiny by the committee. The company's original STA submission therefore remains valid and forms the main basis for the appraisal
- July 2020: The company submitted an addendum to its STA submission in which it provided some new information and outlined a number of amendments. This addendum includes analyses from the unsuccessful FTA submission
- As such, the key documents for this appraisal are:
    - Company STA submission
    - ERG critique of company STA submission
    - Company FTA submission
    - ERG critique of company FTA submission

- Company addendum to STA submission
- ERG critique of company addendum to STA submission

2 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
Issues related to the decision probelm		
Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	• Ozanimod is indicated for 'the treatment of adult patients with relapsing–remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features'. Although the licence incorporates highly active and rapidly evolving severe RRMS, the company does not expect ozanimod to be used to treat these forms of active RRMS in UK clinical practice. • Population in company's original submission and FTA submission is active RRMS, and not highly active and rapidly evolving severe RRMS, which is narrower than the marketing authorisation and aligned with the company's expected use of ozanimod in UK clinical practice. • In its addendum, the company suggests that the proposed position in the treatment pathway should be narrowed further to 'adult patients with RRMS with active disease as defined by clinical or imaging features, **suitable for or requesting an oral treatment**'. • ERG unclear what is meant by 'suitable for or requesting an oral treatment'. • The technical team note that the comparator in the ozanimod key trials, interferon beta-1a, is not an oral treatment (it is administered via subcutaneous injection). Information in relevant documents: • Company submission document B: B.1.1	• Narrowing of the population in the compnay submission to exclude people with highly active and rapidly evolving severe RRMS appears to be appropriate, although clinical expert advice is required to confirm this. • Ozanimod will likely mainly displace other oral treatments. However, some treatments available for active RRMS are injectable, including the trial comparator, so these treatments may be relevant for considertation too. • The text 'suitable for or requesting an oral treatment' may be redundant, because people would not receive a treatment if they were not suitable for it or did not request it. • Clinical advice is required to determine whether people 'suitable for or requesting an oral treatment' could be defined in clinical practice, and whether being suitable for an oral treatment explicitly excludes injectables.

Issue	Summary	Technical Team Preliminary Judgement
	• Company submission addendum: 1.1 • ERG report: 2.5 • ERG addendum: 2.1, 2.3	

Choice of comparators	• The company expect ozanimod to be used in UK clinical practice to treat people with active RRMS, and not highly active and/or rapidly evolving severe RRMS.
	• Company's original STA submission included the following comparators:
	  ○ Beta-interferons
	  ○ Dimethyl fumarate
	  ○ Glatiramer acetate
	  ○ Peginterferon beta-1a
	  ○ Teriflunomide
	• A comparison with ocrelizumab was also provided in an appendix to original submission.
	• ERG considers all treatment options matching the ozanimod 'expected use' (i.e. active RRMS that is not highly active or rapidly evolving severe) are relevant comparators. This includes all comparators in company's original submission, and ocrelizumab.
	• In its STA addendum, company focuses only on comparisons with DMF and teriflunomide because of company's narrowing of the population to people who are 'suitable for or requesting an oral treatment'.
	• The technical team note that the comparator in the ozanimod key trials, interferon beta-1a, is not an oral treatment (it is administered via subcutaneous injection).
	
	Information in relevant documents:
	• Company submission document B: B.1.1
		• Choice of comparators is dependent on the population.
		• If it is not appropriate to narrow the population to people who are 'suitable for or requesting an oral treatment', all treatments established in the NHS for active RRMS (that is not highly active or rapidly evolving severe) are likely to be potential comparators. It is unclear whether ocrelizumab would be used in this population.
		• Pairwise analyses compared with the oral treatments are useful. But all chosen comparators should be compared in a fully incremental analysis, as per the NICE Guide to the methods of technology appraisal.

Issue	Summary	Technical Team Preliminary Judgement
	• Company submission addendum: 1.1, 3.8 • ERG report: 1.1, 2.2, 2.3 • ERG addendum: 2.2 • NHS treatment algorithm for RRMS (note peginterferon beta-1a not included because algorithm developed before positive NICE recommendation [TA624])	
Issues related to clinical effectiveness		

Generalisability of ozanimod clinical trials	• RADIANCE Part B and SUNBEAM are the only trials directly comparing ozanimod with a relevant comparator (interferon beta-1a, Avonex).
	• Clinical advice to the ERG was that the baseline characteristics from these trials were similar to those seen in NHS practice. However, the ERG highlights several differences that may limit generalisability:
	  ○ ~25% of people in the trials had types of MS that are not aligned with the expected use of ozanimod, including types broadly comparable to highly active and rapidly evolving severe RRMS
	  ○ ~30% of people had received a prior disease-modifying therapy (DMT), while the company position ozanimod as a first-line DMT
	  ○ People with specific cardiovascular conditions were excluded but it is unclear if they would receive ozanimod in clinical practice
	  ○ Trials had a high proportion of White and Eastern European people, while the population in the NHS is more diverse.
	
	Information in relevant documents:
	• Company submission document B: B.2.3
		• Although there are some differences between the clinical trials and NHS practice, RADIANCE Part B and SUNBEAM overall provide high quality randomised controlled trial evidence compared with an active comparator, and are likely broadly generalisable.

Issue	Summary	Technical Team Preliminary Judgement
	• Company submission addendum: N/A • ERG report: 3.3.2 • ERG addendum: 6.1.2	

Choice of indirect comparison	• The company submitted the following indirect comparisons:
	  ○ 'Full' network meta-analysis (NMA), including data from trials of all comparators in original submission
	  ○ 'Reduced' NMA, including data from trials of ozanimod, DMF and teriflunomide only (provided at ERG's request during FTA process, not in original STA submission or addendum)
	  ○ Matching-adjusted indirect comparisons (MAICs; provided as aditional scientific evidence to support company claim that ozanimod is similar to DMF or teriflunomide).
	• The company used results of the 'full' NMA as evidence that there are no significant differences between ozanimod and its chosen comparators (DMF and teriflunomide) in terms of key efficacy outcomes.
	• The ERG considers the 'full' NMA should be used to compare ozanimod with all relevant comparators. However, it highlights that the company's approach to using the 'full' NMA to compare ozanimod with DMF and teriflunomide only (as per the company's FTA submission and addendum) is not appropriate because it includes data from comparators that the company has deemed irrelevant, so introduces uncertainty. The ERG therefore prefers the 'reduced' NMA if comparing ozanimod with only DMF and teriflunomide in any cost-effectiveness or or cost-comparison analyses.
		• Choice of indirect comparison is dependent on the comparators.
		• If all comparators from the company's original submission are included, the company's 'full' NMA is the most appropriate source of clinical effectiveness evidence.
		• If only DMF and teriflunomide are comparators, the 'reduced' NMA is likely to be most appropriate.
		• The company has not provided full justification and methods relating to the MAICs so these analyses remain highly uncertain, and it is unclear whether they provide useful supplementary information.

