NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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** from Janssen

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Multiple Sclerosis Society (MS Society)
   b. Multiple Sclerosis Trust
   c. Association of British Neurologists (ABN)
      the Royal College of Physicians endorsed the ABN submission
   d. UK Multiple Sclerosis Specialist Nurse Association

4. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response from Janssen**
   a. Company response
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7. **Technical engagement responses & expert statements from experts:**
   a. Dr Eli Silber– clinical expert, nominated by Multiple Sclerosis Trust
   b. Professor Neil Robertson – clinical expert, nominated by Novartis Pharmaceuticals
   c. Helena Jidborg Alexander – patient expert, nominated by Multiple Sclerosis Trust
   d. Malcolm Qualie – commissioning expert, nominated by NHSE
   e. Sarah Bittlestone– patient expert, nominated by Multiple Sclerosis Society

8. **Technical engagement response from consultees and commentators:**
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   h. Biogen
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9. **Evidence Review Group critique of company response to technical engagement** prepared by by Peninsula Technology Assessment Group (PenTAG)
    a. ERG Technical Engagement response
    b. Addendum 1
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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

29 April 2021

File name	Version	Contains confidential information	Date
Ponesimod Form B Janssen Evidence Submission Updated AIC-CIC_June 2021 V1	V1	Yes	9th June 2021 – Update from 29th April

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Abbreviations

Abbreviation	Definition
9HPT	9-Hole Peg Test
ABN	Association of British Neurologists
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARR	annualised relapse rate
BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA	confirmed disability accumulation
CEAC	cost-effectiveness acceptability curve
CEM	cost-effectiveness model
CESD-7	7-item Center for Epidemiologic Studies Depression
CI	confidence interval
CIS	clinically isolated syndrome
CL	confidence limit
CNS	central nervous system
CrI	credible interval
CSF	cerebrospinal fluid
CUAL	combined unique active lesions
DIC	deviance information criterion
DIS	dissemination in space
DIT	dissemination in time
DMT	disease-modifying therapy
DSU	Decision Support Unit
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPAR	European public assessment report
ESS	effective sample size
FDA	Food and Drug Administration
FSIQ-RMS	Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis
FSIQ-RMS-I	Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis impact domain
FSIQ-RMS-S	Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis symptom domain
FSS	Fatigue Severity Scale
GBP	British pounds

Abbreviation	Definition
Gd+	gadolinium enhancing
HAS	Haute Autorité de santé
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IFN	interferon
IQWiG	Institute for Quality and Efficiency in Health Care
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention-to-treat
JAGS	Just Another Gibbs Sampler
KM	Kaplan-Meier
LS	least square
LY	life year
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
MAO	monoamine oxidase
MCSE	Monte Carlo standard error
MFIS	Modified Fatigue Impact Scale
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MTR	magnetisation transfer ratio
NEDA	no evidence of disease activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OCB	oligoclonal bands
OR	odds ratio
PASAT-3	Paced Auditory Serial Addition Test
PBAC	Pharmaceutical Benefits Advisory Committee
PICOS	population, intervention, comparison, outcomes, study design
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMS	progressive relapsing multiple sclerosis
PRO	patient-reported outcome
QALY	quality-adjusted life year
QD	once daily
QOD	every other day

Abbreviation	Definition
QW	weekly
RCT	randomised controlled trial
RES	rapidly evolving severe
ResDev	residual deviance
Rhat	Gelman-Rubin diagnostic
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing remitting multiple sclerosis
RRMS	rate ratio
S1P	sphingosine-1-phosphate
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-36v2	Version 2 of the 36-item Short Form Health Survey
SF-6D	six-dimension Short Form Health Survey
SLR	systematic literature review
SmPC	Summary of Product Characteristics
SPMS	secondary progressive multiple sclerosis
SUCRA	surface under the cumulative ranking curve
T25FW	Timed 25-Foot Walk
TEAE	treatment-emergent adverse events
THIN	The Health Improvement Network
TIW	three times weekly
TP	treatment period
TSD	Technical Support Document
ULN	upper limit of normal
VAS	visual analogue scale

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

B.1.1 Decision problem

Relapsing multiple sclerosis (RMS) is a neurological disorder affecting more than 100,000 people in England and includes two phenotypes: relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).(1, 2) Ponesimod is a new treatment option for RMS developed by Janssen that is anticipated to receive marketing authorisation for "the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features".(3)

The final scope for ponesimod for multiple sclerosis (MS) was issued by NICE in January 2021.(4) The key evidence in this submission is based on the results of OPTIMUM, a phase 3 randomised controlled trial (RCT) that evaluated the efficacy and safety of ponesimod versus teriflunomide in patients with RMS.(5) However, this submission focuses on part of the technology's anticipated marketing authorisation and describes the clinical and cost-effectiveness of ponesimod as a treatment option for patients with RRMS since the OPTIMUM trial provides limited evidence for the effectiveness of ponesimod in people with SPMS. The decision problem addressed in this submission is summarised in Table 1.

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	People with relapsing MS	People with RRMS (limited to people with active RRMS and people with highly active RRMS)	The decision problem is focused on a sub-population of MS patients because there is limited evidence available for ponesimod in SPMS for health technology evaluation. The evidence presented in the submission is based on a phase 3 RCT (OPTIMUM) that evaluated ponesimod compared to teriflunomide in people with RMS. At study entry, most patients in the trial were diagnosed with RRMS (97.4%). The trial included only a small proportion of patients with SPMS (2.6%). Phase 3 data for people with RRMS is more robust in people with active RRMS and highly active RRMS (35% of trial population) and so the submission focuses on these two subgroups i.e., not in people with RES RRMS.
Intervention	Ponesimod	As per scope	n/a
Comparator(s)	For people with active RRMS: • beta-interferon • dimethyl fumarate • glatiramer acetate • teriflunomide • ocrelizumab • peginterferon beta-1a • ozanimod (subject to ongoing NICE appraisal)	For people with active RRMS: • beta-interferon • dimethyl fumarate • glatiramer acetate • teriflunomide • ocrelizumab • peginterferon beta-1a For people with highly active RRMS • alemtuzumab	At the time of submission, ozanimod and ofatumumab have not been recommended by NICE as treatment options for MS and cannot be considered as standard of care within the NHS. Therefore, they not been considered in the submission. The OPTIMUM trial included only 2.6% SPMS patients, therefore it was deemed that there is insufficient evidence for this population In line with previous clinical trials in MS, the definition of highly active RRMS employed in the OPTIMUM trial was broad, and thus

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• ofatumumab (subject to ongoing NICE appraisal) For people with highly active RRMS despite previous treatment: • alemtuzumab • cladribine • fingolimod • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) • ofatumumab (subject to ongoing NICE appraisal) For people with RES RRMS • alemtuzumab • cladribine • natalizumab • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) • ofatumumab (subject to ongoing NICE appraisal) For people with active SPMS (evidenced by continuing relapses) • established clinical management, including IFN-beta or other DMTs used outside their marketing authorisations	• cladribine • fingolimod • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	also incorporates patients with RES RRMS as defined by NHS England.(6-9) As a result, separate subgroup analyses of patients with RES RRMS were not part of the prespecified analysis.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• siponimod (subject to ongoing NICE appraisal)		
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, EDSS) • disease progression • symptoms of MS (such as fatigue, cognition and visual disturbance) • freedom from disease activity (for example lesions on MRI scans) • mortality • adverse effects of treatment • HRQoL	The outcome measures to be considered include: • relapse rate o ARR o Time to first confirmed relapse • disability o change from baseline in EDSS score • disease progression o 12-week CDA o 24-week CDA • symptoms of MS o change from baseline in FSIQ-RMS score • freedom from disease activity o CUAL o NEDA-3 o NEDA-4 • adverse effects of treatment • mortality • HRQoL o Change from baseline in SF-36 score o Change from baseline in MSFC Z-score	The outcomes captured by the OPTIMUM clinical trial of ponesimod are relevant for patients with active RRMS or highly active RRMS and are representative of current clinical practice in England. Outcomes such as severity of relapse and mortality could not be included in the pharmacoeconomic analyses due to the absence of comparative trial data. The OPTIMUM trial did not formally measure severity of relapse, which is difficult to measure in trials for MS. The OPTIMUM trial captures new Gd+ T1 lesions plus new or enlarging T2 lesions, which can indirectly denote disease severity. OPTIMUM trial outcomes are in line with outcome measures in previous MS trials appraised by NICE.

ARR = annualised relapse rate; CDA = confirmed disability accumulation; CUAL = combined unique active lesions; DMT = disease modifying therapy; EDSS = expanded disability status scale; FSIQ-RMS = Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis; Gd+ = gadolinium enhancing; HRQoL = health-related quality of life; IFN = interferon; MSFC = Multiple Sclerosis Functional Composite; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial; RES = rapidly evolving severe; RMS = relapsing multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; SF-36 = Short Form-36; SPMS = secondary progressive multiple sclerosis

B.1.2 Description of the technology being appraised

A description of ponesimod, the technology being appraised, is presented in Table 2. The draft Summary of Product Characteristics (SmPC) for ponesimod can be found in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Ponesimod (Ponvory®)
Mechanism of action	Ponesimod is a selective sphingosine 1-phosphate (S1P) modulator with high selective affinity for the S1P1 receptor, that prevents lymphocytes from leaving secondary lymphoid organs.(10, 11) S1P modulators inhibit the interaction between the S1P ligand and S1P receptors.(12) By blocking these signals, S1P modulators prevent lymphocytes from entering peripheral tissues, thereby decreasing the number of circulating lymphocytes and resulting in significant immunosuppressive effects.(13) In the presence of ponesimod, lymphocyte trafficking from the lymph node is blocked by the removal of the S1P1 receptor, meaning that lymphocytes are unaffected by the presence of circulating endogenous S1P.(14, 15) Reduced lymphocyte count in the rest of the body is thought to be the main mechanism of action of S1P receptor modulators in the treatment of RMS.(14)
Marketing authorisation/CE mark status	A marketing authorisation application was submitted to the EMA on 4th March 2020. CHMP positive opinion is expected in March 2021 with marketing authorisation anticipated to be granted by the European Commission in May 2021. UK marketing approval is expected from MHRA through the EC Decision Reliance Procedure in June/July 2021.
Indications and any restriction(s) as described in the SmPC	The anticipated indication for ponesimod is: "for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features" Ponesimod is contraindicated in the following patients: - Patients who have hypersensitivity to the active substance or to any of the excipients. - Patients in an immunodeficient state. - Patients who have in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure. - Patients who have presence of Mobitz type II second-degree AV block, third-degree AV block, or sick-sinus syndrome, unless the patient has a functioning pacemaker. - Patients with severe active infections and patients with active chronic infections. - Patients with active malignancies. - Patients with moderate or severe hepatic impairment (Child Pugh class B and C, respectively). - Women who are pregnant and women of childbearing potential not using effective contraception.
Method of administration and dosage	When initiating treatment with ponesimod, patients should use a starter pack to follow a 14-day up-titration schedule. The up-titration protocol is implemented on Day 1 to Day 14, starting with 2 mg once daily (QD) increasing to 10 mg QD on Days 12, 13, and 14 followed by maintenance dosing at 20 mg QD. Ponesimod is administered orally as a film-coated tablet at a maintenance dose of 20 mg QD. If a patient misses a dose on ≥4 consecutive days during treatment maintenance, the up-titration protocol needs to be re-initiated with Day 1 of the titration regimen.

Additional tests or investigations	No additional tests beyond those already employed for patients with MS would be required following the introduction of ponesimod
List price and average cost of a course of treatment	The list price of ponesimod is: • Starter pack (14 film-coated tablets) = [redacted] • Maintenance pack (28 film-coated tablets) = [redacted] The average cost of a course of treatment based on list price is [redacted] per year
Patient access scheme (if applicable)	A patient access scheme representing a simple discount of [redacted] % from the list price of ponesimod. The PAS is a simple discount and has been submitted for review to the Patient Access Scheme Liaison Unit (PASLU). The net price incorporating the PAS is: • Starter pack (14 film-coated tablets) = [redacted] • Maintenance pack (28 film-coated tablets) = [redacted] The average cost of a course of treatment based on net price is [redacted] per year.

AV = atrioventricular; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; MHRA = Medicines and Healthcare products Regulatory Agency; PAS = patient access scheme; PASLU = Patient Access Scheme Liaison Unit; QD = once daily; RMS = relapsing multiple sclerosis; S1PR = S1P receptor; SmPC = summary of product characteristics; UK = United Kingdom

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

Summary of the health condition

- Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) and a leading cause of neurological disability in young and middle-aged adults, affecting an estimated 105,800 people in England.(16-18)
- About 85% of MS patients are diagnosed with relapsing-remitting MS (RRMS), characterised by recurrent inflammatory attacks leading to progressive neuronal degeneration, with intervening periods of relative stability.(16, 19, 20)
    - RRMS can be further subdivided into mutually exclusive subgroups of active RRMS, highly active RRMS and rapidly evolving severe RRMS based on relapse frequency and MRI activity, although the definitions for these subgroups vary in the literature and across clinical trials in MS.(6-8, 21-23)
- The experience of MS varies from patient to patient, depending on the location of inflammatory lesions in the CNS, and can present as a range of abnormal sensory and visual symptoms to disruption of cognitive and motor function. (20, 24-29)
- The health-related quality of life (HRQoL) of patients with MS is worse than the general population and worsens as disease severity increases. (30-32) Relapses are key drivers of reduced HRQoL in patients with RRMS, and the frequency of relapses is a prognostic factor for disability progression.(23, 33-36)
- MS places a high economic burden on society due to the cost of managing relapses and the frequent need for informal caregiving, as well as productivity losses in a patient population commonly affected during prime employment years.(31, 37)

Unmet need

- The key objectives of MS treatments are to reduce the frequency of relapses, slow disease progression and disability, manage symptoms and improve overall HRQoL.(34, 35, 38)
- A wide range of disease-modifying treatments (DMTs) with different risk-benefit profiles are needed for MS due to the disease's heterogeneous clinical presentation, unpredictable progression course, and individual variability in patient treatment response and tolerability.(20, 39, 40) Currently MS is managed using a range of treatments administered via oral, injectable or infusion routes.
    - DMTs with lower efficacy are generally associated with less severe adverse effects, whereas highly efficacious DMTs are often associated with more serious safety issues, leaving patients with a choice between optimising either efficacy or safety.(19, 41)
    - Many of the currently available treatments for RRMS require infusion or injections, while patients with MS have been found to prefer oral treatment administration.(42-44)
    - The long half-life of some oral DMTs can be a challenge for vaccinations and family planning, or when switching treatment.(45)
    - There remains an unmet need for a convenient efficacious treatment that reduces relapse frequency in patients with MS, manages disease symptoms and has a favourable long-term safety profile.

Ponesimod as a treatment option for patients with RRMS

- Ponesimod is a sphingosine 1-phosphate (S1P) modulator with high selective affinity for the S1P1 receptor, causing immunosuppressive effects by reducing the number of circulating lymphocytes.(10, 11) (13)
- Ponesimod has the potential to be the first NICE-recommended S1P modulator for patients with active RRMS and a safer alternative to existing DMTs for patients with highly active RRMS, meeting the unmet needs in the current treatment landscape.

- Clinical trial data from the phase 2 extension study have demonstrated favourable results of ponesimod with regards to long-term efficacy and tolerability.(46-48) Overall, treatment persistence was reported in 61% of patients receiving ponesimod in the trial, with ongoing treatment reported by 52% of patients at approximately 9 years into the trial.(49)
- A once-daily oral dosing regimen and a short half-life with transient effects on lymphocytes offers a convenient treatment option for patients who may be considering family planning.(12)
- As an oral treatment with rapidly reversible immunosuppressive effects, ponesimod offers flexibility during the ongoing COVID-19 pandemic, allowing people with MS to manage their treatments without worry of routine hospital appointments for infusion or additional monitoring, as is the case for some DMTs.(50-53)

B.1.3.1 Disease overview

B.1.3.1.1 Clinical presentation

MS is a chronic, progressive, autoimmune disease characterised by recurrent inflammatory attacks within the central nervous system (CNS) in which the immune system attacks the protective myelin sheath around neurons, resulting in deterioration of axons that transmit electrical impulses between neurons and progressive neuronal degeneration as a result of breakdown of communication between the brain and the rest of the body.(19, 20) Clinically, MS presents with bouts of neurological symptoms that vary depending on the location of inflammatory lesions in the CNS and whether attacks are focal or multifocal in the brain.(20, 24-26) Patients may experience sensorimotor symptoms (e.g., paraesthesia, neuralgia, neuropathic pain), fatigue, visual disturbances and pain with eye movement, impaired balance and gait, ataxia, motor weakness and discoordination, weakness, impaired short term memory, concentration or attention.(25, 27-29) Patients can also experience bowel and bladder dysfunction, sexual dysfunction and issues with walking and mobility, particularly as the disease progresses.(25, 27-29)

Following an initial attack, relapses occur within 2 years in about half of patients who are not treated with disease-modifying therapy (DMT).(26) Recovery from MS relapse is often incomplete and residual deficits accrue with each relapse, leading to increasing disability over time.(20, 54) For example, a study of 182 patients with RRMS in Wales (1999 to 2006), including 279 relapse episodes, found that 49% of patients showed at least some residual worsening of disability following relapse.(55) Other studies have shown that both degree of relapse recovery and frequency of relapse have a substantial impact on disease progression and disability.(56, 57) Therefore, reduction of the frequency and severity of relapses is a key goal in MS treatment.(23)

B.1.3.1.2 Epidemiology

MS is the leading cause of neurological disability in young and middle-aged adults in developed countries.(16, 17) In England, the burden of MS is substantial, affecting 1 in every

500 people.(18) Based on an analysis of data from The Health Improvement Network (THIN) database collected up until 17 January 2018, approximately 105,800 people were living with MS in England, with 4,950 new cases diagnosed each year. (18) The overall prevalence rate of MS in England was estimated to be 190 per 100,000, including a rate of 272 per 100,000 in women and 106 per 100,000 in men while the incidence rate was estimated to be 9 per 100,000 per year overall.(18)

MS typically affects adults during prime employment years, between 20 and 40 years of age, but can also occur in children and older persons.(58-61) Adult women are disproportionately affected by MS; MS prevalence rates are similar across genders in pre-adolescents but begin diverging in adolescence, when prevalence begins to rise among females relative to males.(62) A systematic review of 123 MS epidemiology studies conducted between 1985 and 2011 in European countries, including 26 studies in the UK, reported an average ratio of 2:1 female to male prevalence.(63) Incidence of MS was also found to be generally higher in women, with rates up to 3 times higher than in men.(63)

B.1.3.1.3 Diagnosis

When a patient presents with initial symptoms suggestive of MS, a range of investigational clinical methods are used to inform an MS diagnosis and rule out alternatives. These methods include (but are not limited to) radiological imaging, laboratory testing, and other paraclinical investigations.(28, 64) Magnetic resonance imaging (MRI) of the brain and spinal cord offers a non-invasive and sensitive way of diagnosing and monitoring disease activity in MS using short (T1) or long (T2) timed pulses to the brain and spinal cord. Contrast between regions allows identification of inflammatory lesions at different stages in MS. In T1 images, fat is bright and cerebrospinal fluid (CSF) is dark; in T2 images, fat is dark and CSF is bright.(65, 66)Use of gadolinium during an MRI allows detection of areas of new disease since active inflammation disrupts the blood-brain-barrier allowing gadolinium to pass through and highlight the affected areas. MRI scans for MS include assessments for:

- T1 lesions (without gadolinium) - dark areas that indicate areas of permanent nerve damage
- T1 gadolinium-enhanced lesions – hyperintense (bright) areas that indicate areas of active inflammation
- T2 lesions - show overall disease burden or lesion load (meaning the total number of lesions, both old and new)

The most recent and widely-used set of criteria used in the diagnosis of MS are the McDonald criteria (Table 3), published by the International Panel on the Diagnosis of

MS.(64) For a diagnosis of MS, the McDonald criteria minimally require evidence of disease dissemination in space (DIS; i.e. lesion formation across multiple regions of the CNS) as well as disease dissemination in time (DIT; i.e. new lesions appearing over time).(64, 67, 68)

In 2017, McDonald criteria were updated from the previous 2010 version; the key differences between the 2010 and 2017 versions are:

- The 2017 version allows symptomatic lesions to be used as criteria for DIS and DIT.(64)
- The 2017 version allows the detection of MS-related immunoglobulins in cerebrospinal fluid, called oligoclonal bands (OCBs), to substitute for clinical or MRI evidence of DIT.(64)

Table 3: McDonald criteria for the diagnosis of RMS (2017)(64)

DIS evidence (any one of the following)	DIT evidence (any one of the following)
• ≥2 lesions with objective clinical evidence[a] • 1 lesion + historical objective evidence[a] of previous attack involving a lesion in a different CNS region • ≥1 T2-hyperintense lesions in at least 2 of the following CNS regions: periventricular, cortical, juxtacortical, infratentorial, spinal cord	• ≥2 attacks/relapses (including the initial CIS) • Gadolinium-enhancing and non-enhancing lesions observed simultaneously on T1 scan • Appearance of new T2-hyperintense or gadolinium-enhancing T1 lesions on follow-up MRI (relative to baseline, irrespective of time interval) • Intrathecal OCBs demonstrated as specific to CSF[b]

[a]Objective clinical evidence refers to abnormalities in imaging, neurophysiological tests, or other examinations that suggest a lesion in a CNS area that corresponds with the anatomical location(s) of the CIS
[b]CSF-specific OCBs are not formally evidence of DIT, but can substitute for DIT in patients with a typical CIS who satisfy the criteria for DIS.
CIS = clinically isolated syndrome; CNS = central nervous system; CSF = cerebrospinal fluid; DIS = dissemination in space; DIT = dissemination in time; MRI = magnetic resonance imaging; OCB = oligoclonal band; RMS = relapsing multiple sclerosis.