Issue	Summary	Technical Team Preliminary Judgement
	• The ERG cautions against using the MAIC because of concerns with the company's methods. Information in relevant documents: • Company submission document B: B.2.9 • Company submission addendum: 3.8 • ERG report: 3.10 • ERG addendum: 2.3.2, 6.1.2, 6.2.2 • Company FTA clarification response: A2	
Issues related to cost effectiveness		
Cost minimisation or cost utility analysis	• In a cost minimisation analysis, the effects of interventions and comparators are assumed to be the same, meaning only the differences in total costs are relevant to the decision. • The company argues that a cost minimisation analysis comparing ozanimod with terfiflunomide and DMF is the most appropriate type of economic evaluation because the 3 treatments have similar efficacy o Supported by lack of statistically significant differences between the 3 treatments in terms of 3-month confirmed disability progression (CDP-3M) and 6-month confirmed disability progression (CDP-6M) in the NMAs. • The ERG considers the company had not presented evidence that ozanimod is sufficiently similar (either clinically or pharmalogcally) to DMF or teriflunomide to allow the results from cost minimisation analyses to be used in decision making o Highlights that showing ozanimod is not statistically superior to DMF or teriflunomide is not the same as showing there to be no difference between the treatments, or that they are 'comparable'.	• Cost minimisation unlikely to be appropriate because ozanimod has already been deemed unsuitable for this approach as part of the FTA process. • Full scrutiny of ozanimod's clinical effectiveness in an incremental cost-utility analysis required.

Issue	Summary	Technical Team Preliminary Judgement
	Information in relevant documents: • Company submission document B: N/A • Company submission addendum: 3.8, 5.1 • ERG report: N/A • ERG addendum: 3.2	
Only modelling statistically significant differences between treatments	• In its model, the company included differences between treatments that were not statistically significantly different (for CDP-6M combined endpoint [see 'Other issues for information' below], annualised relapse rates, treatment discontinuation rates and serious adverse event rates). • The ERG considers that a difference in effect should not be modelled if there is not a statistically significant difference in clinical effectiveness results – i.e. the efficacy of any 2 treatments should be assumed to be the same unless there is a significant difference in the NMA. Information in relevant documents: • Company submission document B: B.3.3.2, B.3.3.7 • Company submission addendum: N/A • ERG report: 4.4.3 • ERG addendum: 6.1.3	• All differences (whether statistically significant or not) should be included in the model because they represent the best estimates of effect. • The base case results should be probabilistic to capture uncertainty in the NMA results.
Modelling treatment discontinuation	• In its model, the company obtains rates of discontinuation for each treatment from its NMA, and assumed that these rates remain the same over the entire model horizon. • Clinical advice to the ERG was that, in a scenario in which there is no treatment switching allowed and people only receive 1 DMT, people would only	• The NMA may be more appropriate than individual trials as a source of evidence for discontinuation rates in the model as it draws on all available evidence. • However, the company's approach may overestimate the numbers of people stopping treatment.

Issue	Summary	Technical Team Preliminary Judgement
	discontinue treatment if they were no longer benefitting, even if they still had relapses. • The ERG's preferred approach is to use trial treatment discontinuation rates for the period available, then assume that everybody remains on treatment while they are benefitting. In the company's model, this is until somebody is in Expanded Disability Status Scale (EDSS) state 7 or over, enters the secondary progressive MS state or dies. Information in relevant documents: • Company submission document B: B.3.3.6, B.3.3.7.3.1 • Company submission addendum: N/A • ERG report: 4.4.5 • ERG addendum: 6.1.3	

3 Other issues for information

Issue	Explanation
CDP-6M combined outcome	CDP-6M data were not available for some comparators so the company did an analysis to estimate the missing CDP-6M efficacy using the CDP-3M data. This meant assuming that the hazard ratio of CDP-6M between treatments arms is proportional to the hazard ratio of CDP-3M. The ERG highlighted that the assumption of a linear relationship between the CDP-3M and CDP-6M HRs for ozanimod appears to have been violated and advised caution when drawing conclusions from the combined analysis. Information in relevant documents:

	• Company submission document B: B.3.3.7.1 • ERG report: 1.2.3, 3.11
No treatment switching in model	The company's model did not include the option of treatment switching or sequencing and it was assumed that people only received one DMT over their lifetime. The ERG acknowledged that a model that can simulate treatment switching or treatment sequencing would be complex to construct, and it would be difficult to populate such a model due to limited data. The ERG highlighted that the lack of treatment switching or sequencing in the model may be an over-simplification of what happens in clinical practice and therefore results might be of limited use to decision makers. Information in relevant documents: • Company submission document B: B.3.2.2 • ERG report: 4.4.2
Heterogeneity in NMAs	The ERG was satisfied that there appeared to be minimal heterogeneity present in the company's NMAs and heterogeneity did not have an important impact on results. However, the ERG highlighted that areas of uncertainty and variability such as trial durations, trial dates, use of prior treatments and disease severity should be taken into account when drawing conclusions from the NMAs. Information in relevant documents: • Company response to clarification questions: A15, A16 • ERG report: 3.10
Health-related quality of life versus comparators	Pooled analysis of data from RADIANCE Part B and SUNBEAM did not show any statistically significant difference in health-related quality of life between ozanimod and interferon beta-1b (Avonex). The ERG highlighted that the company did not conduct an NMA for health-related quality of life or present evidence versus other relevant comparators, therefore the ERG considered the effect of ozanimod on health-related quality of life versus comparators to be an area of uncertainty. Information in relevant documents: • Company submission document B: B.2.6.3 • ERG report: 3.7, 3.10 and 3.11

4 Questions for engagement

Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'

1. Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?

2. How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?

3. Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?

Choice of comparators

4. Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?

5. Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?

Generalisability of ozanimod clinical trials

6. Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS practice?

Choice of indirect comparison

7. Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?

8. If DMF and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be the most appropriate source of indirect evidence?

Cost minimisation or cost utility analysis

9. Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?

Only modelling statistically significant differences between treatments

10. Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?

Modelling treatment discontinuation

11. When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale

    a. People tolerating their existing treatment stay on it even if they continue to have relapses, or

    b. People tolerating their existing treatment discontinue it if they continued to have relapses

12. Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5:00pm, Monday 2 November 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 technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Celgene Limited (A BMS Company)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	Yes, it is appropriate to separate people with active RRMS according to the type of treatment choice that is suitable for them. Disease modifying therapies (DMTs) for RRMS are available as infusions (e.g. ocrelizumab etc.), injections (e.g. beta interferon etc) and orals (e.g. dimethyl fumarate etc.). Celgene believe the choice of DMT prescribed in the UK for RRMS is driven by an informed discussion and consensus between the prescribing clinician and the patient based on the level of disease activity, patient risk tolerance, patient preference and patient lifestyle considerations.
How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	As noted in the question above the joint decision between the prescribing clinician and the patient on the selection of a treatment for RRMS would go beyond the clinical definition alone. The clinical rational for favouring an oral DMT could include: • Belief it would positively affect treatment adherence in some patients • Patient/carer ability to administer injections. • Needle phobia Other factors that should be considered include: • Patient ability to attend a centre for infusion. • Local infusion facilities and home care availability. • Work and lifestyle challenges to adherence and management of injections and infusions. • Initiation of treatment during the ongoing COVID-19 pandemic.

	We anticipate the clinical definition and population suitable for treatment with ozanimod would be similar to that currently used to identify dimethyl fumarate and teriflunomide patients.
Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	We anticipate that patients suitable for or requesting an oral treatment cannot tolerate or are not suitable, on clinical or other grounds, for an injection or infusion.
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	Ozanimod should only be used if a patient has failed or is unsuitable for infusion treatments such as ocrelizumab and injectables treatments (beta-interferons, glatiramer acetate, and peginterferon beta-1a) for RRMS.
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?	Ozanimod should only be used if a patient has failed (or intolerant) or is unsuitable for the injectable RRMS treatments beta-interferons, glatiramer acetate, and peginterferon beta-1a.
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS practice?	Clinical advice to the ERG is that these characteristics are not dissimilar to the characteristics of other patients with active RRMS typically recruited to MS trials and are likely to be similar to patients seen in NHS clinical practice in England and Wales. Our SmPC does not exclude any specific adult populations based on ethnicity or race. Therefore, we agree with the technical team's preliminary judgment that "although there are some differences between the clinical trials and NHS practice, RADIANCE Part B and

	SUNBEAM overall provide high quality randomised controlled trial evidence compared with an active comparator, and are likely broadly generalisable".
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	Celgene Limited conducted the MAIC purely as a validation exercise. A NMA assumes that treatment effect modifiers are equally distributed across trials. However, there were differences in the baseline patient characteristics in the ozanimod, teriflunomide and dimethyl fumarate trials. Differences observed in patient populations for these trials were considered important treatment effect modifiers in MS as well as prognostic factors such as EDSS, prior relapse, DMT use, Gd+ lesions, age, sex, geographic region, and weight. Similar to the NMA and reduced NMA, the CDP-3M and CDP-6M results showed no statistically significant difference between ozanimod 1 mg and teriflunomide or dimethyl fumarate at 2 years. The MAIC further suggests that ozanimod is associated with significantly improved ARR, significantly reduced risk of overall AEs and SAEs, and significantly fewer discontinuations.
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be	The impact of selecting one NMA in favour of another is very small. In the full NMA ozanimod is statistically significantly better that teriflunomide on ARR and dimethyl

the most appropriate source of indirect evidence?	fumarate on adverse events. Ozanimod is numerically superior to dimethyl fumarate and teriflunomide in the reduced NMA on all outcomes with the exception of CDP. The key issue is not which NMA to use, it is how confirmed disability progression (CDP) results for ozanimod are utilised in the economic evaluation. The ERG notes in Table 3 of the STA ERG Report, “Although EDSS and CDP are clinically relevant measures, limitations with both measures are widely recognised…”. In both the RADIANCE part B and SUNBEAM trials rates of CDP, defined as a sustained worsening in EDSS of ≥1 point confirmed at 3 or 6 months, were low in each treatment arm which reduced the ability to detect a meaningful difference between treatments. The power analysis assumed a 6% treatment difference between ozanimod and IFN β-1a; however, only a 2% difference in CDP rates between groups was observed. Based on this 2% observed difference in CDP rates, 2,541 patients per arm and 356 total events would have been needed to achieve 80% power to detect a significant difference between ozanimod 1mg and IFN β-1a. If the CDP results from the NMAs are applied in a decision analytic model the results will underestimate the benefit of ozanimod for patients with RRMS. The CDP endpoint should be considered within the context of the robust improvement in annualised relapse rate and number of new or enlarging T2 lesions and gadolinium-enhancing lesions, the reductions in the loss of normalized brain volume and cortical and thalamic brain volume,

	the increased percentage of patients with no evidence of disease activity, the improvement in cognition, and the maintenance of quality of life with ozanimod compared with IFN β-1a.
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?	Yes, there is sufficient evidence that ozanimod has comparable efficacy to teriflunomide and or dimethyl fumarate to make a cost-minimisation approach appropriate. With the exception of the anomalous CDP results, the reduced NMA shows that ozanimod is numerically superior to dimethyl fumarate and teriflunomide on all efficacy and safety measures. Assuming comparable efficacy and safety for dimethyl fumarate and teriflunomide is a conservative assumption. It should be noted that several appraisals for the same population (TA320, TA303, TA527 and TA624) have been able to conclude that the treatments evaluated in the NMAs were "similar", "similarly effective", "as effective" and/or "there were no differences" in the absence of noninferiority evidence. In a further five fast track appraisals, the NICE committee were also able to reach a conclusion based on the NMAs provided by the companies (TAA486, TA497, TA521, TA596 and TA572). We therefore believe that such a conclusion can also be reached in the current appraisal based upon the NMAs provided by the company.

Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	We note that the ERG's pragmatic approach of not modelling differences in effect that are not statistically significant in a cost utility analysis is inconsistent with their comments on the cost-minimisation analysis where they state "showing ozanimod is not statistically superior to dimethyl fumarate or teriflunomide is not the same as showing there to be no difference between the treatments, or that they are 'comparable'" (p8, Technical report). Given the challenges with the ozanimod CDP data outlined above, the ERG acknowledges non-significant differences between dimethyl fumarate and teriflunomide could be modelled in the cost utility analysis. In addition, the clinical Expert Statement states that ozanimod is likely to be used alongside dimethyl fumarate and teriflunomide. Where these assumptions hold for equivalent efficacy and eligibility, a cost-minimisation analysis comparing the three treatments would be the most appropriate form of economic evaluation for this decision problem.
Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale	This is a difficult clinical decision which needs to weigh up the risk/benefit balance for each patient. In this hypothetical scenario, not akin to the clinical setting where many different DMTs would be available for consideration, if however, you were unable to switch treatments, a treatment which may be suboptimal would on balance be more beneficial than no treatment at all. The clinician would make an informed decision on

a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	whether withdrawing a suboptimal treatment would potentially result in deterioration of the patient's condition. Therefore, we believe option 'a' would be the most likely outcome.
Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	A simplifying assumption is required to incorporate treatment discontinuation for MS in a decision analytic model. Celgene Limited are willing to accept the ERG's approach to modelling discontinuation.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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About you

Your name	**Victoria Williams**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**ABN representative**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	No, I do not think this is a meaningful subdivision
How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	**Patient choice not to have injections? There is no clinical subgroup that would only be suitable for oral treatment**
Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	**No**
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	Yes
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the	**Yes**

same population as ozanimod, and are they therefore comparators?	
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS practice?	**Eastern European population, overwhelmingly white, but overall reasonable comparison**
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be the most appropriate source of indirect evidence?	They should not be considered as the only relevant comparators
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?	

Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	
Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	a. This is a highly unrealistic scenario as switching frequently occurs in clinical practice. However if patients have active relapsing disease they are more likely to remain on treatment than be taken off altogether, in case it is providing some benefit. UNTIL they are clearly progressing
Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	Patients who have transitioned into secondary progression, or EDSS >7 are likely to eventually stop treatment (bearing in mind the decision to label secondary progression is often significantly delayed). It is difficult to say how patients would be thought to be

	benefitting from the drug if they are still relapsing/and or progressing. On balance, I think the company's approach is more appropriate.

NICE National Institute for Health and Care Excellence

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About you

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

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	As a patient who has the experience of both injectable and oral MS medication, I have an understanding of the differing demands these dose forms have. For me, it is significantly simpler and easier to take a tablet than injecting. It has made a step change in my compliance. There are some MS patients who do not find the prospect of injecting tolerable and/or have issues with undertaking the injecting due to their motor skills. There will be patients for whom an oral treatment is the best choice. However, MS is a condition that is very individual and requires a suite of medicines to be available to suit the differing requirements of the people who have this condition
How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	I would define them as a patient.
Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	I would not limit those who request an oral treatment to be excluded from having the potential to receive an injectable treatment. Medicine choice is key and may change. There are other elements to why a patient may pick one over another, such as side effect and risk profile, what fits in with their capability and daily living and many patients have a

	journey of different medicines. In 11 years I have taken beta interferon, glatiramer acetate and fingolimod.
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?	
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS practice?	
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be	

the most appropriate source of indirect evidence?	
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?	
Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	
Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale	I have experience of switching between medicines and I understand that this can be the case for many patients with MS. Switching occurs for a multitude of reasons including the side effects felt, the ability to tolerate the medicine, changes in persons MS and when the medicine fails to control relapse rate.

a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	The choice you make at this time depends on what that choice looks like at the particular phase of your MS journey and each individual will make this choice depending on their risk/benefit thinking at that time. For me, I am careful about side effects and risks but this is an individual thing. Others will be more risk adverse, others will be less so. It is key that people have a range of options and make their choices with their healthcare professional. I would choose option a if the other medicines I was offered were not significantly better than the one I was on and if they gave me significant and unpleasant side effects or if significant risks such as PML. I would choose option b if there were other medicines that were in my risk/benefit acceptability at that time. My level of side effect and risk tolerance may change depending on how unwell I had come.
Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	

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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**

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	It may be appropriate to compare ozanimod with just those treatments it is likely to replace, in this case, the two oral first-line treatments, teriflunomide and dimethyl fumarate. Studies have shown that there is a strong preference for once-daily oral treatments for relapsing remitting MS[1,2]. In addition, some people may have needle phobia or manual dexterity, visual or cognitive problems which make self-injectable treatments unsuitable options. The subset of people 'suitable for or requesting an oral treatment' is likely to cover the majority of people with relapsing remitting MS. However, we are concerned that wording of NICE guidance which limits ozanimod to this subset could lead to unanticipated consequences. For example, it may restrict the options available to patients who start with ozanimod but need to switch to another first-line or second-line treatment which is taken by a different route of administration.
How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	We anticipate that this group would be identified as part of shared decision making, bringing together the patient's preference for route of administration (and other factors) and the clinician's expertise.

[1] Wilson LS, et al. Patient preferences for attributes of multiple sclerosis disease-modifying therapies. Int J MS Care 2015; 17(2): 74-82. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399770/.
[2] Utz KS, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. Ther Adv Neurol Disord 2014; 7(6); 263-275. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4218877/.

	A wide range of factors contribute to someone'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.
Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	Yes, some individuals may be unable to manage self-injection due to problems with manual dexterity or vision. Others will have significant needle-phobia which would make self-injection impossible.
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	If the Company's request to limit comparison of ozanimod to only oral first-line therapies is rejected, then we do consider that ocrelizumab would be used in the same population as ozanimod. Ocrelizumab is licensed for active RRMS, and NICE appraisal covers adults with active disease defined by clinical or imaging features. We understand that clinicians are prescribing it as a first-line treatment in England and Wales.
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?	If the Company's request to limit comparison of ozanimod to only oral first-line therapies is rejected, then we do consider that beta interferons, glatiramer acetate and peginterferon would be used in the same population as ozanimod. These are all first-line treatments.
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS	Yes, on the whole we believe so. We note that between the two studies, out of 2659 participants, the majority were white and from Eastern Europe. However, we do not believe that this population would have a different course of relapsing remitting MS

practice?	compared to those seen in NHS practice.
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	No comment.
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be the most appropriate source of indirect evidence?	No comment.
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?	No comment.
Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	No comment.

Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	A Our rationale is based on evidence that a relapse is the clinical manifestation of MS activity. For every relapse there are approximately 10 MRI lesions that occur asymptomatically. For every visible white matter lesion there are many more microscopic white matter lesions. Despite experiencing breakthrough relapses, there is a high probability that the treatment would continue to be effective against 'silent' MS activity and beneficial to the patient. In this scenario with continuing MS activity, we believe it is highly unlikely that a clinician would recommend or a patient would choose to discontinue all treatment. In a scenario where switching is not allowed, we believe it would be more appropriate to assume that a patient would continue treatment until they are no longer eligible.
Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	Given our response to this issue above, we believe the company's approach is most appropriate ie continue on treatment until somebody is in Expanded Disability Status Scale (EDSS) state 7 or over, enters the secondary progressive MS state or dies.

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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.	