B.1.3.1.4 MS Classification

Four phenotypes of MS were formally defined by the international MS Phenotype Group in 2013 (described in Table 4):(54)

- clinically isolated syndrome (CIS),
- primary progressive MS (PPMS),
- RRMS
- secondary progressive MS (SPMS).

CIS describes an initial clinical episode with signs and symptoms suggestive of MS that has the potential to evolve into RRMS if left untreated; however, not all patients with CIS experience a second episode confirming clinically definite MS.

The general category of RMS is made up of two forms of MS: RRMS and SPMS.(69, 70) RRMS is the most common phenotype of MS and occurs in about 85% of all cases of MS at onset.(16, 20, 64) RRMS is characterised by recurrent inflammatory attacks within the central nervous system (CNS) leading to demyelination (when the myelin or insulating material is worn away nerves start to deteriorate), axonal loss (the axon is a component of a nerve and sends messages between neurons, axonal loss slows down the ability for messages to be sent) and progressive neuronal degeneration (the loss of structure or function of neurons, including their death). (19, 20) This results in symptomatic relapses lasting days to months, followed by partial or complete periods of remission during which disease activity may not be symptomatically apparent but may nevertheless continue at a low level.(20, 71, 72) RRMS tends to progress to SPMS within 10 to 15 years (though some variation can be observed), as the disease evolves from a relapsing to a progressive course, characterised by gradual and irreversible worsening of neurologic function and disability without intermittent recovery.(20, 54, 73-76)

Table 4: Phenotypes in MS(16, 20, 26, 39, 54, 64, 77)

Classification	Description	Progression pattern
Clinically isolated syndrome (CIS)	• An initial acute clinical episode with signs and symptoms that suggest inflammatory demyelination in a patient not known to have MS • If further attacks occur and MS is diagnosed, the CIS is referred to as the first MS attack • In contrast to other phenotypes, patients may recover fully without therapy or have some residual deficits	
Primary progressive MS (PPMS)	• Progressive accumulation of neurologic disability from disease onset • Occurs in up to 15% of cases at onset	
Relapsing-remitting MS (RRMS)	• A course of acute attacks with full or incomplete recovery and periods of relative stability between attacks • Over time, residual deficits accrue with each relapse, leading to increasing disability • Occurs in about 85% of cases at onset	
Secondary progressive MS (SPMS)	• Gradual and irreversible worsening following an initial RRMS disease course • About 80% of patients with RRMS develop SPMS with time • Most patients with RRMS progress to a SPMS course within 10 to 15 years	

MS = multiple sclerosis
Sources: Lublin 2014; Confavreux 2014; Miller 2012; Thompson 2018; Dobson 2018; MSIF Atlas 2013; Katz Sand 2015.(16, 20, 26, 39, 54, 64, 77)

B.1.3.1.5 Subtypes of RRMS

RRMS can be further subdivided based on relapse history and magnetic resonance imaging (MRI) outcomes as described below, with implications for treatment options particularly within the context of National Health Service England (NHSE) (described in Section B.1.3.2.1). (7) The definitions of RRMS subtypes are not universal and vary in the literature and in clinical trials in MS.(6-8, 21-23) In general, RRMS is assessed as "active" in patients who have relapses and/or who show new active lesions on MRI, while "highly active" disease is defined based on criteria such as breakthrough disease, disability progression, frequent relapse and presence of new lesions despite treatment with a first-line DMT .(7, 21, 23) The following definitions are used by NHSE to define RRMS subtypes based on clinical characteristics:(7)

- **Active RRMS**: ≤2 relapses in ≤2 years
- **Highly active RRMS**: an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.
- **Rapidly evolving severe (RES) RRMS:** ≥2 disabling relapses in 1 year and ≥1 gadolinium-enhancing (Gd+) lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.

Note: The definitions for highly active RRMS used in clinical trials have been broader than the NHSE definition, often overlapping with the NHSE definition of RES RRMS.(6, 8, 22)

B.1.3.1.6 Impact on Quality of Life

The experience of MS varies from patient to patient as symptoms are dependent on the location of inflammatory lesions in the CNS and can present as a range of abnormal sensory and visual symptoms to disruption of cognitive and motor function (as described in Section B.1.3.1.1). The chronic nature and ongoing symptoms of MS have considerable negative impacts on patients, affecting multiple aspects of their everyday life, from physical and mental health to the ability to work and socialise.(32, 78, 79) The HRQoL of patients with MS is worse than the general population and worsens as disease severity increases. Relapses, disability and symptoms such as pain and fatigue are all drivers of reduced quality of life in MS.(31, 80-86) MS also places a substantial burden on the family and caregivers of patients with MS, impacting their health-related quality of life (HRQoL).

Patients with RRMS usually experience multiple symptoms, all of which can have a varying impact on HRQoL.(87) In a survey of patients in the UK with active or highly active RRMS [redacted] conducted in October 2020 and commissioned by Janssen, the most frequently

reported symptoms with an impact on HRQoL included fatigue, unusual sensations, problems with walking and cognitive difficulties.(78)

A survey of UK Multiple Sclerosis Registry patients found that the mean EQ-5D health index (0.567±0.207) and EQ Visual Analogue Scale (VAS) health status (59.73±22.40) scores for patients with MS were considerably lower than UK population means (EQ-5D: 0.860; EQ-VAS: 82.48).(88) Similarly, an observational study of patients with MS from 2015 to 2016 (N=16,808) in 16 European countries, including the UK, reported that Expanded Disability Status Scale (EDSS) score (used to measure neurological disability) was a major driver of EQ-5D utility score ($p<0.001$), with the reported severity of problems in the EQ-5D domains rising with disease severity.(31)

For those with uncontrolled disease, experiencing a relapse is associated with reduced HRQoL in MS.(80) An analysis of health utilities in patients with MS (N=1,441) based on data from a longitudinal, prospective cohort study in the UK demonstrated that patients who relapsed had lower EQ-5D and six-dimension Short Form Health Survey (SF-6D) utility scores than patients with no relapses in the prior 6 months (mean EQ-5D scores: 0.534 vs. 0.610; mean SF-6D scores: 0.597 vs. 0.649). (80) The largest decreases in utility scores were observed in patients with higher numbers of relapses, relapses lasting ~48 hours or ≤1 week, and relapses that limited everyday activities or resulted in hospital admission. (80)

Impact of symptoms on HRQoL

HRQoL in MS is also affected by specific symptoms such as pain and fatigue which are commonly reported by patients. Both neuropathic and nociceptive pain are prevalent symptoms of MS with a pervasive effect on HRQoL throughout the course of the disease.(89) A cross-sectional study of patients with MS in the Netherlands (N=94) demonstrated that depression and anxiety were significantly associated with pain intensity and pain affect (both $p<0.02$).(90)

Fatigue is a common symptom affecting the vast majority of patients with MS, with a considerable impact on quality of life, mental health and cognition.(78, 81-86) Fatigue also correlates with increased depression, cognition problems, pain and sleep problems.(91-95)

A cross-sectional study of survey data collected in patients with MS in the UK (N=779) found that fatigue and cognitive difficulties were an issue for a majority of patients, as 96% of patients in the study reported experiencing fatigue and 72% reported cognitive difficulties.(79)

In the Janssen commissioned survey, [redacted] of patients experienced MS-related fatigue occasionally, [redacted] experienced fatigue daily and [redacted] experienced fatigue continuously.(78)

The majority of patients [redacted] reported that fatigue had either a moderate or severe effect on their HRQoL.(78) Fatigue also impacted patients' ability to work [redacted] of patients whose fatigue had a severe impact on their HRQoL worked full time.(78) [redacted] patients with RRMS [redacted] reported that fatigue makes other MS symptoms harder to cope with, with cognitive impacts being highlighted in particular by the majority of patients.(78)

According to a discrete choice experiment based on a 2018 survey of 201 patients with RMS from the UK, US, Poland and Russia, most respondents placed high value in improving cognitive and physical fatigue, even if it meant an increase in relapses or a decrease in time to disease progression.(96)

Impact of MS on caregivers

Caregivers of patients with RRMS also experience substantial burden in terms of physical and psychological strain, increasing with patient disability.

A multicentre study in the Netherlands of 173 patients with RRMS and their caregivers found that increased caregiver strain was strongly correlated with lower cognitive functioning and greater neuropsychiatric and fatigue symptoms (including depression and anxiety) of patients with MS.(97) Strain included demands on caregiver time as well as physical and psychological strain.

In a multicentre, cross-sectional and observational study in Spain that included 180 patients with RRMS together with informal caregivers, 19% of all caregivers reported experiencing psychological burden as measured on the Zarit Caregiver Burden scale. (98) Predictors of caregiver burden included patient disability level, duration of time since the start of caregiving, and requirement of administering >1 medication:(98)

- For each increased point on EDSS score: odds ratio (OR) 1.56 (95% confidence interval [CI]: 1.21 to 2.02; *P*=0.0007)
- For each year since start of care: OR 1.11 (95% CI: 1.04 to 1.19; *P*=0.0016)
- ≥2 medications needing administration: OR 4.06 (95% CI: 1.23 to 13.47; *P*=0.02)

In addition, 21% of caregivers in the study were found to exhibit depressive symptoms as measured on the 7-item Centre for Epidemiologic Studies Depression (CESD-7) scale, which correlated with increased patient age and greater amount of caregiving time required.(98)

In the Janssen commissioned survey of patients in the UK with active or highly active RRMS, [redacted] of patients reported needing care or support related to MS.(78) Among patients

who experienced fatigue with a moderate or severe effect on their HRQoL, [redacted] required support.(78)

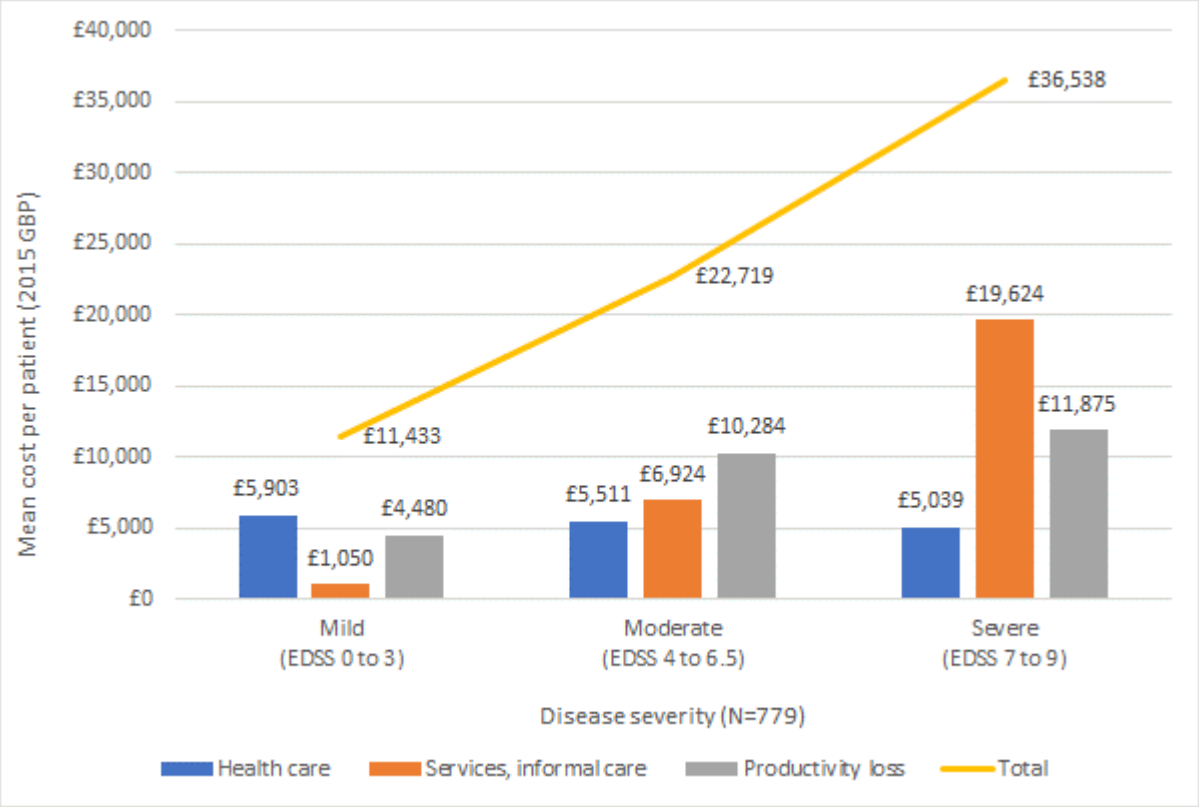
B.1.3.1.7 Economic burden of MS

The economic burden of MS is substantial and estimated at £1.4 billion per year, driven in part as a result of the increased healthcare resource use and associated direct costs incurred with relapses. (36, 79, 99, 100) A cost of illness survey of patients (N=537; 60% with relapsing-remitting MS) in the UK Multiple Sclerosis Register revealed medical cost of £3,229 per patient per annum and non-medical cost of £939 per patient per annum (2018 British pounds [GBP]).(100) Key components of medical costs were outpatient visits (£904 per patient per annum), consultations (£825) and unplanned hospital admissions (£753).(100) Home adaptations, to accommodate for reduced mobility, comprised the majority of non-medical costs.(100) Further, 75% of these non-medical costs were reported as being borne by patients themselves.(100) The survey also found that both groups of costs increased significantly as patient reported disability also increased ($p<0.001$ for both).(100) When the cohort was stratified by treatment paradigm (16% were receiving DMT at the time of the survey), it was shown that the combined costs incurred by patients receiving DMTs was £781 per patient per annum as opposed to £1,935 in those not known to be taking DMTs.(100)

MS also incurs considerable indirect costs due to the frequent need for informal caregiving, as well as productivity losses in a patient population commonly affected during prime employment years.(31, 37) In a cross-sectional study of survey data collected in the UK as part of the European-wide study described by Kobelt et al(31), 84% of employed patients reported that MS affected their productivity at work.(79) Fatigue and cognitive difficulties contributed to decreased productivity, as these were considered the most bothersome symptoms by employed patients.(79) Approximately a fifth (22%) of patients required sick leave in the previous 3 months (mean duration 9.2 days) which was largely attributed to relapses.(79)

The study found that the costs of informal care and productivity losses increased substantially with disease severity (Figure 1).(79) Relapses led to increases in all costs, particularly informal care costs, incurring an average of £792 (over 3 months) per patient with mild disease (EDSS 0 to 3; n=450).(79)

Figure 1: Annual per patient cost of MS in the UK by disease severity



Health care costs: Inpatient, day admission, consultations, tests, medications and DMTs; Services and informal care costs: Community services, investments and informal care; Productivity loss: Work absence, invalidity and early retirement.
DMT = disease modifying treatment; EDSS = Expanded Disability Status Scale; GBP = British Pound.

Source: Thompson 2017.(79)

B.1.3.1.8 Outcome measures in MS

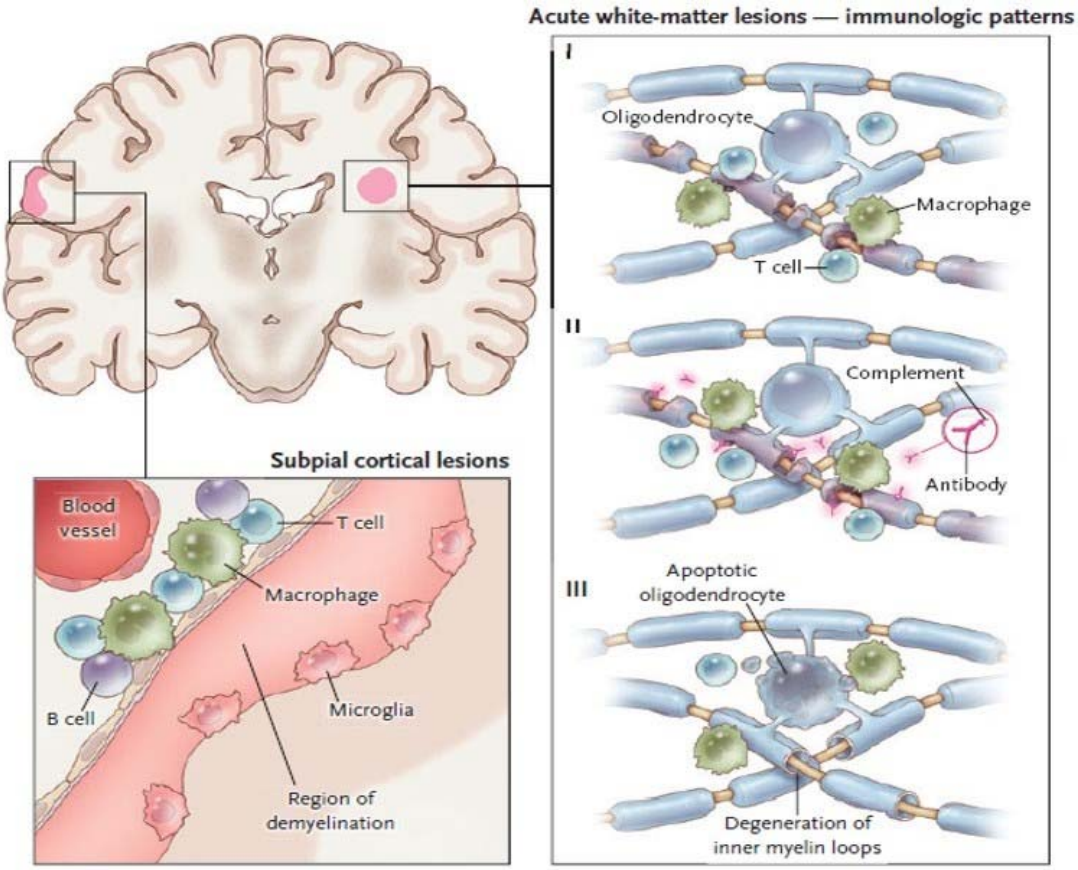
Measurement of disease activity

The frequency of MS relapses is indicative of disease activity and a prognostic factor for disability progression; therefore, reducing the number and severity of relapses is a key goal in MS treatment.(23, 33-35) Annualised relapse rate (ARR) is a measure commonly used in clinical trials to report the number of relapses per patient-year in a cohort, in order to assess the impact of treatment on frequency of relapses.(101)

Even when no relapses are apparent, new/enlarging MRI lesions due to inflammation may be developing in the CNS, leading to demyelination in the grey matter contributing to physical and cognitive impairment, as well as white matter likely contributing to disability progression (Figure 2).(20, 102-105)The International MS Phenotype group recommends MRI assessments to be performed on RMS patients at least annually to monitor for active RRMS.(54) Specifically, an increase in the number and volume of T2 hypersensitive lesions or the presence of Gd+ T1 lesions provide evidence of active RRMS.(54) Changes in the

number and total volume of T1-hypointense lesions are indicative of axonal loss and is associated with increased disability.(106)