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	Biogen does not consider it appropriate to categorise patients with active RRMS by suitability of route of administration alone. Furthermore, MS patients would not receive a treatment if they were not suitable for, or did not request it. The heterogeneity of MS means that tailoring treatment to the individual patient is vital; treatment success can be determined by the factors such as MS type, adherence, frequency of injections, likelihood of developing neutralising antibodies, DMT mechanism of action (MoA) and patient lifestyle (e.g. family planning, travel etc). Unfortunately, there are no disease characteristics or genotypes at present which can predict the success of a particular MOA product to a particular MS type or patient characteristic. The availability of a range of products is therefore essential to allow patients who do not respond to treatment to receive an alternative with a different characteristic. The ABN recommends starting treatment as early as possible in eligible patients and in order to meet the clinical and individual needs of each patient, it is essential that the full range of DMTs can be prescribed by neurologists. Biogen believe that in an evolving treatment landscape, all treatments should be available as an option; where the choice of treatment should be tailored to each patient's need after shared conversations between clinician and patient.

How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	Please refer to the prior response.
Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	Biogen expects that people with RRMS seeking treatment would consider all relevant treatments based on factors described previously. However, in the minority of cases there may be instances where patients have needle phobia, are intolerant to, or have contraindication to a specific treatment. All treatment possibilities should be discussed with the patient and physician to accommodate patient preference and circumstances.
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	Biogen considers ocrelizumab is a relevant comparator. This is consistent with recent appraisals in MS (TA624 and TA533) where all the listed comparators are aligned with this current appraisal and all were considered relevant despite different routes of administration. Ocrelizumab is widely used in RRMS including the target population for ozanimod, active RRMS. Biogen does not agree with the company position in excluding ocrelizumab as a comparator on the basis that ocrelizumab is used in patients "where alemtuzumab is contraindicated or otherwise unsuitable". Following section article 20, alemtuzumab is restricted as a treatment option for HA RRMS and RES RRMS and only for patients without certain heart, circulation or bleeding disorders or autoimmune disorders other than MS. As a result, alemtuzumab is not considered as a relevant comparator in this active RRMS population (that is not HA or RES) and therefore the conditional statement applied to ocrelizumab is redundant in this case.

	Patients considered for ocrelizumab are not systemically different to those considering a first-line therapy in active RRMS, and given the risk-benefit profiles of the two therapies patient preference and shared clinical decision making should be based on the disease burden.
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?	Biogen agrees with the Evidence Review Group conclusions on clinical effectiveness and relevant comparators. Treatments used first line in active RRMS include interferons, peginterferon beta-1a and glatiramer acetate (as well as ocrelizumab) which are well established first line therapies in NHS clinical practice. Furthermore, the submission the ozanimod clinical trial programme pivotal Phase III SUNBEAM and RADIANCE trials have been designed and powered using interferon beta-1a (Avonex) as a comparator in a population including active RRMS.
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS practice?	Biogen believes the baseline characteristics of RADIANCE (part B) and SUNBEAM trials to be generalisable to the UK population and NHS clinical practice.
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	Biogen has concerns on the MAIC methods in using the results of the NMA in the economic model. On the specified point noted by the Technical Team and ERG, the CDP6M combined outcome (i.e. the CDP outcome used to populate the company economic model and which enables CDP6M outcomes to be generated when CDP6M data are not reported in trials) requires the assumption that the CDP3M hazard ratio (HR)

	is proportional to the CDP6M HR. CDP6M is more indicative of permanent disability progression whereas CDP3M can be more influenced by a recent relapse. Biogen does not consider these endpoints to be interchangeable and therefore should be considered separately.
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be the most appropriate source of indirect evidence?	Biogen do not consider dimethyl fumarate and teriflunomide to be the only relevant comparators in this appraisal, ocrelizumab, beta-interferons, glatiramer acetate, and peginterferon beta-1a should all be considered. However, should the decision problem comparator be limited to oral therapies only, the 'reduced' NMA would be the most appropriate source of indirect evidence.
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?	Biogen agrees with the Evidence Review Group that the evidence presented is insufficient to demonstrate that ozanimod is similar to dimethyl fumarate either clinically or pharmacologically and that a cost minimisation approach is inappropriate in this instance. Furthermore, dimethyl fumarate is not clinically equivalent to teriflunomide to make a cost-minimisation approach appropriate. Analysis of propensity score matched cohort real-world studies has observed statistically significant differences in efficacy between dimethyl fumarate and teriflunomide on important outcomes such as time to first relapse and ARR with dimethyl fumarate showing a superior effect (Braune et al., 2018; Buron et al. 2019). *Braune S, Grimm S, van Hövell P, Freudensprung U, Pellegrini F, Hyde R, Bergmann A; NTD Study Group. Comparative effectiveness of delayed-release dimethyl fumarate versus interferon, glatiramer acetate, teriflunomide, or fingolimod: results from the*

	German NeuroTransData registry. J Neurol. 2018 Dec;265(12):2980-2992. doi: 10.1007/s00415-018-9083-5. Epub 2018 Oct 16. *Buron MD, Chalmer TA, Sellebjerg F, Frederiksen J, Góra MK, Illes Z, Kant M, Mezei Z, Petersen T, Rasmussen PV, Roshanisefat H, Hassanpour-Kalam-Roudy H, Sejbæk T, Tsakiri A, Weglewski A, Sorensen PS, Magyari M. Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. Neurology. 2019 Apr 16;92(16):e1811-e1820. doi: 10.1212/WNL.0000000000007314. Epub 2019 Mar 15.*
Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	Non-statistically significant differences in clinical effectiveness between treatments should be included in the model to provide the best estimate of treatment effect, aligned with prior NICE appraisals in multiple sclerosis.
Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale	It would be more clinically plausible to model scenario b which would reflect clinical management of the condition. With the nature of the disease, disease management aims to achieve NEDA (no evidence of disease activity) through close management of relapses and disease progression. With the broad options for treatment along with support from the physician, following a discussion with the physician patients with continued relapses are likely to discontinue treatment.

a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	
Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	Biogen would particularly arise the issue of the plausibility of the ERG preferred approach: to use trial discontinuation rates for the observation period, then assume no treatment discontinuation unless it is due to a stopping rule e.g. Expanded Disability Status Scale (EDSS) state 7 or over, enters the secondary progressive MS state or dies. It is implausible to model discontinuation being 0% following the trial period available. Further work would be needed to explore the issue as early discontinuations are noted to be driven by intolerance, and later discontinuations due to lack of efficacy. Biogen agrees with the company approach for treatment discontinuation should be applied consistently throughout model cycles until stopping rules are applicable. However, consideration must be given to the limitations of the data used to inform the NMA that may not be representative of treatment discontinuation, in particular: the definition of discontinuation and reasons for discontinuation in addition to the length of follow up informing the estimate.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

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We need your comments and feedback on the questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5:00pm, Monday 2 November 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

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- 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.
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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**

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	No. People with active relapsing-remitting multiple sclerosis (RRMS) who are "suitable for an oral treatment" may be equally suitable for a number of other treatments, including injectables or infusions, and in practice the patient and their clinician will be making a choice from the full range of treatments for which a patient is suitable. Meanwhile people "requesting an oral treatment" may not in fact be suitable for an oral treatment, or, as above may be equally suited to a variety of other treatments including injectables or infusions. This proposed population does not exclude comparators such as beta interferons or ocrelizumab, as patients who ultimately receive such disease modifying therapies (DMTs) may also be suitable for oral treatment.
How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	The direct question would be more properly answered by clinical experts, but as explained above we do not consider that the suggested population is mutually exclusive with patients who are suitable for injectables or infusions and therefore the full set of comparators listed by the Evidence Review Group (ERG) should be considered in the appraisal.

Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	No, they are not mutually exclusive descriptions as many people with active RRMS may be simultaneously suitable for oral, injectable or infusion-based DMTs and the choice of DMT is made by the clinician and patient on the basis of many factors, not the route of administration alone.
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	Novartis agrees with the ERG that ocrelizumab is a relevant comparator and is used in the same population as ozanimod would be if it were to be approved, namely as one of the first-line DMT options for patients with active RRMS. Such use is confirmed by the NHS England Treatment Algorithm for DMTs, and by NICE TA533, as well as being clearly stated in the Final Scope for the present appraisal where ocrelizumab is listed as a comparator in active RRMS. Ocrelizumab was recommended by NICE in TA533 as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features "if alemtuzumab is contraindicated or otherwise unsuitable". Alemtuzumab has, subsequent to TA533, had its licence restricted by the European Medicines Agency (EMA) to the highly active (HA) and rapidly-evolving severe (RES) RRMS subgroups only, making all patients in the active RRMS population "unsuitable" for alemtuzumab. As a result, ocrelizumab is now in practice recommended by NICE in the active RRMS population without restriction.
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?	Novartis agrees with the ERG that beta-interferons, glatiramer acetate, and peginterferon beta-1a are relevant comparators and are used in the in the same population as ozanimod would be if it were to be approved, namely as options for first-line DMT for patients with active RRMS. Novartis disagrees with any narrowing of the population being considered for ozanimod (see response to Issue 1 above), and considers all first-line

	DMTs to be relevant comparators. The availability of a range of DMTs, including the beta-interferons, glatiramer acetate and peginterferon beta-1a, as first line treatment options is confirmed by the NHS England Treatment Algorithm for DMTs, as well as being clearly stated in the Final Scope for the present appraisal where these options are all listed alongside ocrelizumab, dimethyl fumarate and teriflunomide as comparators in active RRMS.
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials broadly comparable to those seen in NHS practice?	This question would more properly be answered by clinical experts; therefore, Novartis offers no comment.
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 deals with the situations in which use of matching-adjusted indirect comparison (MAIC) methodology may be considered appropriate. Given the availability of a connected network of randomised controlled trials, allowing for a conventional network meta-analysis (NMA), TSD18 would require the company to establish that the network of trials contained an imbalance of effect modifiers to justify undertaking an MAIC. Having reviewed the Technical Engagement papers, Novartis was unable to find any appraisal of effect modifiers in the evidence package and therefore contend that the requirements for

	undertaking an MAIC have not been addressed. As such the company MAIC cannot be considered an appropriate source of supporting clinical effectiveness evidence. In addition to the lack of justification for undertaking an MAIC, insufficient details of the company MAIC are available in the Technical Engagement papers to allow critique of the methodology used, and Novartis agrees with the ERG conclusion that "due to limited details and concerns regarding the methods, the ERG considers that the company's MAICs should not be used for decision making". In conclusion, Novartis believes that the company MAIC should be disregarded and the full NMA remains the most relevant source of comparative evidence for the appraisal.
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be the most appropriate source of indirect evidence?	As contended in our response to Issue 1 above, all the comparators for active RRMS listed in the scope for the present appraisal are relevant and therefore the full NMA remains the most appropriate source of evidence. If the appraisal committee was to consider only teriflunomide and dimethyl fumarate as comparators, the reduced NMA is theoretically preferable.
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or	The full NMA results provided by the company in their submission found ozanimod to be more efficacious than both teriflunomide and dimethyl fumarate when considering annualised relapse rate (ARR), [redacted] efficacious than both teriflunomide and

DMF to make a cost minimisation approach appropriate?	dimethyl fumarate when considering disability progression confirmed at either 3 or 6 months. Taken together, these results do not support the contention that ozanimod has comparable efficacy to either DMT. In order to fully capture the relative efficacy of ozanimod and comparators across both relapses and disability progression, and to weight these outcomes on a scale relevant to patients and decision makers it is necessary to undertake a cost-utility analysis in accordance with the NICE reference case. As such, Novartis agrees with the ERG and NICE Technical Team that a full incremental cost-utility analysis is required for ozanimod. This is aligned with the judgement that NICE gave in determining that this appraisal was not suitable for the fast-track appraisal (FTA) process. In addition to the requirement for a cost-utility analysis, Novartis would re-emphasise in line with our response to Issue 1 above that this cost-utility analysis needs to consider all comparators for active RRMS specified in the Final Scope, irrespective of route of administration.
Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	Novartis agrees with the NICE Technical Team that all differences (irrespective of nominal significance at any arbitrary threshold) should be incorporated within the cost-effectiveness model because they represent the best estimates of effect. The NMA should be incorporated in a fully probabilistic analysis to reveal the joint impact of the uncertainty in multiple parameters on the expected costs, benefits and on decision uncertainty, as

	required by the NICE *Guide to the methods of technology appraisal* 2013 (paragraph 5.8.7) and elucidated in NICE DSU TSD6. Including all differences in clinical effectiveness would also be in line with many previous NICE appraisals of DMTs in multiple sclerosis (MS), and across NICE appraisals generally. More broadly, it should be recalled that NMA exists to synthesise all the evidence available to generate the best estimate of effect (and the uncertainty around that estimate) to populate a decision-analytic model. In contrast, the concept of a "statistically significant difference" exists within a formal hypothesis testing paradigm, where a well-designed, appropriately powered randomised controlled trial (RCT) is undertaken to provide data to test a pre-specified hypothesis according to a pre-specified statistical analysis plan. In contrast, NMA is inherently a post hoc analysis and is not designed (or powered) to be a mechanism for formal hypothesis testing analogous to a well-designed RCT. Therefore interpreting the results of an NMA as though they were from a non-inferiority RCT is inappropriate and the suggestion in effect to "throw away" data for not meeting an arbitrary definition of "significance" (with no measure of statistical power) in this context is methodologically inappropriate.
Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what	Before considering the question posed for Technical Engagement, it is important to consider *why* the cost-effectiveness analysis in this appraisal – which is in line with other