Figure 2: Pathophysiology of demyelination and formation of MS lesions in the brain



MS = multiple sclerosis

Source: Adapted from Reich 2018.(102)

Measuring the presence of new/enlarging lesions on MRI and the cumulative number of combined unique active lesions (CUAL) allows monitoring of disease activity; the cumulative number of CUALs has been shown to be one of the most sensitive MRI outcome measures.(107, 108) The increasingly important treatment goal of “no evidence of disease activity” (NEDA) also uses the number and volume of lesions to describe the amount of disease activity in MS patients.(20, 35) The composite endpoint of NEDA-3 reports the absence of disease activity based on three commonly measured components (an absence of relapses, no EDSS progression and no new/enlarging T2 or Gd+ T1 lesions on MRI), but may also include a lack of brain atrophy (NEDA-4) or biomarkers (NEDA-5).(20, 41) NEDA-3 has been proposed as a principal aim in the management of RRMS as it leads to better long-term outcomes, with the composite endpoint having higher sensitivity than a single component measure, and better early prediction of long-term stability.(109, 110)

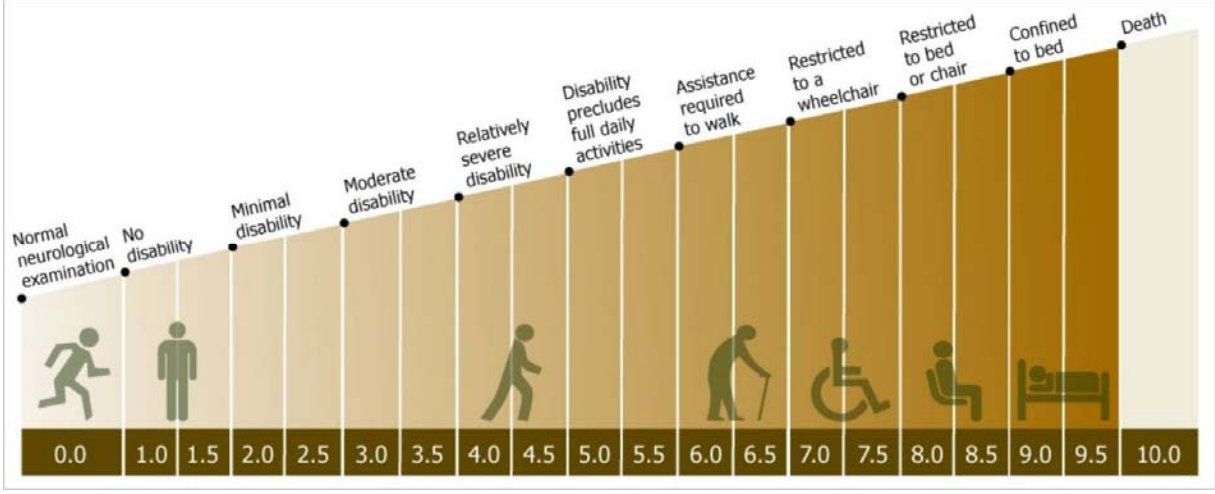
Radiologic assessment of brain atrophy or brain volume loss is also important in MS as it is associated with worsening disability and disease progression.(106, 111) While brain volume loss occurs naturally with aging, it is more extensive in MS and its acceleration is more pronounced with secondary and primary progressive disease.(112)

Clinical measures of disability

Accumulating neurological disability has a substantial negative impact on the HRQoL of patients with RRMS.(31, 113) Reducing long-term disability progression is one of the key goals of MS treatment and it is therefore necessary to assess patient disability using specific, reliable and sensitive tools.(113)

Disability during MS is commonly assessed using the EDSS, an instrument that assesses 8 neurological functional areas in addition to an ambulatory assessment to produce an EDSS score from 0 to 10 (0 representing a normal neurological exam, and 10 representing MS-related death; Figure 3).(114)

Figure 3: Expanded Disability Status Scale (EDSS) scores



SOURCE: Buzzard et al.(115)

In clinical trials, a wide range of endpoints have been used to evaluate disability progression – a systematic review of the RRMS literature suggests at least 12 disability measures have been employed in phase 3 clinical trials.(113) In the majority, worsening EDSS scores were utilised, though the manner and duration over which definitions were applied has also been shown to vary.(113) For example, previous studies have applied sustained disability progression over 3 months, defined as sustained changes to the EDSS for this same period and according to varying baseline EDSS thresholds.(51, 116) Regardless of these variations, EDSS remains a key disability outcome that is recommended by regulatory

authorities.(117) N.B., in the OPTIMUM trial of ponesimod, disability was captured via the assessment of time to 12-week and 24-week confirmed disability accumulation (CDA). Definitions are provided in Section B.2.3.

The Multiple Sclerosis Functional Composite (MSFC) is another clinical outcome measure used to assess physical and cognitive disability in patients with MS.(6) The MSFC has been validated and shown to correlate with EDSS scores as well as HRQoL in patients with MS.(113, 118) The MSFC Z-score is the mean of the Z-scores (standardised to a reference population) from the following clinical examinations: upper extremity function (9-HPT), lower extremity function (T25FW), and cognitive function (Paced Auditory Serial Addition Test [PASAT-3]).(6, 113)

Measurement of fatigue

Patient-reported outcome (PRO) instruments such as the Fatigue Severity Scale (FSS)(119) and Modified Fatigue Impact Scale (MFIS)(120) that have previously been used to assess fatigue in MS may not comprehensively measure MS fatigue symptoms as well as their impact. For example, the FSS does not include items relating to cognitive fatigue. Consequently, a new measure called the Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis (FSIQ-RMS) was developed as a comprehensive, valid and reliable measure of fatigue-related symptoms and impacts. The FSIQ-RMS consists of two domains:(6, 121)

- The FSIQ-RMS symptom domain (FSIQ-RMS-S) consists of 7 items assessing fatigue-related symptoms measured on an 11-point numeric rating scale: the total domain score ranges from 0 to 77 with a higher score indicating greater fatigue.
- The FSIQ-RMS impact domain (FSIQ-RMS-I) consists of 13 items assessing impacts of fatigue-related symptoms measured on a 5-point Likert scale, ranging from no impact to extreme impact: the total domain score ranges from 0 to 65 with a higher score indicating greater impact.

A detailed description of the symptoms and impacts measured by the FSIQ-RMS is provided in Appendix E.3.

B.1.3.2 MS Treatment Pathway

B.1.3.2.1 Current treatments for MS

There is no curative therapy for MS, but a number of treatments that can improve symptoms and the course of the disease are available, including DMTs.(19, 20) The key objectives of

MS treatments are to reduce the number and severity of relapses, decrease disease activity, slow disease progression and delay disability, manage common symptoms such as fatigue and improve overall quality of life.(34, 35, 38) A wide range of treatment options are needed for MS due to the disease's heterogeneous clinical presentation, unpredictable progression course, and individual variability in patient treatment response and tolerability.(20, 39, 40)

DMTs vary by specific indication and by route of administration, as outlined in Table 5 and Table 6. Further, DMTs have different benefit-risk profiles, which need to be considered for individual patient needs (see Section B.1.3.2.2). While DMTs are recommended in all patients with active RRMS, no recommendations are provided on the preferred first- and second-line therapy.(7, 122)

Currently available DMTs for MS can generally be grouped into one of the five categories listed below. Of these, fingolimod, an S1P modulator, is only available for highly active RRMS: (45, 51, 53, 123-130)

1) Injectables: including all doses of interferon beta 1-a, peginterferon beta 1-a, interferon beta 1-b and glatiramer acetate.
2) Oral sphingosine 1-phosphate (S1P) modulators (immunosuppressant): fingolimod
3) Other oral agents: including dimethyl fumarate and teriflunomide
4) Monoclonal antibodies (mAbs): including ocrelizumab, alemtuzumab, and natalizumab
5) Antineoplastic (chemotherapy) agents: cladribine

DMTs for MS vary by specific indication and by route of administration, including intramuscular injection, subcutaneous injection, intravenous infusion, and oral administration. DMT’s also differ in terms of how they are used in a treatment strategy—that is, whether they are used for maintenance/escalation therapy on a chronic basis or for immune reconstitution on short term basis: (20, 64)

- Maintenance and escalation therapies can be immunomodulatory or immunosuppressive
    - Interferon-beta (1a and 1b), glatiramer acetate, and teriflunomide are generally considered immunomodulatory
    - Fingolimod, natalizumab, dimethyl fumarate, and ocrelizumab are generally considered immunosuppressive (plus ponesimod)
- Immune reconstitution therapies may be selective or non-selective for the adaptive (or specific) or innate (or non-specific) immune systems:
    - Alemtuzumab affects both the adaptive and innate immune systems
    - Cladribine has selective effects on the adaptive immune system

Table 5: Overview of relevant comparators for ponesimod in active RRMS

DMT (Brand name)	Mode of administration	NICE ID	NICE Recommendation
Teriflunomide (AUBAGIO®)(131)	Oral	TA303	Teriflunomide is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if they do not have highly active or RES-RRMS
Dimethyl fumarate (TECFIDERA)(132)	Oral	TA320	Dimethyl fumarate is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if they do not have highly active or RES-RRMS
Glatiramer acetate (COPAXONE®)(133)	Injectable	TA527	Glatiramer acetate is recommended as an option for treating multiple sclerosis, only if the person has RRMS
Interferon beta-1a (AVONEX®)(133)	Injectable	TA527	IFN beta-1a is recommended as an option for treating RRMS
Interferon beta-1a (REBIF®)(133)	Injectable		
Interferon beta-1b (EXTAVIA®)(133)	Injectable	TA527	IFN beta-1b is recommended as an option for treating MS in patients with RRMS who have had 2 or more relapses within the last 2 years or with SPMS with continuing relapses
Ocrelizumab (OCREVUS®)(134)	Infusion	TA533	Ocrelizumab is recommended as an option for treating RRMS in adults with active RRMS defined by clinical or imaging features when alemtuzumab is contraindicated or otherwise unsuitable
Peginterferon beta-1a (PLEGRIDY®)(135)	Injectable	TA624	Peginterferon beta-1a is recommended, within its marketing authorisation, as an option for treating RRMS in adults.

DMT = disease-modifying therapy; ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; MRI = magnetic resonance imaging; MS = multiple sclerosis; NICE = National Institute for Clinical Excellence; QALY = quality-adjusted life year; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis.

Table 6: Overview of relevant comparators for ponesimod in highly active RRMS

DMT (Brand name)	Mode of administration	NICE ID	NICE Recommendation
Fingolimod (GILENYA®)(136)	Oral	TA254	Fingolimod is recommended as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.
Alemtuzumab* (LEMTRADA®)(137)	Infusion	TA312	Alemtuzumab is recommended as an option, within its marketing authorisation, for treating highly active RRMS in adults with highly active RRMS despite a full and adequate course of treatment with at least 1 DMT or in adults with RES RRMS defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.

Cladribine (MAVENCLAD®)(138)	Oral	TA616	Cladribine is recommended as an option for treating highly active multiple sclerosis in adults, only if the person has: • rapidly evolving severe relapsing–remitting multiple sclerosis, that is with at least: • 2 relapses in the previous year and • 1 T1 gadolinium-enhancing lesion at baseline MRI or a significant increase in T2-lesion load compared with a previous MRI, or • relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.
Ocrelizumab (OCREVUS®)(134)	Infusion	TA533	Ocrelizumab is recommended as an option for treating RRMS in adults with active RRMS defined by clinical or imaging features when alemtuzumab is contraindicated or otherwise unsuitable

* A European Medicines Agency safety review in November 2019 resulted in a change to the marketing authorisation indication for alemtuzumab with new warnings and precautions for use. As a result, NICE updated Sections 1 and 2 of TA312 regarding alemtuzumab in March 2020 restricting its use.
Note: RES is defined by ≥2 disabling relapses in 1 year, and ≥1 gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.

The choice of therapy for RRMS is dependent on disease activity, with some treatments only being recommended for patients with highly active RRMS (Table 6). Guidelines from the Association of British Neurologists (ABN) recommend considering DMT in all patients with active RRMS (Table 7); however, given the heterogeneous nature of the disease, no specific recommendations are provided on the preferred first- and second-line therapy, ultimately leaving the treatment decision to physicians and patients.(122, 139)

The choice of MS treatment is generally discussed with the patient, considering their treatment preferences.(140, 141) Several studies have shown that patients with MS prefer oral versus non-oral administration, particularly when oral drugs can be taken once daily.(42-44)

Table 7: ABN* guidelines on the use of DMTs for treating RRMS(122, 139)

Starting DMTs in RRMS	• All patients with active RRMS should be considered for DMT • **First-line for most patients:** IFN beta, PEG-IFN beta, GA, teriflunomide, DMF, or fingolimod (termed category 1 agents); ocrelizumab◊ • **First-line for patient with high disease activity:** natalizumab or alemtuzumab (termed category 2 agents); ocrelizumab (if a patient needs a high-efficacy drug and are not eligible for natalizumab)
Switching DMTs in RRMS	• **Risk-averse patients or those with less disease activity:** switch to another category 1 agent (IFN beta, PEG-IFN beta, GA, teriflunomide, DMF, or fingolimod‡); ocrelizumab • **High-disease activity with first-line agent:** category 2 agent (natalizumab or alemtuzumab†); ocrelizumab
Stopping DMTs in RRMS	• Consider stopping if significant AEs or development of SPMS • While a woman is trying to conceive and during pregnancy

	• All injectables and oral medications should be paused, and infusions should be delayed in cases of MS and severe COVID-19

ABN = Association of British Neurologists AE = adverse event; DMF = dimethyl fumarate; DMT = disease-modifying therapy; GA = glatiramer acetate; IFN = interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

*N.B. ABN guidelines were updated in 2020 the context of the ongoing SARS-CoV-2 pandemic. As a result, while recommended, ocrelizumab is not referred to as 'category 1 or category 2'

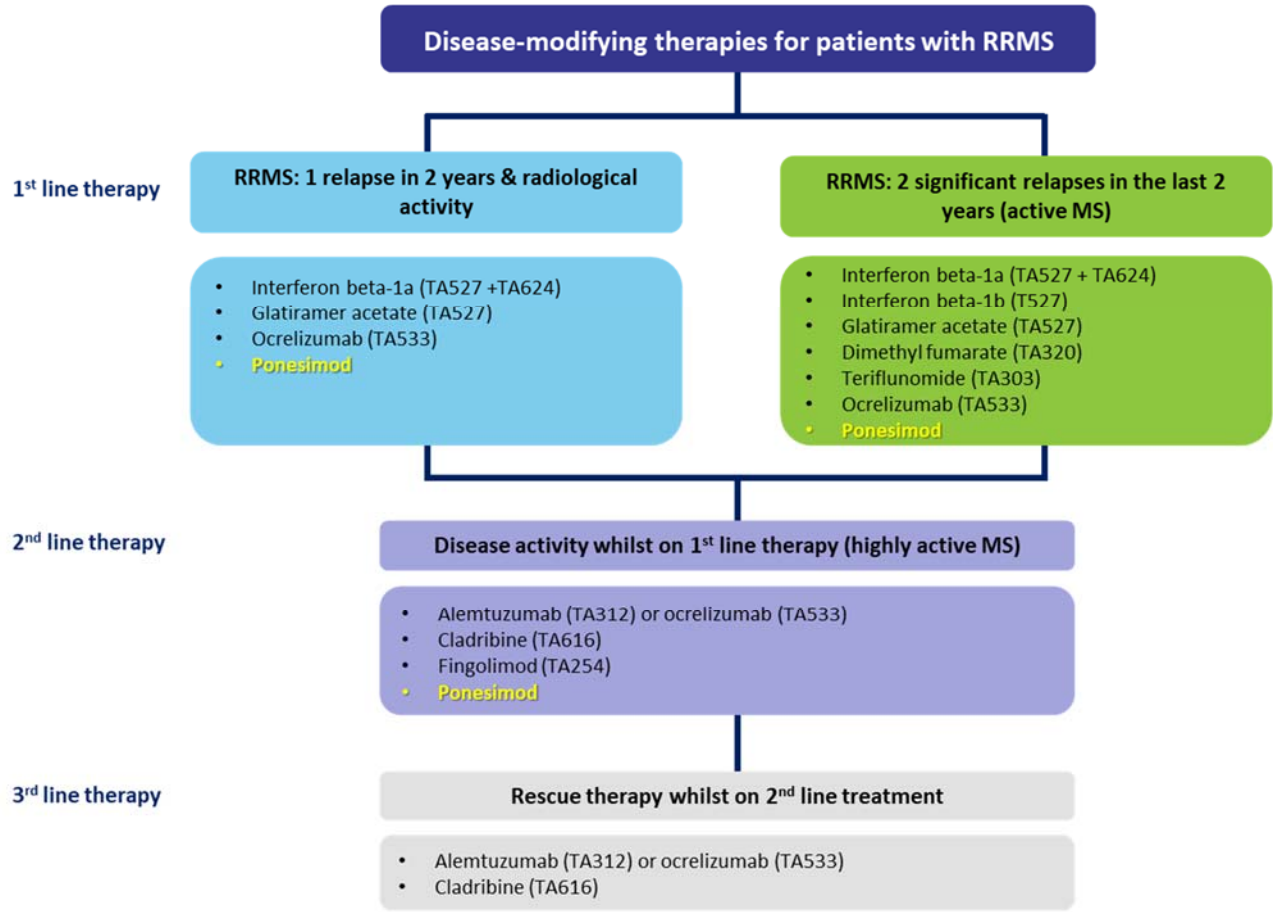
◊ For those already on ocrelizumab, the ABN recommend delaying further infusions until the risk of coronavirus infection is clarified or has passed.

‡ For those with disease breakthrough on first-line therapies, fingolimod has the advantage over ocrelizumab of being able to be stopped in the event of a coronavirus infection

† As the risk of viral infections is significantly higher in the 3 to 6 months after alemtuzumab (and cladribine), treatment should not be started during the coronavirus epidemic

The NHSE guidance on treatment of RRMS, along with the proposed positioning of ponesimod, is shown in Figure 4.

Figure 4: NHSE treatment algorithm for DMTs in RRMS with proposed positioning of ponesimod (yellow)



N.B. the most recent version of the NHSE treatment algorithm (updated in March 2019) does not reflect revisions required following a European Medicines Agency safety review in November 2019 that resulted in a change to the marketing authorisation indication for alemtuzumab with new warnings and precautions for use.
Note: Treatments for RES MS are not shown.
DMT = disease modifying treatment; JCV = John Cunningham Virus; IFN = interferon; MS = multiple sclerosis; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis.
Adapted from: NHSE 2019(7)

B.1.3.2.2 Limitations of current treatment options

A wide range of treatment options are needed for MS due to the disease's heterogeneous clinical presentation, unpredictable progression course, and individual variability in patient treatment response and tolerability.(20, 39, 40) While there are several treatment options available for patients with RRMS, each treatment is associated with particular limitations, including issues such as safety, efficacy, convenience of administration and contraindications as summarised in Table 8.(19)

Table 8: Key limitations of relevant comparators for ponesimod in MS

DMT	Key limitations
Oral treatments	
Cladribine(130)	• Contraindicated for use in patients with chronic infection, active malignancy, moderate or severe renal impairment and in immunocompromised patients • Treatment is associated with a risk of lymphopenia that can persist for up to 9 months
Dimethyl fumarate(123, 124)	• Regular monitoring for AEs required • Treatment is associated with a risk of PML, which can be serious or fatal in some cases
Fingolimod(51, 124)	• Regular monitoring for AEs required, and cardiac monitoring required at treatment initiation and interruption • Treatment is associated with a risk of PML, which can be serious or fatal in some cases • Contraindicated for use in patients with severe hepatic impairment • Should not be co-administered with St. John's Wort and caution is advised when co-administering with other CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin and efavirenz) or CYP3A4 inhibitors (protease inhibitors, azole antifungals and some macrolides) due to potential risk of reduced efficacy • Return of disease activity (rebound) after fingolimod discontinuation • A 6-week therapy-free interval is required to clear fingolimod from the circulation when stopping treatment. Lymphocyte counts return to a normal range within 1-2 months of stopping therapy in most patients; full recovery can take considerably longer in some patients. Starting other therapies during this interval will result in concomitant exposure to fingolimod.
Teriflunomide(45)	• Contraindicated for use in patients with severe hepatic impairment • A slow elimination rate of up to 2 years can impact on ability to switch to subsequent treatments and on unplanned pregnancies
Injectable treatments	
Glatiramer acetate(125, 126)	• Injection-site reactions can lead to non-adherence
IFN beta-1a, IFN beta-1b and peginterferon beta-1a(124-129)	• Regular monitoring for AEs required • Injection-site reactions can lead to non-adherence

DMT	Key limitations
	• Associated with the development of neutralising antibodies, which can reduce treatment effectiveness to variable degrees in individual patients • Contraindicated for use in patients with severe hepatic impairment • Has warnings for the risk of depression, suicidal ideation, and/or psychosis and use may be avoided in patients with a history of depression • May interact with medicinal products with a narrow therapeutic index that are dependent on the hepatic cytochrome P450 system for clearance, e.g., antiepileptics and some antidepressants
Infusion mAbs	
Alemtuzumab(19, 53, 124-126)	• Regular monitoring for AEs required • Injection-site reactions can lead to non-adherence • Treatment is associated with a risk of PML, which can be serious or fatal in some cases • Treatment is associated with the development of neutralising antibodies which can reduce treatment effectiveness to variable degrees in individual patients • Treatment can cause severe autoimmune-related side effects and infections
Ocrelizumab(52, 125, 126)	• Contraindicated for use in patients in a severely immunocompromised state or with known active malignancy

AE = adverse event; DMT = disease-modifying therapy; IFN = interferon, mAbs = monoclonal antibodies; PML = progressive multifocal leukoencephalopathy.

Given the chronic nature of the disease, tolerability and convenience are important aspects of MS treatment. In general, DMTs with lower efficacy, such as interferons, are associated with less severe adverse effects, whereas highly active drugs, such as mAbs, are often associated with more serious safety issues.(19, 41) Highly active drugs are generally reserved for patients with particularly aggressive disease, or who opt for more effective treatment, while other patients may choose to be sub-optimally treated with more tolerable agents with lower efficacy.(41, 142)

Patient preferences for convenience of administration are also considered when making treatment decisions in order to optimise treatment adherence.(140) Many of the currently available treatments for RRMS require IV infusion or injections (Table 5), while patients with MS have been found to prefer oral treatment administration.(42-44) The long half-life and prolonged impact on lymphocyte levels of oral DMTs can also be a challenge for vaccinations and family planning, or when considering treatment discontinuation and switching.(45) As an oral treatment with rapidly reversible immunosuppressive effects, ponesimod offers flexibility during the ongoing COVID-19 pandemic, allowing people with MS to manage their treatments without worry of routine hospital appointments for infusion or additional monitoring, as is the case for some DMTs(50-53)

Patients with MS typically require symptomatic treatments in addition to DMTs to ameliorate the many symptoms resulting from nervous system damage caused by MS.(20, 38, 143). Potential drug-drug interactions (DDIs) with currently available DMTs such as fingolimod can make selecting a treatment more challenging. [41,121]

In addition to efficacy, safety and convenience, patients with MS place considerable value on the management of fatigue as part of their treatment. In a survey of patients in the UK with active or highly active RRMS ([redacted]) conducted in 2020, [redacted] of patients reported that they would like new treatments for MS to be available that managed fatigue.(78) Existing treatments for RRMS have not been assessed in randomised controlled trials (RCT) in terms of their impact on fatigue.

B.1.3.2.3 Unmet need for ponesimod in RRMS

There remains an unmet need for a convenient efficacious treatment for delaying relapse in patients with MS while having proven long-term safety and managing disease symptoms. Current treatment options leave patients with a choice between optimising either efficacy or safety. Clinical experts in the UK highlighted the need for a first-line treatment option for active RRMS with a balanced safety profile and moderate efficacy.(141) Additionally, clinicians noted the importance of long-term safety and reduced monitoring burden in MS treatment, given the chronic nature of the disease.

Ponesimod provides a new treatment option, with significantly greater reduction in the frequency of relapses compared with teriflunomide (30.5% reduction), while having a favourable tolerability profile and high treatment persistence demonstrated up to 9 years of follow-up. Results from a network meta-analysis (NMA) indicate that in people with RRMS, ponesimod has a [redacted] probability of reducing the frequency of relapses compared with [redacted] while having [redacted] (Section B.2.9). Ponesimod also compared favourably against [redacted] with regards to 3-month and 6-month disability progression, ranking [redacted] than [redacted] Currently, there is no approved S1P modulator available as a treatment option for active RRMS; if approved by NICE, ponesimod could address this unmet need. Additionally, if approved for highly active RRMS, ponesimod would be the second S1P modulator used as maintenance therapy for highly active RRMS and provide an alternative to fingolimod. The potential for DDIs with ponesimod is low because it has no active metabolites.(46) Treatment with ponesimod is convenient due to once-daily oral dosing and no further monitoring requirements compared with available treatments. Unlike

some other treatments for MS (Table 8), ponesimod has transient effects on lymphocytes. After stopping treatment with ponesimod, lymphocyte counts return to baseline in up to seven days.(142) The short half-life of ponesimod also facilitates responsiveness to unplanned events such as infection, pregnancy and vaccination, particularly within the context of the ongoing COVID-19 pandemic, as well as facilitating rapid switches to subsequent therapies,.(12) In contrast, fingolimod (currently the only recommended S1P inhibitor) can take as long as 2 months to be cleared from the body.(144)

Overall, ponesimod has the potential to be the first NICE-recommended S1P modulator for patients with active RRMS and provide a safer alternative to existing DMTs for patients with highly active RRMS, meeting the unmet needs in the current treatment landscape. In active RRMS, patients selecting DMTs with moderate efficacy such as teriflunomide and dimethyl fumarate are likely to be most appropriate comparators for ponesimod, while in highly active RRMS patients who would receive fingolimod are most likely to receive ponesimod, since it is the most relevant highly active comparator.

B.1.4 Equality considerations

No equity issues are expected for ponesimod in patients with relapsing MS. However, as previously noted, MS is a disease that disproportionally affects more women than men.(63)

B.2 Clinical effectiveness

Clinical effectiveness summary

- The key clinical evidence for patients with RRMS for this submission is based on the OPTIMUM trial, a randomised, double-blind, parallel-group, global phase 3 superiority study of ponesimod vs. teriflunomide (N=1,133; Sections B.2.1-B.2.7)
- Additional data on the efficacy and safety of ponesimod in RRMS are available from two phase 2 studies (AC-058B201 and AC-058B202) and a phase 3 extension study of the OPTIMUM trial (OPTIMUM-LT) (Section B.2.12)
- In the pivotal phase 3 OPTIMUM trial:
    - Ponesimod demonstrated a clinically meaningful, statistically significant and robust reduction in relapse rates, as measured by annualised relapse rate (ARR), compared with another oral MS treatment, teriflunomide (0.202 vs. 0.290, respectively; 30.5% reduction, p=0.0003).(46, 145)
    - Treatment with ponesimod numerically decreased the risk of disability progression compared with teriflunomide, as measured by 12- and 24-week confirmed disability accumulation (CDA), by 17% and 16%, respectively (12-week CDA: 10.1% vs. 12.4%; 24-week CDA: 8.1% vs. 9.9%, respectively).(46) The differences were not statistically significant, but the study was not powered for these endpoints.(6)
    - Ponesimod significantly reduced the cumulative number of combined unique active lesions (CUAL) indicative of disease activity and progression by 56% compared with teriflunomide (1.405 vs. 3.164, respectively; p<0.0001).(46, 54, 106, 145)
    - OPTIMUM is the first study to implement a validated disease-specific fatigue measure as a prespecified endpoint, which suggested that ponesimod is the first DMT to demonstrate stabilisation of fatigue symptoms when compared with another oral DMT (LS mean change from baseline: −0.01 vs. 3.56, respectively; mean difference −3.57; p=0.0019).(46, 47)
    - Exploratory analyses of Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC)-Z scores suggest a lower risk of disability worsening and a benefit on physical and cognitive impairment with ponesimod versus teriflunomide, sustained through week 108 of the trial.(6, 47)
    - Ponesimod improved the proportion of patients achieving a disease-free state compared with teriflunomide, described by an absence of relapses and disease activity, as measured by “no evidence of disease activity” (NEDA)-3 and NEDA-4.(6)
    - Exploratory analyses of magnetic resonance imagining (MRI)-based endpoints consistently demonstrated benefits with ponesimod over teriflunomide in terms of reducing brain volume loss and the appearance of new or enlarging lesions in the brain caused by MS.(6) Brain atrophy occurred in a smaller proportion of patients in the ponesimod group ([redacted]) compared with the teriflunomide group (42%).(5)
    - Safety results were consistent with previous observations in phase 2 trials as well as with other sphingosine-1-phosphate (S1P) functional antagonists.(6)
    - Patients receiving ponesimod experienced a similar proportion of treatment-emergent adverse events (TEAEs; 88.8% vs. 88.2%) or serious adverse events (SAEs; 8.7% vs. 8.1%) compared with teriflunomide, respectively.(46)
- A pooled safety analysis of ponesimod data from phase 2 and 3 trials (n=1,148) indicates that most TEAEs with ponesimod are mild or moderate in severity, with no cases of progressive multifocal leukoencephalopathy (PML) reported.(47)
- In the double-blind long-term phase 2 extension study, treatment persistence was reported in 61% of patients over 9 years of follow-up.(46, 47, 49)

- Although the extension study was not powered to test ARR or disability, there was a trend toward improvement with ponesimod treatment.
    - The mean estimate of ARR for confirmed relapses using the ponesimod analysis set up to the end of AP3 for the 20 mg dose group was [redacted]).
    - The Kaplan-Meier estimate for the percentage of subjects in the ponesimod 20 mg dose group who had experienced a 24-week CDA at Week 432 was [redacted])

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant RCTs describing efficacy and safety of ponesimod and comparator treatments for RMS. Broadening of the scope beyond RRMS allowed identification of all studies that may have evaluated RRMS patients as a subset of a larger population. The literature search was conducted in May 2020 and updated in October 2020 and finally in January 2021. Details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix D.3.

B.2.2 List of relevant ponesimod clinical effectiveness evidence

The key clinical evidence for this submission was generated during the OPTIMUM (AC-058B301) trial, a randomised, double-blind, active-controlled, parallel-group, global phase 3 superiority study to compare the efficacy of ponesimod with that of teriflunomide in patients with RMS(46) (Table 9).

Table 9: Clinical Effectiveness Evidence(6)

<table>
<tr><td>Study</td><td colspan="5">OPTIMUM (AC-058B301)</td></tr>
<tr><td>Study design</td><td colspan="5">A randomised, double-blind, active-controlled, parallel-group, global phase 3 superiority study of ponesimod vs. teriflunomide in patients with RMS</td></tr>
<tr><td>Population</td><td colspan="5">Adult patients (age 18 to 55 years) with RMS (N=1,133)</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Ponesimod 20 mg once daily over a 108-week treatment period</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Teriflunomide 14 mg once daily over a 108-week treatment period</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Most relevant clinical evidence for the efficacy of ponesimod vs. a relevant active comparator</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• ARR
• Time to first confirmed relapse
• Change from baseline in EDSS score
• 12-week CDA
• 24-week CDA
• Change from baseline in FSIQ-RMS score</td></tr>
</table>

	• CUAL • NEDA-3 • NEDA-4 • **Adverse effects of treatment** • Change from baseline in SF-36 score • Change from baseline in MSFC Z-score
All other reported outcomes	• MRI-based exploratory endpoints: Percent change in brain volume, number of Gd+ T1 lesions, number of new or enlarging T2 lesions, volume of MRI lesions, absence of lesions, proportion of Gd+ lesions at baseline evolving to persistent black holes • Absence of confirmed relapse, baseline to Week 60 and Week 108 • Other exploratory endpoints • Pharmacoeconomic endpoints • Pharmacokinetic and pharmacodynamic endpoints

ARR = annualised relapse rate; CDA = confirmed disability accumulation; CUAL = combined unique activity lesions; EDSS = Expanded Disability Status Scale; FSIQ-RMS = Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis; Gd+ = gadolinium enhancing; MACBETH = Measuring attractiveness by a categorical based evaluation technique; MSFC = Multiple Sclerosis Functional Composite; MTR = magnetization transfer ratio; NEDA = no evidence of disease activity; RMS = relapsing multiple sclerosis; SDMT = Symbol Digit Modalities Test; SF-36v2 = 36-Item Short Form Health Survey version 2; WPAI:MS = Work Productivity and Activity Impairment: Multiple Sclerosis

Note: All outcomes incorporated into the economic model are marked in **bold**.

Additional clinical evidence for ponesimod 20 mg, including long-term efficacy and safety data described in Section B.2.12, is available from two phase 2 trials (AC-058B201 and AC-058B202)(49, 142) and a phase 3 extension trial (OPTIMUM-LT, AC-058B303).(146)

- AC-058B201 was a randomised, double-blind, placebo-controlled, dose-finding phase 2b study to assess the efficacy, safety, and tolerability of ponesimod 10 mg, 20 mg, and 40 mg once daily (QD) in patients with RRMS.(142)
- AC-058B202 is an ongoing randomised, double-blind, multiple-dose, uncontrolled, parallel group extension study to assess the long-term safety, efficacy, and tolerability of ponesimod 10 mg, 20 mg, and 40 mg QD in patients with RRMS who have completed dose-finding study AC-058B201.(147)
    - As a single arm extension trial, AC-058B202 was not included in the NMA or economic model. However, as this study provides long-term efficacy and safety data for patients who were treated with ponesimod for up to 9 years, further details are provided in Section B.2.12.

- OPTIMUM-LT is an ongoing open-label, non-comparative, long-term extension study of OPTIMUM to assess the long-term safety, tolerability and efficacy of ponesimod 20 mg in patients with RMS.(146)
    - OPTIMUM-LT is an uncontrolled study and no hypotheses were pre-specified as all analyses are considered exploratory; OPTIMUM-LT is therefore not included in the NMA or economic model.(47, 146) Further details on this study are provided in Section B.2.12.

To determine whether any safety signals could be observed beyond those identified in individual studies, safety data from AC-058B201, AC-058B202, OPTIMUM and OPTIMUM-LT were included in a pooled safety analysis presented in Section B.2.10. Scientific advice indicating approval with the pooling strategy for summarising clinical safety of ponesimod was received from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use in February 2019. No pooling of efficacy data was performed between the phase 2 and phase 3 studies due to differences in study design, comparator, study duration, objectives, and primary endpoint.

B.2.2.1 Relevant clinical effectiveness studies identified by the SLR

In total, the SLR identified 53 eligible RCTs described across 329 records, including two trials for ponesimod (OPTIMUM and Study AC-B058B201 – data for these trials were provided directly by Janssen). Of these, 260 records were journal articles, conference abstracts, clinical study reports, or clinical trial registry records. Journal articles or conference abstracts that presented pooled trial data were excluded, unless comparable outcome data were unavailable for the respective individual trials, as was the case for 32 records. The remaining 69 included records were either regulatory or health technology assessment reports specific to the interventions of interest, which often reported relevant data for multiple eligible trials.

The PRISMA flow diagram for the selection of these studies is presented in Appendix D. See appendix D.3 for full details of the included comparative clinical evidence relevant to ponesimod in RRMS.

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

B.2.3.1 Overview of study design

OPTIMUM was a randomised, double-blind, parallel-group, global phase 3 superiority study of ponesimod vs. teriflunomide in patients with RMS.(145) A total of 1,133 patients were randomised 1:1 to receive either ponesimod 20mg or teriflunomide 14mg.(6) Randomisation was stratified by the use of MS DMT (yes, no) in the last 2 years prior to randomisation and by baseline EDSS score (≤3.5, >3.5).(6)

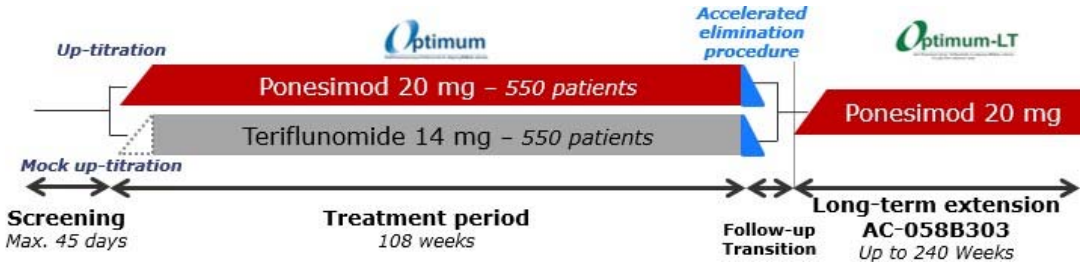
The study consisted of the following periods:(6)

- Screening Period (pre-randomisation): up to 45 days prior to randomisation and included Visit 1 (Screening) and Visit 2 (Baseline)
- Treatment Period (double-blind): from Day 1 until study treatment discontinuation or the scheduled end of treatment (EOT) at Week 108
- Follow-up Period (posttreatment): from the last dose of study treatment until the End-of-Study (EOS) Visit.

Patients who completed treatment until Week 108 were eligible for enrolment into a long-term extension study with open-label ponesimod (OPTIMUM-LT; AC-058B303). Patients who prematurely discontinued study treatment before Week 108 were entered into a post-treatment observation period that lasted from the last dose of the study drug until Week 108. For each study patient, the EOS Visit occurred at the completion of treatment, safety follow-up, and the post-treatment observation period, if applicable.(6)

An overview of the design of OPTIMUM is presented in Figure 5.

Figure 5: Overview of the OPTIMUM study design



Due to the slow elimination period of teriflunomide from plasma (mean = 8 months to reach plasma concentrations < 0.02 mg/L), all patients at EOT and subsequently entering the long-term extension study underwent an accelerated elimination procedure consisting of either of the following procedures: administration of cholestyramine 8 g three times a day (i.e., every 8 h) for 11 days. If cholestyramine 8 g three times a day was not well tolerated, cholestyramine 4 g three times a day was available: administration of 50 g oral activated charcoal two times a day (i.e., every 12 h) for 11 days.

Teriflunomide 14 mg was considered an appropriate comparator for ponesimod 20 mg due to its oral mode of administration as well as efficacy in terms of statistically significant reductions in relapse rates and disability versus placebo, as demonstrated in two pivotal studies.(116, 148) Furthermore, teriflunomide is recommended by NICE as a first-line treatment option for patients with RRMS (Section B.1.3.2.1).(131) Demonstration of superiority over teriflunomide 14 mg in terms of ARR is clinically relevant, as it provides evidence of significant benefit of a new investigational drug compared with an approved, effective, first-line oral therapy that has been shown to reduce relapse rate and accumulation of disability.

B.2.3.1.1 Study objectives

The primary objective of OPTIMUM was to evaluate the safety and efficacy of ponesimod compared with teriflunomide in reducing relapses in patients with RMS.(6)

The secondary objectives were to evaluate the effect of ponesimod on disability accumulation and other aspects of MS disease control, and to evaluate the safety and tolerability of ponesimod in patients with RMS.(6)

B.2.3.1.2 Patient eligibility

The inclusion and exclusion criteria for OPTIMUM are summarised in Table 10.