would happen (hypothetically) in clinical practice? Please provide your rationale a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	NICE appraisals of DMTs for RRMS – makes a simplifying assumption with regard to treatment sequencing in its structure: • In clinical practice treatment discontinuation may occur for many disparate reasons, including adverse events, lack of tolerance, lack of efficacy (which may be defined in many ways, not just relapses or disability progression), or changes in risk–benefit profile (e.g. prolonged natalizumab treatment in John Cunningham virus (JCV)-positive patients). • The choice of DMT in RRMS is highly individualised, not just for the choice of initial DMT but also for any subsequent DMTs. Reflecting this, the NHS England Treatment Algorithm for DMT does not specify any rigid sequences of DMTs, although the reasons for discontinuation of the prior DMT do modify the selection of subsequent DMTs available under the algorithm. • Modelling the full set of choices and potential pathways available under the NHS England algorithm would result in considerable economic model complexity while also requiring significant volumes of new data to fully parameterise the sequence model, much of which is likely to be unavailable and therefore require assumptions – this is acknowledged in the Technical Report in Section 3. As a pragmatic response to this situation cost-effectiveness models for DMTs in MS used in NICE appraisals (including by the independent academic Assessment Group in TA527)

	have therefore only modelled a single line of DMT, with treatment discontinuation to best supportive care (BSC). This approach avoids the model results becoming primarily driven by assumptions regarding subsequent treatment, rather than focussing on the effect of the intervention being appraised. As a result of the points detailed above, the question for the Committee to determine is not which of the two approaches given in the Technical Engagement question would occur in a hypothetical world where only one line of DMT treatment is allowed – that is not the decision problem at hand – but rather which simplifying structural assumption (company [trial-based discontinuation over time] or ERG [no discontinuation until EDSS 7 or SPMS is reached]) is least biased for decision making when it is acknowledged that neither scenario reflects clinical reality. Two further crucial points that are obscured by the hypothetical choices listed in the consultation question are: 1. Discontinuation occurs for many reasons not listed in the question including, but not limited to, adverse events, lack of tolerance, lack of efficacy (broadly defined) or changes in risk-benefit profile (e.g. prolonged natalizumab treatment in JCV-positive patients)

	2. No DMT abolishes the occurrence of relapses (or, more pertinently, progression), they each have demonstrated evidence that they reduce the rate at which relapses occur Given all of the above, Novartis would contend that in the model patients should discontinue gradually over time for any reason (as modelled by the company) – not limited to, or even primarily related to, relapses. The ERG assumption of remaining on initial DMT until the patient reaches EDSS 7 or is reclassified as displaying the SPMS phenotype does not reflect clinical reality and is likely to grossly overestimate the time on treatment for all DMTs, while the alternative proposed in the consultation question – that patients discontinue treatment if they experience *any* relapse – is contrary to clinical practice and the RCT evidence which underpins it, and likely to lead to a significant underestimation of time on treatment.
Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	As explained in the response above, the company's approach is most appropriate for decision making and Novartis agrees with the NICE Technical Team that the NMA is the most appropriate source for discontinuation data. Novartis also note that the company model includes an assumption of arbitrary waning of treatment effect after two years of treatment, and a further dramatic reduction in treatment effect after five years of treatment, for all DMTs, without providing any supporting clinical evidence. This is contrary to the Committee decision in NICE TA533 where all-cause

	discontinuation was considered a proxy for waning of treatment effect. Given that, in clinical practice, treatment is likely to be discontinued if loss of efficacy occurs, as discussed above, the inclusion of an arbitrary waning parameter will result in “double-counting” of loss of effect as this is already contained within trial all-cause discontinuation. Novartis therefore request that waning be removed from the decision-making ICERs.

NICE National Institute for Health and Care Excellence

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Deadline for comments **5:00pm, Monday 2 November 2020**

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- 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.
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About you

Your name	
~~Organisation name – stakeholder or respondent~~ (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Celgene Limited (A BMS Company)**
~~Disclosure~~ Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Population in company's submission addendum narrowed to only include people 'suitable for or requesting an oral treatment'	
Is it appropriate to separate people with active RRMS according to whether they are 'suitable for or requesting an oral treatment'?	Yes, it is appropriate to separate people with active RRMS according to the type of treatment choice that is suitable for them. Disease modifying therapies (DMTs) for RRMS are available as infusions (e.g. ocrelizumab etc.), injections (e.g. beta interferon etc) and orals (e.g. dimethyl fumarate etc.). Celgene believe the choice of DMT prescribed in the UK for RRMS is driven by an informed discussion and consensus between the prescribing clinician and the patient based on the level of disease activity, patient risk tolerance, patient preference and patient lifestyle considerations.
How would the population who are 'suitable for or requesting an oral treatment' be defined clinically?	As noted in the question above the joint decision between the prescribing clinician and the patient on the selection of a treatment for RRMS would go beyond the clinical definition alone. The clinical rational for favouring an oral DMT could include: • Belief it would positively affect treatment adherence in some patients • Patient/carer ability to administer injections. • Needle phobia Other factors that should be considered include: • Patient ability to attend a centre for infusion. • Local infusion facilities and home care availability. • Work and lifestyle challenges to adherence and management of injections and infusions. • Initiation of treatment during the ongoing COVID-19 pandemic.

	We anticipate the clinical definition and population suitable for treatment with ozanimod would be similar to that currently used to identify dimethyl fumarate and teriflunomide patients.
Would people who are 'suitable for or requesting an oral treatment' be excluded from receiving injectable treatments?	We anticipate that patients suitable for or requesting an oral treatment cannot tolerate or are not suitable, on clinical or other grounds, for an injection or infusion.
ERG comment	**No additional comment.**
Issue 2: Choice of comparators	
Is ocrelizumab likely to be used in the same population as ozanimod? Is it a relevant comparator?	Ozanimod should only be used if a patient has failed or is unsuitable for infusion treatments such as ocrelizumab and injectables treatments (beta-interferons, glatiramer acetate, and peginterferon beta-1a) for RRMS.
Are beta-interferons, glatiramer acetate, and peginterferon beta-1a likely to be used in the same population as ozanimod, and are they therefore comparators?	Ozanimod should only be used if a patient has failed (or intolerant) or is unsuitable for the injectable RRMS treatments beta-interferons, glatiramer acetate, and peginterferon beta-1a.
ERG comment	**No additional comment.**
Issue 3: Generalisability of ozanimod clinical trials	
Are baseline characteristics of people in the RADIANCE Part B and SUNBEAM trials	Clinical advice to the ERG is that these characteristics are not dissimilar to the characteristics of other patients with active RRMS typically recruited to MS trials and are