Table 10: OPTIMUM study inclusion and exclusion criteria(6, 149)

Inclusion criteria
• Patients aged 18 to 55 years • Patients with a diagnosis of RMS, as per revised McDonald Diagnostic Criteria for MS (2010) • Patients who have experienced any of the following: o ≥1 documented MS attacks within 12 months to 1 month prior to baseline EDSS assessment o ≥2 documented MS attacks within 24 months to 1 month prior to baseline EDSS assessment o ≥1 Gd+ lesions of the brain on an MRI within 6 months prior to baseline EDSS assessment • Treatment-naïve or previous treatment with IFN beta-1a, IFN beta-1b, glatiramer acetate, natalizumab, or dimethyl fumarate • Ambulatory and EDSS score of 0 to 5.5 at Screening (Visit 1) and Baseline (Visit 2) • Agreement with accelerated elimination procedure for teriflunomide after the last dose • Reliable contraception for women of childbearing potential and fertile men • Signed informed consent form prior to initiation of any study-mandated procedure
Exclusion criteria
• Pregnancy or breastfeeding, or wishing to parent a child during the study • Relapsed disease within 30 days of baseline EDSS assessment or between baseline EDSS assessment and randomisation • Primary progressive MS or progressive relapsing MS • Treatment with the following ≤7 days of randomisation:

- IFN beta-1a, IFN beta-1b, or glatiramer acetate

- Treatment with the following ≤15 days of randomisation:
  - Beta-blockers, diltiazem, verapamil, digoxin (or other anti-arrhythmic/heart rate lowering systemic therapy), cholestyramine, or activated charcoal
- Treatment with the following ≤30 days of randomisation:
  - Adrenocorticotropic hormone or systemic corticosteroids, dimethyl fumarate, live vaccines
- Treatment with the following ≤90 days of randomisation:
  - Plasmapheresis, cytapheresis, intravenous immunoglobulin, investigational drug treatment (≤90 days or 5 half-lives, whichever is longer), except biological agents
- Treatment with the following ≤180 days of randomisation:
  - Azathioprine, methotrexate, cyclophosphamide, natalizumab, other systemic immunosuppressive treatments (e.g., cyclosporine, sirolimus, mycophenolic acid), non-lymphocyte-depleting experimental biological agents (e.g., daclizumab)
- Treatment with the following ≤24 months of randomisation:
  - Lymphocyte-depleting biological agents such as rituximab or ocrelizumab, cladribine
- Treatment with the following at any point prior to randomisation:
  - Alemtuzumab, mitoxantrone, leflunomide, teriflunomide, fingolimod, ponesimod, other investigational S1P modulators, stem cell transplantation
- Significant medical conditions or receiving therapies for such conditions (e.g., cardiovascular, metabolic, pulmonary, immunological, renal, hepatic, ophthalmological, ocular, and malignancy)
- Abnormal laboratory values for hematologic parameters at Screening (Visit 1) or Baseline (Visit 2)
- Known hereditary problems of galactose intolerance (e.g., Lapp lactase deficiency, glucose-galactose malabsorption)
- Known history of clinically significant drug or alcohol abuse
- Known allergy to any of the ponesimod or teriflunomide formulation excipients
- Contraindications for MRI or any other clinically relevant medical or surgical conditions that would put the patient at risk by participating

EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; IFN = interferon; MRI = magnetic resonance imaging; MS = multiple sclerosis; RMS = relapsing multiple sclerosis; S1P = sphingosine-1-phosphate.

B.2.3.2 Outcomes assessed

The endpoints assessed in the OPTIMUM trial are summarised in Table 11.(6)

In clinical trials, a wide range of endpoints have been used to evaluate disability progression in MS; most studies utilise worsening EDSS scores, though exact definitions vary.(113) Confirmed disability accumulation (CDA) was assessed as a secondary efficacy endpoint in the OPTIMUM trial, defined as: an increase of ≥1.5 in EDSS score for patients with a baseline EDSS score of 0.0, or an increase of ≥1.0 for patients with a baseline score of 1.0 to 5.0, or an increase of ≥0.5 for patients with a baseline score of ≥5.5 which is to be confirmed after 12 weeks. This definition is closely aligned to measures of disability progression used in previous trials in MS, such as the TEMSO trial of teriflunomide, where sustained disability progression was defined as: an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks. (22, 116, 148, 150)

Table 11: Outcomes assessed during OPTIMUM(6)

Study endpoint	Assessments included
Primary efficacy endpoint	• Annualised relapse rate (ARR; confirmed relapses* per year) *Relapse defined as new, worsening, or recurrent neurological symptoms occurring ≥30 days following the onset of a prior relapse and sustained ≥24 hours without fever or infection
Secondary efficacy endpoints	• Fatigue-related symptoms as measured by the Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis (FSIQ-RMS), change from baseline to Week 108. • Combined unique active lesions (CUALs) from baseline to Week 108 • Time to 12-week confirmed disability accumulation (CDA)* from baseline to end of study • Time to 24-week confirmed disability accumulation (CDA)* from baseline to end of study *CDA defined as an increase of ≥1.5 in Expanded disability status scale (EDSS) score for patients with a baseline EDSS score of 0.0, or an increase of ≥1.0 for patients with a baseline score of 1.0 to 5.0, or an increase of ≥0.5 for patients with a baseline score of ≥5.5 which is to be confirmed after 12 weeks (baseline EDSS score was the last score prior to randomisation); this is similar to measures of disability used in other MS trials(6, 116)
MRI-based exploratory endpoints	• Percent change in brain volume from baseline to Week 108, based on longitudinal brain volume measurements derived from MRI scans by using Structural Image Evaluation, using Normalisation, of Atrophy methodology • Number of Gd+ T1 lesions at Week 60 and Week 108 • Cumulative number of new or enlarging T2 lesions, baseline to Week 108 • Volume of T2 and T1 hypointense lesions, change from baseline to Week 60 and Week 108 • Absence of Gd+ T1 lesions or new/ enlarging T2 lesions at Week 60 and Week 108 • Proportion of baseline Gd+ lesions evolving to persistent black holes by Week 108 • Magnetisation transfer ratio (MTR) values in normal appearing white matter, change form baseline to Week 108 (select sites only) • Gd+ lesional MTR values, change from baseline to Week 108 (remyelination, select sites only) • Cumulative new cortical lesions on double inversion recovery images from baseline to Week 108 (select sites only)
Clinical exploratory endpoints	• Time to first confirmed relapse • Absence of confirmed relapses from baseline to Weeks 60 and 108 • EDSS, change from baseline to Week 108 • No evidence of disease activity (NEDA)* status through end of study *NEDA-3 was defined as the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions and 12-week CDA from baseline up to the specified time point. This definition is expanded to include brain atrophy in NEDA-4
Other exploratory endpoints	• Multiple Sclerosis Functional Composite (MSFC) Z-score, change from baseline by visit, up to Week 108

Study endpoint	Assessments included
Quality of life instruments	• Short Form-36 (SF-36) v2 domain and component scores, change from baseline to Week 108
Other relapse analyses	• Relapse characteristics and relapse symptoms

EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; MRI = magnetic resonance imaging

B.2.3.3 Summary of methodology

A summary of the methodology used in OPTIMUM is presented in Table 12. The primary endpoint and secondary endpoints (described in Section B.2.3.2) were assessed in the intent-to-treat (ITT) population, which includes all randomised participants and is the basis for this submission.(6) All available efficacy data up to the EOS were included.(6)

Table 12: Summary of trial methodology(6, 149)

Trial	OPTIMUM (AC-058B301)	
Location	Multicentre: 171 sites[a] across 28 countries Belarus (5 sites), Bosnia and Herzegovina (1 site), Bulgaria (8 sites), Canada (4 sites), Croatia (5 sites), Czech Republic (9 sites), Finland (2 sites), France (5 sites), Georgia (5 sites), Germany (5 sites), Greece (3 sites), Hungary (5 sites), Israel (4 sites), Italy (5 sites), Latvia (3 sties), Lithuania (3 sites), Mexico (3 sites), Poland (12 sites), Portugal (4 sites), Romania (4 sites), Russia (29 sites), Serbia (5 sites), Spain (6 sites), Sweden (3 sites), Turkey (1 site), Ukraine (16 sites), United Kingdom (4 sites), United States of America (12 sites)	
Trial design	Multicentre, phase 3, randomised, double-blind, parallel group, active-controlled superiority study	
Trial drugs	Intervention: Ponesimod n=567	Comparator: Teriflunomide n=566
	Ponesimod was administered orally once daily on a gradual up-titration[b] from a 2mg starting dose to a 10mg dose (film-coated tablet) over Days 1 to 14, and as a 20mg dose (over-encapsulated tablet) starting Day 15 until Week 108 (EOT)	Teriflunomide was administered as a 14mg dose (film-coated tablet) orally once daily from Day 1 until Week 108 (EOT) During the ponesimod up-titration phase, a mock-up titration was used for teriflunomide administration to maintain study blind; study drugs were administered in a double-dummy manner. See Table 15 for further details on study blinding
Permitted and disallowed concomitant medication	For relapses requiring corticosteroid treatment during the study, a 3- to 5-day course of IV methylprednisolone 1g daily was recommended; use of other corticosteroids, dosage/route, or ACTH was not recommended and permitted only if it was absolutely needed Other permitted concomitant medications included dalfampridine, IV atropine, short-acting beta$_2$-agonists and non-live vaccines Concomitant medications that were prohibited during the study included systemic corticosteroids and ACTH; disease-modifying agents for MS other than those specified in the protocol; immunosuppressive treatment; IV immunoglobulin, plasma exchange or total lymphoid irradiation; live vaccines; anti-arrhythmic or heart rate-lowering systemic therapy; cholestyramine or activated charcoal; any investigational procedure for MS or any other investigational drug	

Trial	OPTIMUM (AC-058B301)
Primary outcome	ARR, defined as the number of confirmed relapses according to the treatment neurologist/principal investigator per patient-year Relapse was defined as new, worsening, or recurrent neurological symptoms occurring ≥30 days following the onset of a prior relapse and sustained for ≥24 hours, without fever or infection. The primary endpoint was assessed in ITT, which included all patients randomly assigned to study treatment. All available efficacy data up to end of study were included.
Pre-planned subgroups	• Baseline EDSS score (≤3.5, >3.5) • Geographical region (Western Europe, Eastern Europe, North America, Latin America, Rest of the World) • Gender (male, female) • Age (<40, ≥40) • MS subtype (RRMS, SPMS) • Prior MS treatment (yes, no) • Relapse in the year prior to study entry (≤1, ≥2) • Gd+ T1 lesions at baseline (present, absent) • Highly active RRMS[c] (yes, no)

ACTH = adrenocorticotropic hormone; ARR = annualised relapse rate; CDA = confirmed disability accumulation; CUAL = combined unique active lesion; EDSS = Expanded Disability Status Scale; EOS = end of study; EOT = end of treatment; Gd+ = gadolinium-enhancing; ITT = intent-to-treat; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; IFN = interferon; IV = intravenous; MS = multiple sclerosis; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

[a] Patients were screened at 171 centres; however, 1 patient in Hungary was transferred during the study to a centre at which no patients were screened; therefore, the study was conducted at 172 centres.

[b] If treatment was interrupted for >3 days, the up-titration regimen was used again on re-initiation of treatment.

[c] Highly active RRMS was defined as patients fulfilling one or both of the following criteria:

- Any DMT for MS received within 12 months prior to randomisation and one or both of the following:
  - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions.
  - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for patients with at least one relapse within 2 years prior to study entry.
- ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.

B.2.3.3.1 Baseline patient and disease characteristics

A total of 1,133 patients (ponesimod: n=567, teriflunomide: n=566) were randomised across 28 countries. Demographic and baseline characteristics were well balanced between the two treatment groups (Table 13). The median age of the patient population was 37 years (range 18 to 55 years).(6) Overall, 97.4% of the patient population had RRMS and 2.6% of patients had SPMS. A similar proportion of patients in each treatment arm had highly active RRMS (ponesimod: 35.6%, teriflunomide: 35.3%).(6) The proportion of patients who had received any DMT for MS prior to randomisation was comparable between treatment arms (ponesimod: 42.9%, teriflunomide: 43.3%).(6) Prior DMTs received by patients in the OPTIMUM trial are summarised in Appendix E.2.

Table 13: Characteristics of participants in OPTIMUM across treatment groups (ITT)(6, 46)

	Ponesimod 20 mg (n=567)	Teriflunomide 14 mg (n=566)	Total (N=1,133)
Age, years, n (%)			
18 to 30	[redacted]	[redacted]	[redacted]
31 to 40	[redacted]	[redacted]	[redacted]
41 to 55	[redacted]	[redacted]	[redacted]
Mean (SD)	36.7 (8.74)	36.8 (8.74)	36.7 (8.74)
Median (IQR)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	363 (64.0)	372 (65.7)	735 (64.9)
Race, n (%)			
White	551 (97.2)	553 (97.7)	1,104 (97.4)
Black or African American	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]	[redacted]
Body mass index (kg/m^2)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
EU + UK	[redacted]	[redacted]	[redacted]
UK	[redacted]	[redacted]	[redacted]
Europe non-EU + Russia	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Rest of World	[redacted]	[redacted]	[redacted]
Baseline EDSS score			
Mean (SD)[a]	2.57 (1.174)	2.56 (1.229)	2.56 (1.201)
Median[a] (IQR)	[redacted]	[redacted]	[redacted]
>3.5, n (%)	94 (16.6)	95 (16.8)	189 (16.7)
Any DMT within 2 years prior to randomisation, n (%)[a]			
Yes	213 (37.6)	211 (37.3)	424 (37.4)
No	354 (62.4)	355 (62.7)	709 (62.6)
Any DMT received prior to randomisation, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Time since first symptoms at randomisation			
Mean (SD)	7.63 (6.781)	7.65 (6.782)	7.64 (6.779)
Median (IQR)	[redacted]	[redacted]	[redacted]

	Ponesimod 20 mg (n=567)	Teriflunomide 14 mg (n=566)	Total (N=1,133)
Time since most recent relapse at screening, months			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Number of relapses in last year prior to study entry			
Mean (SD)	1.2 (0.61)	1.3 (0.65)	1.3 (0.63)
Median (IQR)	[redacted]	[redacted]	[redacted]
FSIQ-RMS weekly symptoms score at baseline			
Mean (SD)[b]	31.9 (20.4)	32.8 (19.1)	-
MS subtype, n (%)			
RRMS	552 (97.4)	552 (97.5)	1,104 (97.4)
SPMS	15 (2.6)	14 (2.5)	29 (2.6)
Presence of Gd+ T1 lesions at baseline, n (%)[c]			
Yes	226 (39.9)	256 (45.4)	482 (42.6)
No	341 (60.1)	308 (54.6)	649 (57.4)
Number of T2 lesions at baseline, n (%)[c]			
<9	[redacted]	[redacted]	[redacted]
≥9	[redacted]	[redacted]	[redacted]
Highly active RRMS, n (%)[d]			
Yes	202 (35.6)	200 (35.3)	402 (35.5)
No	365 (64.4)	366 (64.7)	731 (64.5)

DMT = disease-modifying treatment; EU = European Union; Gd+ = gadolinium-enhancing; IQR = interquartile range; ITT = intent-to-treat; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SPMS = secondary progressive multiple sclerosis; UK = United Kingdom.

[a] From electronic Case Report Form.
[b] The total FSIQ-RMS weekly symptoms domain score ranges from 0 to 77 with a higher score indicating greater fatigue.
[c] From central reader.
[d] Highly active RRMS was defined as having one or both of the following characteristics:

- Any DMT for MS received within 12 months prior to randomisation and one or both of the following:
  - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions
  - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for patients with at least one relapse within 2 years prior to study entry
- ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.

Source: OPTIMUM CSR Table 5 and Table 6.

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

A summary of the statistical analyses undertaken in this study is provided in Table 14.

Table 14: Summary of statistical analyses(6, 149, 151)

Trial	OPTIMUM (AC-058B301)
Hypothesis objective	The primary efficacy endpoint was ARR based on the number of confirmed relapses per patient-year. The primary null hypothesis (H0) was that there is no difference in the ARR between ponesimod 20 mg and teriflunomide 14 mg
Statistical analysis	A multiple testing strategy was used in which the primary endpoint was tested first at full alpha, followed hierarchically by a fallback type procedure for the secondary endpoints; all of these endpoints were analysed using the ITT population (included all randomised patients). The multiple testing strategy was conducted at an overall two-sided 5% alpha and the primary H0 was tested at a two-sided Wald test 1% alpha level (conclusive evidence) and two-sided 5% alpha level (positive study) If the primary H0 was rejected, then the alpha was to be split evenly (1/3 of the alpha) between the first 3 of the 4 secondary endpoints listed above[a] The primary statistical analysis included data up to EOS and was performed using a negative binomial regression model for confirmed relapses, with treatment as a factor and including the stratification variables (baseline EDSS score; disease-modifying treatments within last 2 years prior to randomisation), number of relapses in the year before study entry and an offset variable defined as log of years on study from randomised up to EOS
Sample size, power calculation	Approximately 1,100 participants (550 per treatment group) were required to provide 90% power (significance level of 0.01) to detect a reduction of 33% in ARR (assuming ARR: 0.215 for ponesimod versus 0.320 for teriflunomide)
Data management, patient withdrawals	For patients who withdrew after receiving ≥1 dose of study treatment and before completing the study, the reason for withdrawal was documented on the electronic Case Report Form and source document Patients who prematurely discontinued study treatment were not considered withdrawn from the study and were followed up to Week 108 or until 30 days after study drug discontinuation, whichever came later All confirmed relapses from randomisation up to the EOS visit for the ITT population were to be used in the primary endpoint analysis, regardless of study drug compliance

ARR = annualized relapse rate; CDA = confirmed disability accumulation; CUAL = combined unique active lesion; EDSS = Expanded Disability Status Scale; EOS = end of study; ITT = intent-to-treat; Gd+ = gadolinium-enhancing; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; H0 = null hypothesis.

[a]For each successful secondary endpoint in the sequence, the preserved alpha was transferred to the next secondary endpoint in the sequence and the summed alpha was used for testing that endpoint; the fourth secondary endpoint (time to 24-week CDA) was tested in the last step with the remaining alpha.

B.2.4.1 Study population

In OPTIMUM, 1,133 patients were randomised in the study (567 in the ponesimod group, 566 in the teriflunomide group) and 1,131 patients received study treatment (565 in the ponesimod group, 566 in the teriflunomide group).(6) All 1,133 randomised patients were included in the ITT that was used for analysis of the primary endpoint and other efficacy endpoints; 1,131 patients were included in the safety set (SAF) as 2 individuals in the ponesimod 20 mg group did not receive study treatment.(6) The mean treatment exposure, irrespective of interruptions, was 96.7 weeks in the ponesimod 20 mg group and 97.5 weeks

in the teriflunomide 14 mg group.(6) Mean time in-study was 1.97 years in the ponesimod 20 mg group and 2.01 years in the teriflunomide 14 mg group.(6)

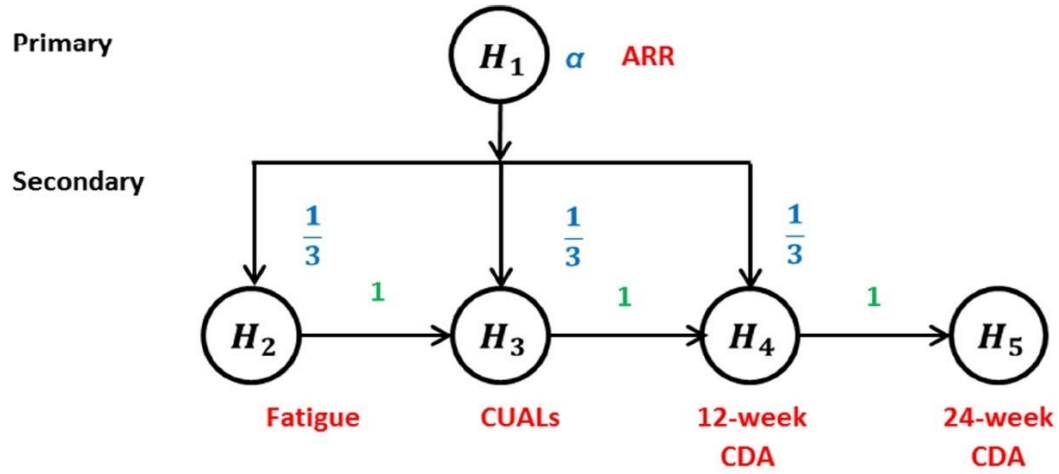
Prespecified subgroup analyses were performed based on MS subtype (RRMS vs. SPMS) and highly active RRMS (yes vs. no) to evaluate the primary efficacy endpoint of ARR, using an unadjusted negative binomial model, with treatment as a covariate and the log of the time from randomisation to EOS as an offset variable, in both the ITT and in the per-protocol population.(6, 149)

B.2.4.2 Statistical analyses

The sample size estimation for this study was based on the primary endpoint, using negative binomial distribution.(6) A total of 1,110 participants (550 per treatment group) would provide 90% power (significance level of 0.01) to detect a reduction of 33% in ARR (assuming ARR: 0.215 for ponesimod versus 0.320 for teriflunomide).(6) Assumptions for annual dropout rates were approximately 15% for the first year and 7.5% for the second year.(6)

A multiple testing strategy was used in which the primary endpoint was tested first at full alpha, followed hierarchically by a fallback type procedure for the secondary endpoints (Figure 6).(6, 151) If the primary null hypothesis (H0) was rejected, then the alpha was to be split evenly (1/3 of the alpha) between the first 3 of the 4 secondary endpoints (FSIQ-RMS, CUALs, time to 12-week CDA).(6, 151) For each successful secondary endpoint in the sequence, the preserved alpha was transferred to the next secondary endpoint in the sequence and the summed alpha was used for testing that endpoint; the fourth secondary endpoint (time to 24-week CDA) was tested in the last step with the remaining alpha.(6, 151)

Figure 6: Overall testing strategy in OPTIMUM



ARR = annualised relapse rate; CDA = confirmed disability accumulation; CUAL = combined unique active lesion

The multiple testing strategy was conducted at an overall two-sided 5% alpha and the primary H0 was tested at a two-sided Wald test 1% alpha level (conclusive evidence) and two-sided 5% alpha level (positive study).(6, 151)

The primary statistical analysis was performed using a negative binomial regression model for confirmed relapses, with treatment as a factor and including the binary stratification variables (baseline EDSS score ≤3.5 versus >3.5; DMTs within the last 2 years prior to randomisation [yes/no]), number of relapses in the year before study entry (categories ≤1 [or missing] and ≥2) and an offset variable defined as log of years on study from randomised up to EOS.(6, 151) All confirmed relapses from randomisation up to the EOS visit for the ITT population were to be used in the primary endpoint analysis, regardless of study drug compliance.(149, 151)

B.2.4.3 Patient withdrawals

If a patient withdrew after receiving ≥1 dose of study treatment and before completing the study, the reason for withdrawal was documented on the electronic Case Report Form and source document.(6)

Patients who prematurely discontinued study treatment were not considered withdrawn from the study and were followed up to Week 108 or until 30 days after study drug discontinuation, whichever came later (provided the patient had not withdrawn consent in the study).(6) For patients who permanently discontinued study treatment due to any reason, the investigator was required to consider prescribing appropriate treatment for MS according to the local clinical practice and availability, exercising caution when considering a switch to another immunomodulatory MS treatment.(6) Between initiation of study treatment and Week 108, [redacted] in the ponesimod arm vs. [redacted] in the teriflunomide arm ([redacted]) received a DMT for MS, which included dimethyl fumarate ([redacted]), fingolimod ([redacted]), alemtuzumab ([redacted]), cladribine ([redacted]), natalizumab ([redacted]), glatiramer acetate ([redacted]), IFN beta-1a ([redacted]), peginterferon beta-1a ([redacted]), and methotrexate ([redacted]).(6) Patients also received glucocorticoids to treat relapses ([redacted] in the ponesimod arm; [redacted] in the teriflunomide arm). (6)

Patient disposition during the OPTIMUM study is summarised in Appendix E.1.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

B.2.5.1 Appraisal of the quality of the OPTIMUM trial

The primary source of data from the randomised, controlled OPTIMUM study was the clinical study report.

In order to assess the risk of bias and generalisability of the trial, a quality assessment was conducted using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).(152) A complete quality assessment of OPTIMUM can be seen in Table 15.

Overall, the risk of bias was found to be low in the OPTIMUM trial, considering all relevant aspects of quality assessment: randomisation and blinding was carried out per protocol; the treatment groups were balanced in terms of baseline demographics with no unexpected differences in study dropouts; all outcomes assessed were reported in the CSR for appropriate analysis populations.

Table 15: Quality assessment of the relevant clinical effectiveness evidence in this submission

	OPTIMUM	**Risk of bias**
Was randomisation carried out appropriately?	Yes, randomisation was carried out as per the study protocol; patients were randomised to treatment using an IRT	Low
Was the concealment of treatment allocation adequate?	Yes, the IRT was used to ensure no one at study sites became unblinded to study treatment	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, demographic and baseline characteristics were well balanced between the two treatment groups (Table 13)	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, the study was fully blinded to all investigators, associated staff* and patients until closure. Access to functional events identified as unblinding events was restricted and key data were reported and processed independently. Measures were enacted to ensure that efficacy assessments were conducted independently; processes for variable counts and imaging were reviewed to minimise the potential for bias	Low
Were there any unexpected imbalances in dropouts between groups?	No, of the 567 patients randomised in the ponesimod group, 565 received treatment. There were no dropouts in the teriflunomide arm (n=566)	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were	All 1,133 randomised patients in OPTIMUM were included in the ITT that was used for analysis of the primary endpoint and other efficacy endpoints	Low

	OPTIMUM	Risk of bias
appropriate methods used to account for missing data?	1,131 patients were included in the SAF as 2 individuals in the ponesimod 20 mg group did not receive study treatment	

ITT = intent-to-treat; IRT = interactive response technology; SAF = safety set

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)(152)

* With the exception of sponsor staff responsible for clinical trial supply distribution

B.2.5.2 Generalisability of OPTIMUM trial to clinical practice in England

OPTIMUM was a multinational phase 3 study of ponesimod vs. teriflunomide in patients with RMS conducted in 28 countries across 171 sites, including four sites in the UK; [redacted] of patients ([redacted]) were recruited in the EU+UK, of whom [redacted].(6) The OPTIMUM study population is comparable to the UK MS population in terms of sex, age and ethnicity.(31, 153) As observed in UK population-based studies of MS (Section B.1.3.1.2), and as MS affects more females than males,(154) the majority (64.9%) of patients enrolled in OPTIMUM were female.(6)

The population enrolled in OPTIMUM was reflective of a typical RMS population where RRMS is the most common phenotype, occurring in the vast majority of all cases of MS at onset.(16, 20, 64) The majority of patients in OPTIMUM had RRMS (97.4%) and a small proportion of patients had SPMS (2.6%).(6) Overall, 35.5% of patients in the OPTIMUM trial had highly active RRMS, based on the broad definition of 'highly active' commonly used in MS trials (Section B.2.7).(6) Results of prespecified subgroup analyses in patients with highly active RRMS are described in Section B.2.7. Patients entering the trial were either treatment-naïve ([redacted] of patients in the ITT) or had received previous treatment ([redacted]). The most common previous DMTs for MS included IFN beta-1a ([redacted] of patients in the ITT), glatiramer acetate [redacted] and IFN beta-1b ([redacted]); all other treatments were received by [redacted] patients in the trial (Appendix E.2). Natalizumab is only recommended for the treatment of RES RRMS by NICE; although prior natalizumab therapy was allowed in OPTIMUM due to it being a global trial, however [redacted] of patients in the ITT received natalizumab.(6) The NHSE treatment algorithm for DMTs in RRMS (Section B.1.3.2.1) recommends IFN beta products, glatiramer acetate, teriflunomide, ocrelizumab and dimethyl fumarate as first-line therapies in patients with RRMS.(7) Prior treatment exposure and the use of comparator treatment in the OPTIMUM trial are therefore closely aligned with NHS guidance on the treatment of RRMS in England.

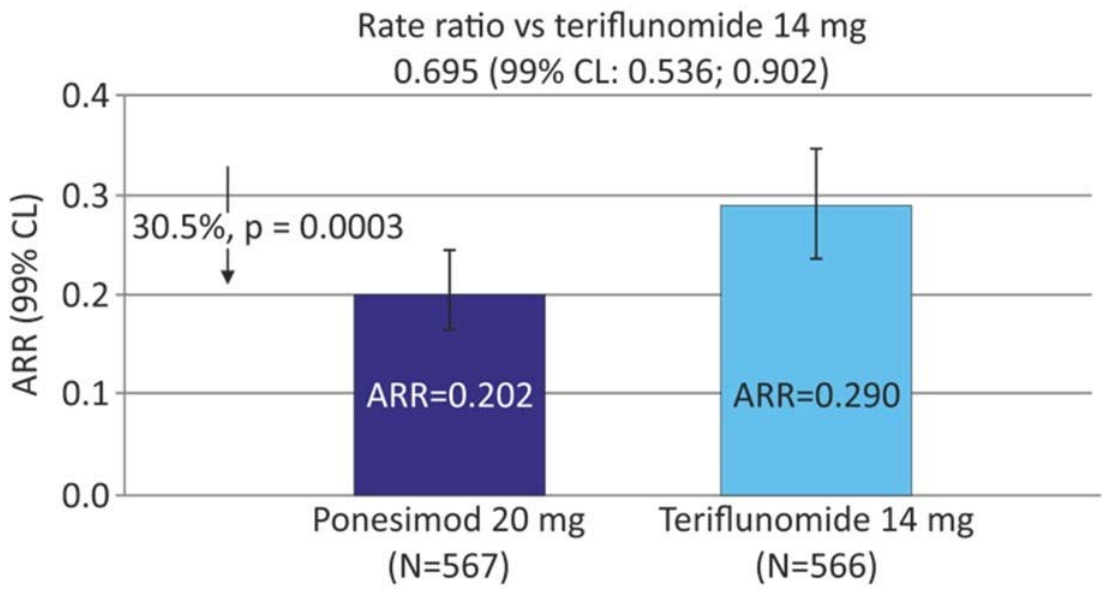
B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Primary endpoint: Annualised Relapse Rate

Relapses are key drivers of reduced HRQoL in patients with RRMS, and the frequency of relapses is indicative of disease activity and a prognostic factor for disability progression; therefore, reducing the rate of relapse is a key treatment goal in MS.(23, 33-36) The results from the OPTIMUM trial demonstrate that ponesimod significantly reduces the risk of relapse in patients with RRMS versus teriflunomide, another oral DMT that is currently used as first-line therapy in the UK.

The ARR (confirmed relapses per year) for the ITT population is presented in Figure 7 and Table 16. Ponesimod significantly reduced ARR up to EOS by 30.5% compared with teriflunomide (ARR: 0.202 vs. 0.290; rate ratio [RR]: 0.695; 99% confidence limit [CL]: 0.536, 0.902; p=0.0003).(46, 145)

Figure 7: OPTIMUM: Confirmed Relapses up to EOS (Primary Analysis, ITT)(46)



Adjusted for stratification factors and number of relapses in the 12-month period prior to study entry

ARR = annualised relapse rate; CL = confidence limit; EOS = end of study; ITT = intent-to-treat

Source: Kappos 2019

Table 16: OPTIMUM: Confirmed Relapses up to EOS (Primary Analysis, ITT)(6)

	Ponesimod 20 mg N=567	**Teriflunomide 14 mg N=566**
Mean estimate (ARR)	0.202	0.290
99% CL	0.165, 0.246	0.244, 0.345
95% CL	0.173, 0.235	0.254, 0.331
Treatment effect (RR)	0.695	
99% CL	0.536, 0.902	
95% CL	0.570, 0.848	
p-value	p=0.0003	
Total number of relapses (n)	242	344

Adjusted for stratification factors and number of relapses in the 12-month period prior to study entry

ARR = annualised relapse rate; CL = confidence limit; EOS = end of study; ITT = intent-to-treat

B.2.6.2 Secondary endpoint: Confirmed Disability Accumulation

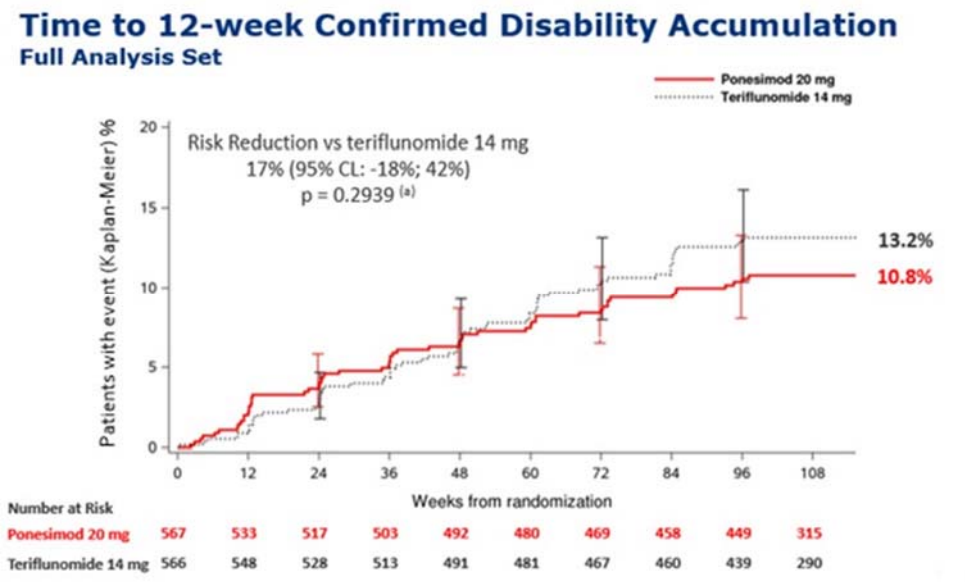
Accumulating neurological disability has a substantial negative impact on the HRQoL of patients with RRMS, and reducing long-term disability progression is one of the key goals of MS treatment.(31, 113) Disability progression was assessed in the OPTIMUM trial as CDA which utilises worsening EDSS scores, in line with other trials in MS (further information in Section B.2.3.2). It should be noted that short-term changes in EDSS may not correctly identify patients with irreversible disease progression and should be interpreted with caution, particularly in a trial (such as OPTIMUM) where the intervention and comparator have similar efficacy profiles.(113, 155) A prospective observational study of 16,636 patients (totalling 112,584 patient-years) from the MS Base registry showed that changes in EDSS scores measured at 3 and 6 monthly periods may overestimate long-term irreversible disability.(156) Regression of disability was found to be common in RRMS and more so in younger patients.

The results for 12- and 24-week CDA in OPTIMUM are presented in Figure 8. 12-week CDA was observed in 10.1% of patients in the ponesimod group and in 12.4% of patients in the teriflunomide group.(6) Treatment with ponesimod decreased the risk of a 12-week CDA event by 17% compared with teriflunomide; however, the difference was not statistically significant and thereafter the formal testing procedure was stopped (risk reduction: 17%; 95% CL: -18%, 42%; p=0.2939).(46)

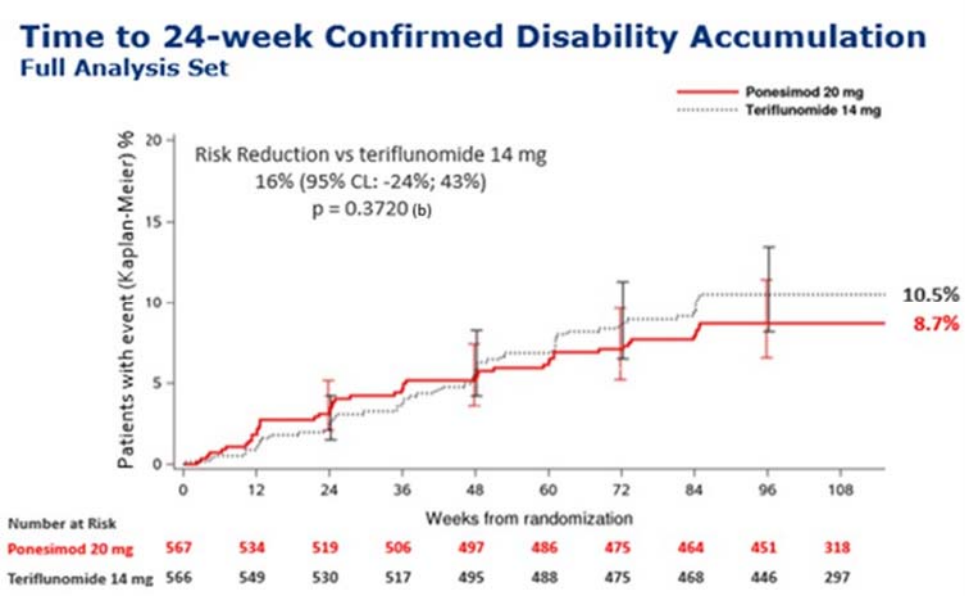
Consequently, 24-week CDA was only evaluated in an exploratory manner.(6) 24-week CDA was observed in 8.1% of patients in the ponesimod group and in 9.9% of patients in the teriflunomide group; the risk of a 24-week CDA event was 16% lower with ponesimod compared with teriflunomide (risk reduction: 16%; 95% CL: -24%, 43%; p=0.3720).(46)

Figure 8: OPTIMUM: 12-week (A) and 24-week CDA (B) up to EOS (ITT)(46)

A.



B.



Unstratified Kaplan-Meier curve with KM-estimate at EOS presented; Event=12- or 24-week CDA up to EOS

(a) Non-significant result: Formal testing procedure stopped. Stratified log-rank test p-value and stratified Cox regression risk reduction estimate displayed. Analyses stratified by EDSS strata and DMTs in the 2 years prior to randomisation strata.

(b) Exploratory, not formally tested. Stratified log-rank test p-value and stratified Cox regression risk reduction estimate displayed. Analyses stratified by EDSS strata and DMTs in the 2 years prior to randomisation strata.

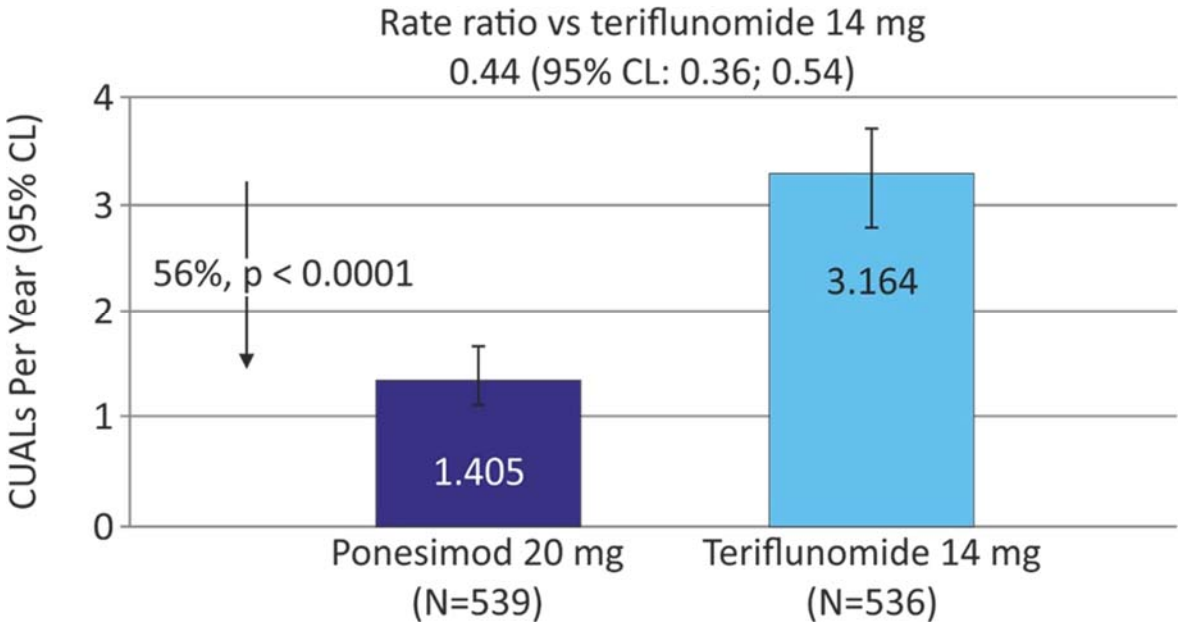
CL = Confidence limit; EOS = end of study; ITT = intent-to-treat

Adapted from: Kappos 2019

B.2.6.3 Secondary endpoint: Combined Unique Active Lesions

Measuring the presence of new/enlarging lesions on MRI by assessing the cumulative number of combined unique active lesions (CUAL) allows monitoring of disease activity and progression in patients with RRMS.(54, 106-108) Ponesimod significantly reduced the number of inflammatory lesions on brain MRI by 56% compared with teriflunomide (RR: 0.444; 95% CLs: 0.364, 0.542; p<0.0001; Figure 9).(46, 157) The mean CUALs per year were 1.405 for the ponesimod group compared with 3.164 for teriflunomide group.(157) Reduction in the inflammatory activity marked by lesions in turn would suggest significantly reduced disease activity associated with ponesimod over teriflunomide.