broadly comparable to those seen in NHS practice?	likely to be similar to patients seen in NHS clinical practice in England and Wales. Our SmPC does not exclude any specific adult populations based on ethnicity or race. Therefore, we agree with the technical team's preliminary judgment that "although there are some differences between the clinical trials and NHS practice, RADIANCE Part B and SUNBEAM overall provide high quality randomised controlled trial evidence compared with an active comparator and are likely broadly generalisable".
ERG comment	**No additional comment.**
Issue 4: Choice of indirect comparison	
Is the company's MAIC an appropriate source of supporting clinical effectiveness evidence?	Celgene Limited conducted the MAIC purely as a validation exercise. A NMA assumes that treatment effect modifiers are equally distributed across trials. However, there were differences in the baseline patient characteristics in the ozanimod, teriflunomide and dimethyl fumarate trials. Differences observed in patient populations for these trials were considered important treatment effect modifiers in MS as well as prognostic factors such as EDSS, prior relapse, DMT use, Gd+ lesions, age, sex, geographic region, and weight. Similar to the NMA and reduced NMA, the CDP-3M and CDP-6M results showed no statistically significant difference between ozanimod 1 mg and teriflunomide or dimethyl fumarate at 2 years. The MAIC further suggests that ozanimod is associated with

	significantly improved ARR, significantly reduced risk of overall AEs and SAEs, and significantly fewer discontinuations.
If dimethyl fumarate and teriflunomide were to be considered the only relevant comparators, would the company's 'full' or 'reduced' NMA be the most appropriate source of indirect evidence?	The impact of selecting one NMA in favour of another is very small. In the full NMA ozanimod is statistically significantly better that teriflunomide on ARR and dimethyl fumarate on adverse events. Ozanimod is numerically superior to dimethyl fumarate and teriflunomide in the reduced NMA on all outcomes with the exception of CDP. The key issue is not which NMA to use, it is how confirmed disability progression (CDP) results for ozanimod are utilised in the economic evaluation. The ERG notes in Table 3 of the STA ERG Report, "Although EDSS and CDP are clinically relevant measures, limitations with both measures are widely recognised…". In both the RADIANCE part B and SUNBEAM trials rates of CDP, defined as a sustained worsening in EDSS of ≥1 point confirmed at 3 or 6 months, were low in each treatment arm which reduced the ability to detect a meaningful difference between treatments. The power analysis assumed a 6% treatment difference between ozanimod and IFN β-1a; however, only a 2% difference in CDP rates between groups was observed. Based on this 2% observed difference in CDP rates, 2,541 patients per arm and 356 total events would have been needed to achieve 80% power to detect a significant difference between ozanimod 1mg and IFN β-1a.

	If the CDP results from the NMAs are applied in a decision analytic model the results will underestimate the benefit of ozanimod for patients with RRMS. The CDP endpoint should be considered within the context of the robust improvement in annualised relapse rate and number of new or enlarging T2 lesions and gadolinium-enhancing lesions, the reductions in the loss of normalized brain volume and cortical and thalamic brain volume, the increased percentage of patients with no evidence of disease activity, the improvement in cognition, and the maintenance of quality of life with ozanimod compared with IFN β-1a.
ERG comment	**No additional comment.**
Issue 5: Cost minimisation or cost utility analysis	
Is there sufficient evidence that ozanimod has comparable efficacy to teriflunomide and/or DMF to make a cost minimisation approach appropriate?	Yes, there is sufficient evidence that ozanimod has comparable efficacy to teriflunomide and or dimethyl fumarate to make a cost-minimisation approach appropriate. With the exception of the anomalous CDP results, the reduced NMA shows that ozanimod is numerically superior to dimethyl fumarate and teriflunomide on all efficacy and safety measures. Assuming comparable efficacy and safety for dimethyl fumarate and teriflunomide is a conservative assumption. It should be noted that several appraisals for the same population (TA320, TA303, TA527 and TA624) have been able to conclude that the treatments evaluated in the NMAs were “similar”, “similarly effective”, “as effective” and/or “there were no differences” in the

	absence of noninferiority evidence. In a further five fast track appraisals, the NICE committee were also able to reach a conclusion based on the NMAs provided by the companies (TAA486, TA497, TA521, TA596 and TA572). We therefore believe that such a conclusion can also be reached in the current appraisal based upon the NMAs provided by the company.
ERG comment	**No additional comment.**
Issue 6: Only modelling statistically significant differences between treatments	
Should non-statistically significant differences in clinical effectiveness between treatments be included in the model? Or, should differences in effect not be modelled if there is not a statistically significant difference?	We note that the ERG's pragmatic approach of not modelling differences in effect that are not statistically significant in a cost utility analysis is inconsistent with their comments on the cost-minimisation analysis where they state "showing ozanimod is not statistically superior to dimethyl fumarate or teriflunomide is not the same as showing there to be no difference between the treatments, or that they are 'comparable'" (p8, Technical report). Given the challenges with the ozanimod CDP data outlined above, the ERG acknowledges non-significant differences between dimethyl fumarate and teriflunomide could be modelled in the cost utility analysis. In addition, the clinical Expert Statement states that ozanimod is likely to be used alongside dimethyl fumarate and teriflunomide. Where these assumptions hold for equivalent efficacy and eligibility, a cost-minimisation

	analysis comparing the three treatments would be the most appropriate form of economic evaluation for this decision problem.
ERG comment	**Generally, health economists model differences in treatment effects, even when statistically significant differences have not been demonstrated. However, the ERG considers that when there are no statistically significant differences between treatments, a scenario should also be presented that assumes no differences to allow the committee to reach a decision.**
Issue 7: Modelling treatment discontinuation	
When modelling a scenario in which switching to a different treatment is not allowed, which of the following approaches best reflects what would happen (hypothetically) in clinical practice? Please provide your rationale a. People tolerating their existing treatment stay on it even if they continue to have relapses, or b. People tolerating their existing treatment discontinue it if they continued to have relapses	This is a difficult clinical decision which needs to weigh up the risk/benefit balance for each patient. In this hypothetical scenario, not akin to the clinical setting where many different DMTs would be available for consideration, if however, you were unable to switch treatments, a treatment which may be suboptimal would on balance be more beneficial than no treatment at all. The clinician would make an informed decision on whether withdrawing a suboptimal treatment would potentially result in deterioration of the patient's condition. Therefore, we believe option 'a' would be the most likely outcome.

Is the ERG's or company's approach to modelling treatment discontinuation most appropriate?	A simplifying assumption is required to incorporate treatment discontinuation for MS in a decision analytic model. Celgene Limited are willing to accept the ERG's approach to modelling discontinuation.
ERG comment	**No additional comment.**