Figure 9: OPTIMUM: CUALs from Baseline to EOS (ITT)(46)



CUAL, defined as new gadolinium-enhancing (Gd+) T1 lesions plus new or enlarging T2; lesions (without double counting).. Based on negative binomial regression adjusted by EDSS strata, DMT strata, presence of T1 Gd + lesion. Missing data: 28 and 30 patients in the ponesimod 20 mg and teriflunomide 14 mg arms respectively had a missing baseline and/or post-baseline MRI

CUALs = Combined Unique Active Lesions; CL = confidence limits; EOS = end of study; ITT = intent-to-treat

Adapted from: Kappos 2019

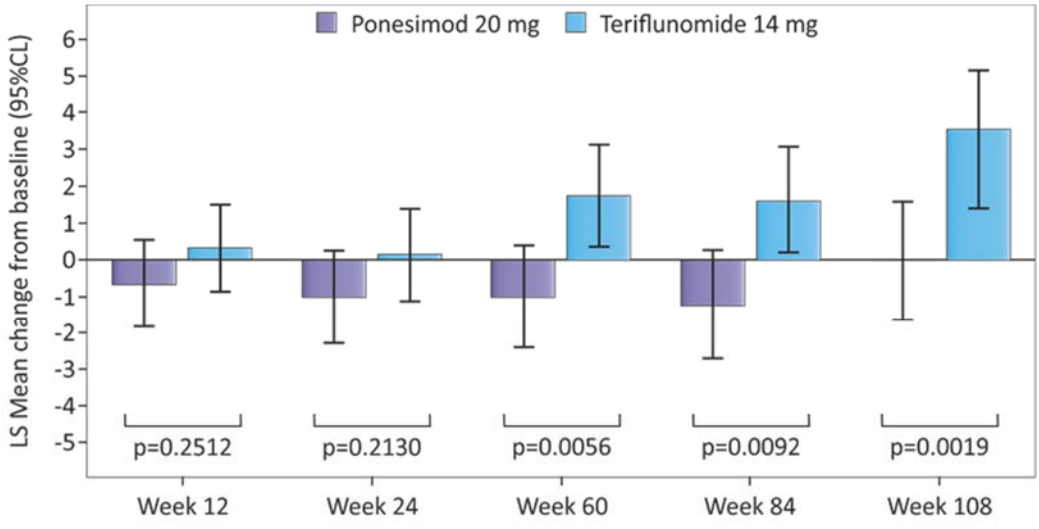
B.2.6.4 Secondary endpoint: Fatigue

Fatigue is a common symptom affecting the vast majority of patients with MS, with a considerable impact on quality of life, mental health and cognition.(78, 81-86) The impact of treatment with ponesimod versus teriflunomide on fatigue was assessed using the MS-specific FSIQ-RMS instrument as described in Section B.1.3.1.8; an increase from baseline in FSIQ-RMS scores indicates worsening in fatigue symptoms.

Change from baseline to Week 108 in the FSIQ-RMS weekly symptoms score was statistically significantly lower in the ponesimod 20 mg group compared with the

teriflunomide 14 mg group (least square [LS] mean change from baseline: −0.01 vs. 3.56, respectively), with a mean difference of −3.57 (95% CL: −5.83, −1.32; p=0.0019) (Figure 10).(46, 157) In a post hoc responder analysis, the OR (ponesimod vs. teriflunomide) for patient improvement or stable response (i.e. a change from baseline of ≤6.3) was [redacted], suggesting a [redacted] at the patient level.(47) Using a validated MS-specific PRO instrument(121), ponesimod is the first DMT to demonstrate stabilisation of fatigue symptoms compared to another oral DMT in a large pivotal trial.

Figure 10: OPTIMUM: FSIQ-RMS Symptom Domain Change from Baseline to EOS (ITT)(46)



Number of subjects					
Ponesimod 20 mg N=567	412	417	409	386	344
Teriflunomide 14 mg N=566	421	422	417	389	328

FSIQ-RMS is based on the Mixed effect Model Repeat Measures (MMRM) analysis with unstructured covariance, treatment, visit, treatment by visit interaction, baseline by visit interaction as fixed effects, baseline FSIQ score, EDSS strata (≤ 3.5, > 3.5), DMT in last 2 years prior randomisation strata (Y,N) as covariates. Least square (LS) means and 95% CLs are displayed. Includes patients with baseline and at least one post baseline assessment. N = patients in analysis set. P = p-value for Wald test on mean difference between treatment arms. A negative change from baseline indicates an improvement in fatigue symptoms

CL = confidence limit; EOS = end of study; ITT = intent-to-treat; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; LS = least square

Adapted from: Kappos 2019

B.2.6.5 Exploratory endpoint: Expanded Disability Status Scale

As described in Section B.1.3.1.8, EDSS is widely used as a measure of disability in patients with RRMS.(114) An increase in EDSS score suggests a worsening of disability and is associated with decreased HRQoL.(31) The LS mean changes in EDSS scores from baseline to EOS with ponesimod and teriflunomide are presented in Figure 11. The LS mean change from baseline to EOS was [redacted] in the ponesimod group and [redacted] in the teriflunomide group, with a LS mean difference of [redacted](6)

Additionally, in post hoc analyses, a composite endpoint of disability[a], EDSS+, was assessed to identify worsening in upper or lower extremity function or 12-week CDA. Ponesimod showed a [redacted] relative risk than teriflunomide of an EDSS+ event [redacted], indicating [redacted] disability worsening with ponesimod versus teriflunomide.(47)

Figure 11: OPTIMUM: Change from Baseline in EDSS Score up to EOS (ITT)(6)

LS means and associated 95% CLs from a MMRM, including fixed effects for treatment, visit and interaction between treatment and visit; adjusted for baseline EDSS score (continuous) and DMT within last 2 years prior to randomisation.

CL = confidence limit; EDSS = Expanded Disability Status Scale; EOS = end of study; ITT = intent-to-treat; LS = least squares; MMRM = mixed effects repeated measurements model

Source: OPTIMUM: CSR

B.2.6.6 Exploratory endpoint: Time to First Confirmed Relapse

Treatment with ponesimod [redacted] the time to first confirmed relapse up to EOS compared with teriflunomide (hazard ratio [HR]: [redacted] Figure 12). The Kaplan-Meier (KM) estimate of patients with a confirmed relapse at EOS was [redacted] in the ponesimod group compared with [redacted] in the teriflunomide group.(6) These results from the OPTIMUM trial demonstrate that treatment with ponesimod delays the time to relapse, a key driver of reduced HRQoL, in patients with RRMS compared with teriflunomide.(36)

[a] EDSS+ is a composite of a 12-week confirmed 20% worsening in upper extremity function (9 HPT), lower extremity function (T25FW), or 12-week CDA

Figure 12: OPTIMUM: Time to First Confirmed Relapse up to EOS (ITT)(6)

Adjusted for stratification factors and number of relapses in the 12-month period prior to study entry

CL = confidence limit; EOS = end of study; ITT = intent-to-treat

Source: OPTIMUM: CSR

B.2.6.7 Exploratory endpoint: No Evidence of Disease Activity

In clinical practice, the treatment goal of “no evidence of disease activity” (NEDA) uses the number and volume of lesions to describe the amount of disease activity even in the absences of relapses.(20, 35) NEDA-3 has been proposed as an important goal in the management of RRMS as it is associated with an improvement in long-term outcomes.(109, 110)

NEDA-3 was defined as the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions and 12-week CDA from baseline up to the specified time point.(6)

At EOS, [redacted] of patients in the ponesimod (n=564) and teriflunomide groups (n=558), respectively, had achieved NEDA-3 status (OR: 1.70; 95% CL: 1.27, 2.28; p=0.0004).(6)

NEDA-4 was defined as the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA and annual brain volume decrease ≥0.4% from baseline up to the specified time point.(6) At EOS, [redacted] of patients in the ponesimod (n=526) and teriflunomide groups (n=532), respectively, had achieved NEDA-4 status (OR: 1.85; 95% CL: 1.24, 2.76; p=0.0026).(6)

Overall, ponesimod improved the proportion of patients achieving a disease-free state, as defined by NEDA-3 and NEDA-4, compared with teriflunomide.(6) Although regarded as exploratory, the NEDA-3/NEDA-4 findings from OPTIMUM suggest that the odds of achieving a disease-free state after 108 weeks are higher with ponesimod treatment compared to teriflunomide.(47)

B.2.6.8 Exploratory endpoint: MRI-based Endpoints

Results from exploratory MRI-based analyses in the OPTIMUM trial consistently demonstrate [redacted] with ponesimod compared to teriflunomide in terms of reducing brain volume loss and the appearance of new or enlarging lesions in the brain.(6)

MRI-based endpoints are summarised below:(6)

- Brain atrophy or brain volume loss in patients with RRMS is associated with worsening disability and disease progression.(106, 111) Ponesimod reduced brain volume loss compared with teriflunomide; the LS mean percent change from baseline to EOS in brain volume was lower in the ponesimod group (n=436; −0.91%) compared with the teriflunomide group (n=434; −1.25%). The LS mean difference was 0.34% (95% CL: 0.17, 0.50; p<0.0001).(157) Brain atrophy (annual brain volume decrease ≥0.4% from baseline) occurred in a smaller proportion of patients in the ponesimod group (33%) compared with the teriflunomide group (42%).(5)
- The mean numbers of new or enlarging T2 lesions per year were [redacted] and [redacted] in the ponesimod and teriflunomide groups, respectively [redacted], based on a negative binomial (NB) regression model adjusted for stratification factors and Gd+ T1 lesions at baseline.
- The LS mean difference in change from baseline to EOS in total volume of T2 lesions with ponesimod compared with teriflunomide was [redacted]

[redacted], based on a MMRM adjusted for stratification factors, Gd+ T1 lesions at baseline and T2 lesion volume at baseline.

- The mean number of new Gd+ T1 lesions per scan was 0.178 and 0.429 in the ponesimod and teriflunomide groups, respectively (RR: 0.415; 95% CL: 0.307, 0.561; p<0.0001), based on an NB regression model adjusted for stratification factors and Gd+ T1 lesions at baseline.
- At EOS, [redacted] of patients in the ponesimod group [redacted] and [redacted] in the teriflunomide group [redacted] had 0 Gd+ T1 lesions [redacted].

B.2.6.9 Exploratory endpoint: Change from baseline in MSFC Z

MSFC is a validated clinical outcome measure used to assess physical and cognitive disability in patients with MS; higher MSFC Z-scores correspond with better outcomes.(6, 113)

Ponesimod was associated with [redacted] MSFC Z-scores, suggesting a [redacted] on physical and cognitive impairment, compared with teriflunomide.(6) At EOS, the LS mean change from baseline in MSFC Z-score was [redacted] in the ponesimod group [redacted] and [redacted] in the teriflunomide group [redacted]; the LS mean difference between the groups was [redacted].(6)

B.2.6.10 Other relapse analyses: Relapse characteristics and relapse symptoms

The total number of confirmed relapses up to EOS was 242 in the ponesimod group and 344 in the teriflunomide group.(6) The proportion of patients with at least one confirmed relapse up to EOS was [redacted] and [redacted] in the ponesimod [redacted] and teriflunomide groups [redacted], respectively. In the ponesimod group, the median duration per confirmed relapse was [redacted] days, and corticosteroid treatment was necessary for [redacted] patients. In the teriflunomide 14 mg group, the median duration per confirmed relapse was [redacted] days and corticosteroid treatment was necessary for [redacted] patients.(6) Ambulation and most functional systems were affected in more patients in the teriflunomide group than in the ponesimod group.(6)

B.2.6.11 Quality of life results: Change from baseline in SF-36

The impact of treatment with ponesimod on HRQoL was assessed using the SF-36 questionnaire. For the SF-36 domains of physical and social functioning, improvements from

baseline to EOS were observed in the ponesimod group compared with the teriflunomide group (no formal statistical testing was performed).(6)

Mental health domain scores were improved from baseline at EOS in the teriflunomide group compared with the ponesimod group.(6)

At EOS, the proportion of patients who rated their health as “much better” on the health transition item of the SF-36 (i.e., ‘*compared to 1 year ago, how would you rate your health in general now?*’) was [redacted] in the ponesimod group than in the teriflunomide group [redacted]. Note, in contrast, these scores were [redacted] at baseline for ponesimod and teriflunomide, respectively.(6)

B.2.7 Subgroup analysis

B.2.7.1 Patients with highly active RRMS (OPTIMUM definition, prespecified analysis)

A pre-planned subgroup analysis of OPTIMUM was conducted in patients with highly active RRMS, defined as patients fulfilling one or both of the following criteria:(6)

- Any DMT for MS received within 12 months prior to randomisation and one or both of the following:
- ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions.
- Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for patients with at least one relapse within 2 years prior to study entry.
- ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.

N.B. in line with previous clinical trials in MS, the definition of highly active RRMS employed during OPTIMUM was broad, and thus also incorporates patients with RES RRMS as defined by NHSE.(6, 7)

Overall, 35.5% (n=402) of patients in the ITT population had highly active RRMS at baseline as defined by the criteria above.(6) Results for primary and secondary endpoints in the highly active RRMS subgroup were consistent with those observed in the main analysis, demonstrating improvements in ARR, CDA, fatigue and inflammatory lesions on MRI with ponesimod compared to teriflunomide (Table 17).(6)

Results of treatment-by-subgroup interaction tests showed [redacted] interaction between the subgroups with highly active RRMS and non-highly active RRMS for the primary and secondary endpoints suggesting that disease state may not be a treatment-effect modifier (Table 17).

Table 17: OPTIMUM: Subgroup analysis results for treatment effect in patients with highly active RRMS versus non-highly active RRMS (ITT)(6)

	P-Value for Interaction[a]	Ponesimod 20 mg		Teriflunomide 14 mg		Ponesimod 20 mg vs. Teriflunomide 14 mg
		Number of Patients	Outcome	Number of Patients	Outcome	
ARR (confirmed relapses up to EOS: primary endpoint)						
Highly active RRMS: Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Highly active RRMS: No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed Disability Accumulation up to EOS (secondary endpoint)						
Patients with 12-week CDA						
Highly active RRMS: Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Highly active RRMS: No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with 24-week CDA						
Highly active RRMS: Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Highly active RRMS: No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FSIQ-RMS Change from Baseline to Week 108 (secondary endpoint)						
Highly active RRMS: Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Highly active RRMS: No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CUALs from Baseline to Week 108 (secondary endpoint)						
Highly active RRMS: Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

			[redacted]		[redacted]	[redacted]
Highly active RRMS: No		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARR = annualised relapse rate; CDA = Confirmed Disability Accumulation; CL = confidence limit; CUALs= Combined Unique Active Lesions; EOS = end of study; ITT = intent-to-treat; FSIQ-RMS=Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; LS=least squares

[a]P-value estimated from model with treatment, subgroup, and treatment by subgroup interaction.

Unadjusted results are presented.

B.2.7.2 Patients with highly active RRMS (NICE definition, post hoc analysis)

A post-hoc subgroup analysis of OPTIMUM was conducted in patients with highly active RRMS, defined according to NICE criteria as patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with a DMT.(158)

Results were consistent with those observed in the main analysis [redacted] with ponesimod compared with teriflunomide for patients with highly active RRMS.(158) Similar results were observed using the NICE definition of 'highly active' compared with the definition used in the OPTIMUM trial (Figure 13 and Table 18).(158)

Figure 13: OPTIMUM: Subgroup analysis results for treatment effect in patients with highly active RRMS per OPTIMUM and NICE criteria for ARR (ITT)(158)

ARR = annualised relapse rate; CL = confidence limit; ITT = intent-to-treat; NICE = The National Institute for Health and Care Excellence; RR = rate ratio
Source: Janssen data on file, 2021(158)

Table 18: OPTIMUM: Subgroup analysis results for treatment effect in patients with highly active RRMS per OPTIMUM and NICE criteria for 12-week CDA (ITT)(158)

	Ponesimod 20 mg		Teriflunomide 14 mg		Ponesimod 20 mg vs. Teriflunomide 14 mg
	Number of Patients	Outcome	Number of Patients	Outcome	
Highly active RRMS (OPTIMUM definition)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Highly active RRMS (NICE definition)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARR = annualised relapse rate; CDA = Confirmed Disability Accumulation; CL = confidence limit; ITT = intent-to-treat population; NICE = The National Institute for Health and Care Excellence; RR = rate ratio
Source: Janssen data on file, 2021(158)

B.2.7.3 Patients with RRMS excluding SPMS (prespecified analysis)

A pre-planned subgroup analysis of OPTIMUM was conducted in patients with RRMS (excluding SPMS).(6)

Overall, 97.4% (n=1,104) of patients in the OPTIMUM ITT had RRMS disease at baseline.(6) Results for primary and secondary endpoints in the RRMS subgroup were consistent with those observed in the main analysis, demonstrating improvements in ARR, CDA, fatigue and inflammatory lesions on MRI with ponesimod compared to teriflunomide (Table 19).(6)

Results of treatment-by-subgroup interaction tests showed a [redacted] interaction between the RRMS and SPMS subgroups for the cumulative number of CUALs but not for the primary or other secondary endpoints (Table 19).

Table 19: OPTIMUM: Subgroup analysis results for treatment effect in patients with RRMS (ITT)(6)

	p-value for Interaction[a]	Ponesimod 20 mg		Teriflunomide 14 mg		Ponesimod 20 mg vs. Teriflunomide 14 mg
		Number of Patients	Outcome	Number of Patients	Outcome	
ARR (confirmed relapses up to EOS; primary endpoint)						
RRMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed Disability Accumulation up to EOS (secondary endpoint)						
Patients with 12-week CDA						
RRMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with 24-week CDA						

	p-value for Interaction[a]	Ponesimod 20 mg		Teriflunomide 14 mg		Ponesimod 20 mg vs. Teriflunomide 14 mg
RRMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FSIQ-RMS Change from Baseline to Week 108 (secondary endpoint)						
RRMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CUALs from Baseline to Week 108 (secondary endpoint)						
RRMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARR = annualised relapse rate; CDA = Confirmed Disability Accumulation; CL = confidence limit; CUALs = Combined Unique Active Lesions; EOS = end of study; ITT = intent-to-treat; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; LS = least squares; RRMS = relapsing-remitting multiple sclerosis

[a]P-value estimated from model with treatment, subgroup, and treatment by subgroup interaction.

Unadjusted results are presented.
Source: Janssen data on file, 2020(6)

B.2.8 Meta-analysis

The SLR identified only a single trial (OPTIMUM) that included a head-to-head comparison of ponesimod and teriflunomide. Therefore, a meta-analysis is not required.

B.2.9 Indirect and mixed treatment comparisons

Summary points

- The SLR (described in Section B.2.1) identified 46 trials with ≥80% patients with RRMS, that were eligible for inclusion in a NMA to determine the relative efficacy and safety of ponesimod to other DMTs (at dosages licenced in the UK).
- NMAs were conducted for the outcomes of ARR, 3-month CDA, 6-month CDA and treatment discontinuation. The base case NMAs compared the ITT populations of eligible trials for each outcome and a subgroup analysis was conducted for the three efficacy outcomes on people with highly active RRMS.
- [redacted] In the base case NMAs, ponesimod had a [redacted] probability of reducing ARR compared with [redacted]
  - [redacted] evaluated in the NMA for ARR and was ranke [redacted]
- [redacted] In the subgroup analysis, ponesimod performed [redacted] in terms of reducing ARR, while having a [redacted] probability of reducing ARR compared with [redacted]
  - [redacted] evaluated in the NMA for ARR and was ranked [redacted]

- In the base case NMAs, ponesimod behaved [redacted] with respect to disability accumulation at 3 months and 6 months
  - In the subgroup analysis, [redacted] for the two CDA outcomes.
- With regards to treatment discontinuation, ponesimod was [redacted] robability of premature treatment discontinuation compared to [redacted].

RCTs identified in the SLR (detailed in Section B.2.1 and Appendix D.3) informed the network meta-analyses (NMAs) to compare the efficacy and safety of ponesimod against DMTs listed in the final scope with positive reimbursement decisions from NICE in patients with RRMS. Several studies identified in the SLR included a mixed population of patients with RRMS and SPMS. Since the decision problem in the company submission focuses on RRMS, only studies which included ≥80% RRMS patients were included in the NMA, based on IQWiG guidance.(159) The main analysis was focused on the ITT population of OPTIMUM (97.5% RRMS) and a subgroup analysis was conducted separately for patients with pre-specified highly active RRMS (35% of ITT population). These two sets of analyses informed the comparative effectiveness of ponesimod against NICE-recommended first-line and second-line treatments in RRMS. Subgroup analyses of patients with active RRMS only were not feasible due to lack of comparator data.

In line with recent NICE appraisals in MS (TA533, TA616, TA624)(134, 160, 161) and the outcomes considered in the cost-effectiveness model (CEM) for ponesimod (described in Section B.3), NMAs were conducted for the outcomes of ARR, 3-month CDA, 6-month CDA and treatment discontinuations. The four planned outcomes were analysed as follows:

- ARR: Total exposure (in person-years) per arm was considered and treatment effects were reported as rate ratios (RR) (see Appendix D.4). For the outcome of ARR, data were modelled using a Poisson model with log link and relative treatment effects were reported as RRs. Three trials reported a range of follow-up duration(148, 162, 163) (i.e., minimum and maximum follow-up duration); therefore, the mean or median treatment duration was considered for analyses of ARR.
- Confirmed disability accumulation over 3 months / 6 months: For the two CDA outcomes, a normal model with identity link for treatment difference data was used to derive comparisons between interventions for the two CDA outcomes. Mean HR for the time-to-event outcome and its 95% CI were preferentially extracted for the two CDA outcomes.

- Treatment discontinuation was based on premature discontinuation rates reported in clinical trials and was analysed as a dichotomous outcome based on the proportion of patients who discontinued study treatments due to any cause during the duration of the trials. In order to ascertain the frequency of treatment discontinuations, discontinuations from the clinical study was combined with discontinuations from treatment (where patients remained on-study and where this was clearly reported and mutually exclusive from study discontinuations), and therefore, captured all patients who stopped treatment across all trials and with broad consistency for this outcome. A binomial model with logit link was used to compare interventions for all-cause withdrawals and ORs were used as the treatment effect measures.

All NMAs were performed using a Bayesian framework based on Markov Chain Monte Carlo simulation, as described in NICE Decision Support Unit Technical Support Document (DSU TSD 2).(164-166) Unadjusted, random effects models as well as fixed effects models were used to conduct analyses. The model with the best fit based on the deviance information criterion (DIC) was selected for the main analysis of each outcome; model fit statistics are presented in Appendix D.4. In accordance with NICE Evidence Synthesis DSU TSD 2 series, vague prior distributions that assume no pre-existing information were assigned for treatment effects, trial baselines, and common regression terms. NMAs with an informed prior distribution were conducted as a sensitivity analysis.

Additional information on the methodology used in the NMA, inclusion and exclusion criteria, the full list of included studies and exemplar code for the main analyses of each endpoint are provided in Appendix D.4. The heterogeneity between trials included in the NMA is summarised in B.2.9.5.

B.2.9.1 Summary of trials

A summary of the trials used in the main NMAs for the ITT populations is provided in Table 20.

Table 20: Summary of trials used in the NMA of patients with RRMS

Trial name	Intervention	ARR	3-month CDA	6-month CDA	Treatment discontinuations
ADVANCE(167)	Peginterferon 125 µg 2W	✓	✓	✓	✓
	Placebo				
AFFIRM(168)	Natalizumab 300 mg 4W	✓	✓	✓	✓
	Placebo				
APEX Part I (169)	Dimethyl fumarate 240 mg BID	✓			✓
	Placebo				

Trial name	Intervention	ARR	3-month CDA	6-month CDA	Treatment discontinuations
ASSESS(170)	Glatiramer acetate 20 mg QD	✓			✓
	Fingolimod 0.5 mg QD				
BEYOND(171)	Glatiramer acetate 20 mg QD	✓			✓
	Interferon beta-1b 250 µg QOD				
Boiko, 2018 (172)	Glatiramer acetate 20 mg QD	✓			✓
	Placebo				
BRAVO(173)	Interferon beta-1a 30 µg IM QW	✓	✓	✓	✓
	Placebo				
CAMMS223 (174)	Alemtuzumab 12 mg QD	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
CARE-MS I (175)	Alemtuzumab 12 mg QD	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
CARE-MS II (176)	Alemtuzumab 12 mg QD	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
CLARITY(8)	Cladribine 3.5 mg/kg QD	✓	✓	✓	✓
	Placebo				
CombiRx (177)	Glatiramer acetate 20 mg QD	✓			✓
	Interferon beta-1a 30 µg IM QW				
CONFIRM(178)	Glatiramer acetate 20 mg QD	✓	✓	✓	✓
	Dimethyl fumarate 240 mg BID				
	Placebo				
COPOLYMER 1 (179)	Glatiramer acetate 20 mg QD	✓			✓
	Placebo				
DEFINE(180)	Dimethyl fumarate 240 mg BID	✓	✓	✓	✓
	Placebo				
Eur/Can GA (181)	Glatiramer acetate 20 mg QD	✓			✓
	Placebo				
EVIDENCE (182)	Interferon beta-1a 30 µg IM QW	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
FREEDOMS (150)	Fingolimod 0.5 mg QD	✓	✓	✓	✓
	Placebo				
FREEDOMS II (183)	Fingolimod 0.5 mg QD	✓	✓	✓	✓
	Placebo				
GALA (184)	Glatiramer acetate 40 mg TIW	✓			✓
	Placebo				
GATE (185)	Glatiramer acetate 20 mg QD (brand name)	✓			✓
	Glatiramer acetate 20 mg QD (generic)				

Trial name	Intervention	ARR	3-month CDA	6-month CDA	Treatment discontinuations
	Placebo				
GLACIER (186)	Glatiramer acetate 20 mg QD				✓
	Glatiramer acetate 40 mg TIW				
IFNB-MS (187)	Interferon beta-1b 250 µg QOD	✓			
	Placebo				
IMPROVE(188)	Interferon beta-1a 44 µg SC TIW				✓
	Placebo				
INCOMIN(189)	Interferon beta-1b 250 µg QOD	✓			✓
	Interferon beta-1a 30 µg IM QW				
Mokhber, 2015 (190)	Interferon beta-1a 30 µg IM QW				✓
	Interferon beta-1a 44 µg SC TIW				
	Interferon beta-1b 250 µg QOD				
MSCRG(191)	Interferon beta-1a 30 µg IM QW	✓			
	Placebo				
OPERA I(22)	Ocrelizumab 600 mg 24W	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
OPERA II(22)	Ocrelizumab 600 mg 24W	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
OPTIMUM(149)	Ponesimod 20 mg QD	✓	✓	✓	✓
	Teriflunomide 14 mg QD				
Ph2/Evobrutinib/ Montalban(192)	Dimethyl fumarate 240 mg BID	✓			✓
	Placebo				
Ph2/NAT/ Saida(193)	Natalizumab 300 mg 4W	✓			✓
	Placebo				
Ph2/OCR/ Kappos(194)	Ocrelizumab 600 mg 24W	✓			✓
	Interferon beta-1a 30 µg IM QW				
	Placebo				
Ph2/PON/ Olsson(142, 195)	Ponesimod 20 mg QD	✓			✓
	Placebo				
PRISMS(196-198)	Interferon beta-1a 22 µg SC TIW	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW				
	Placebo				
RADIANCE A* (199)	Ozanimod 1 mg QD	✓			✓
	Placebo				
RADIANCE B (200)	Ozanimod 1 mg QD	✓	✓	✓	✓
	Interferon beta-1a 30 µg IM QW				

Trial name	Intervention	ARR	3-month CDA	6-month CDA	Treatment discontinuations
REFORMS(201)	Interferon beta-1a 44 µg subcutaneous TIW				✓
	Interferon beta-1b 250 µg QOD				
Saida, 2012 (FIN)(202)	Fingolimod 0.5 mg QD	✓			✓
	Placebo				
SUNBEAM(162)	Ozanimod 1 mg QD	✓	✓	✓	✓
	Interferon beta-1a 30 µg IM QW				
TEMSO(116)	Teriflunomide 14 mg QD	✓	✓	✓	✓
	Placebo				
TENERE(163)	Teriflunomide 14 mg QD	✓			✓
	Interferon beta-1a 44 µg SC TIW				
TER-MS(203)	Teriflunomide 14 mg QD	✓			✓
	Placebo				
TOWER(148)	Teriflunomide 14 mg QD	✓	✓	✓	✓
	Placebo				
TRANSFORMS(204)	Fingolimod 0.5 mg QD	✓	✓		✓
	Interferon beta-1a 30 µg IM QW				

*Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission.

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ARR = annualised relapse rate; BID = twice daily; CDA = confirmed disability accumulation; HR = hazard ratio; IM = intramuscular; NMA = network meta-analysis; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TIW = three times per week

Note: Dosages not approved by the EMA were not included in the analysis and are not shown in the table.

B.2.9.2 Results of the base case NMAs (ITT Populations)

The main analysis of the NMA evaluated the relative efficacy and safety of ponesimod compared with NICE-recommended DMTs for the treatment of patients with RRMS. Based on the model fit statistics, a fixed effects model with vague priors was determined to be the best fit to analyse ARR, 3-month CDA and 6-month CDA, whereas a random effects model with vague priors was the best fit for treatment discontinuations. Sensitivity analyses for each of these outcomes using the alternate framework (i.e., random effects for efficacy outcomes and fixed effects for treatment discontinuation) are described in Appendix D.

B.2.9.2.1 ARR

There were 41 RCTs and 17 regimens (including placebo) included in the network for ARR (Figure 14). All DMTs specified in the PICOS and at licenced dosages in the UK were represented in the network, with most connections supported by one or two trials. With the exception of alemtuzumab, all DMTs were anchored directly to the placebo node.

The results of the ARR analysis in the ITT populations of the trials are presented in a forest plot in Figure 15 and a league table in Appendix D.8. Overall, ponesimod ranked [redacted] evaluated in the NMA for ARR in patients with RRMS and was ranked [redacted] Ponesimod was found to have a [redacted] probability of reducing relapses compared with [redacted]. In line with previous appraisals, [redacted].(205)

Sensitivity analyses of the ARR outcome are discussed in Section B.2.9.6 and presented in Appendix D.9.

Figure 14: Network diagram for the base-case NMA of ARR (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

Figure 15: Forest plot of ponesimod versus treatments in the base case NMA for ARR (ITT Population)

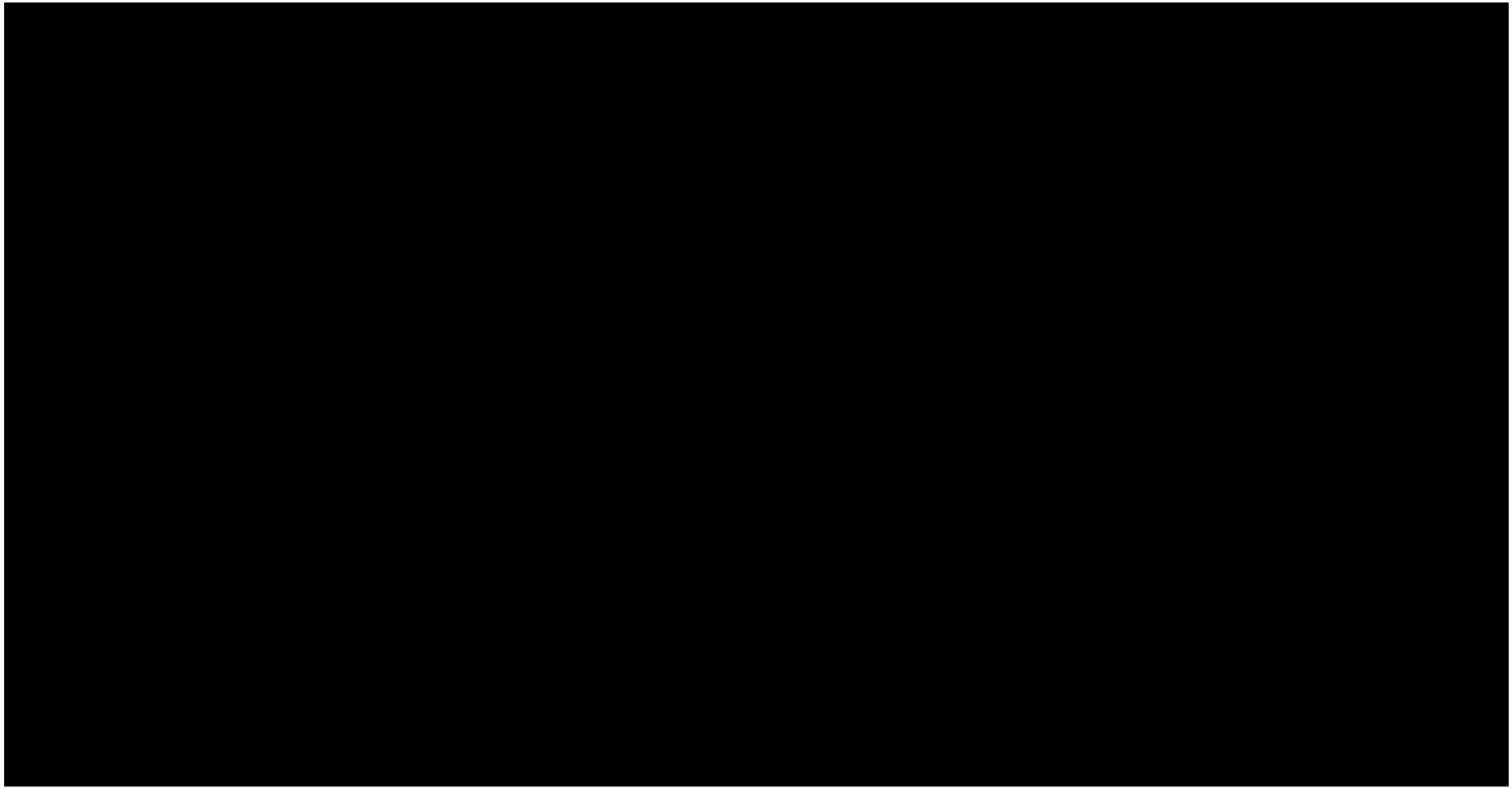
2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; CrI = credible interval; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

B.2.9.2.2 3-month CDA

There were 21 RCTs and 15 regimens (including placebo) included in the network for 3-month CDA (Figure 16). All DMTs specified in the PICOS, and all UK approved regimens except glatiramer acetate (40 mg TIW) and IFN beta-1b (250 µg QOD) were represented in the network.

Figure 16: Network diagram for the base case NMA of 3-month CDA (ITT Population)



2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

The relative efficacy of ponesimod versus other treatments for 3-month CDA based on the NMA in the ITT populations of the trials are presented in the forest plot in Figure 17 and a league table in Appendix D.8. [redacted] probability at [redacted] the proportions of patients with [redacted] Overall, ponesimod ranked [redacted]

Figure 17: Forest plot of ponesimod versus treatments in the base case NMA for 3-month CDA (ITT Population)

[redacted]

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; CrI = Credible interval; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

B.2.9.2.3 6-month CDA

There were 20 RCTs and 14 regimens (including placebo) included in the network for 6-month CDA (Figure 18). All DMTs specified in the PICOS and all UK approved regimens except glatiramer acetate (40 mg TIW), IFN beta-1a (22 µg SC TIW) and IFN beta-1b (250 µg QOD) were represented in the network. Heterogeneity in trial duration was also noted, although all trials included in the NMA were of more than 1 year in duration.

Figure 18: Network diagram for the base case NMA of 6-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

The results of the NMA in the ITT populations of the trials are presented in the forest plot in Figure 19 and a league table in Appendix D.9. [redacted]. Overall, ponesimod ranked [redacted].

Figure 19: Forest plot of ponesimod versus treatments in an NMA for 6-month CDA in patients with RRMS

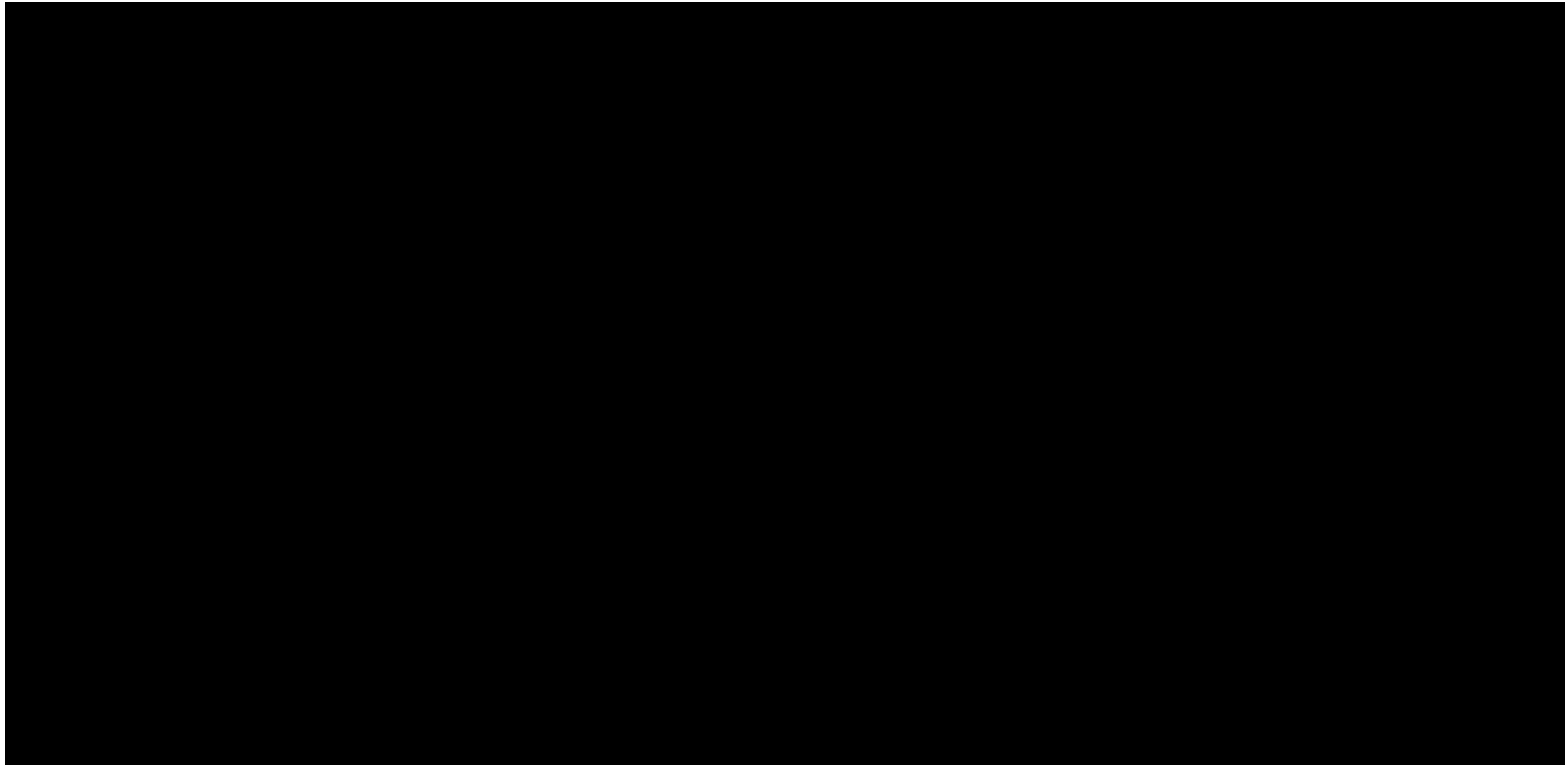
2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; CrI = credible interval; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

B.2.9.2.4 Treatment discontinuations

There were 43 RCTs and 17 regimens (including placebo) included in the network for treatment discontinuations in the ITT populations of the trials (Figure 20). All DMTs specified in the PICOS and all UK approved regimens were represented in the network.

Figure 20: Network diagram for the base case NMA of treatment discontinuation (ITT Population)



2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; RRMS = relapsing-remitting multiple sclerosis; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

The results of the NMA for treatment discontinuations are described in a forest plot in Figure 21 and a league table in Appendix D.8. All DMTs except [redacted] for this outcome. [redacted] probability of low treatment discontinuations compared with [redacted]. Overall, ponesimod was ranked [redacted] included in the analysis and ranked [redacted]

Figure 21: Forest plot of ponesimod versus treatments in an NMA for treatment discontinuations in patients with RRMS

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CLA = cladribine; CrI = credible interval; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; QD = every day; QOD = every other day; QW = weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the draft scope but is not reported here since it is still undergoing appraisal and is not a NICE-recommended treatment option at the time of submission

A sensitivity analysis of treatment discontinuations using a fixed effects model showed similar results to the base case analysis (described in Section B.2.9.6).

B.2.9.3 Results of NMAs in highly active RRMS

The efficacy of ponesimod versus NICE recommended DMTs in patients with highly active RRMS was evaluated separately as a subgroup analysis in line with the decision problem

(section B.1.1). For this analysis, the comparators were restricted to NICE-recommended treatments for highly active RRMS (i.e., alemtuzumab, cladribine, fingolimod and ocrelizumab) and other DMTs were only included if they were essential for connecting the network. Natalizumab was excluded from this analysis since it is not recommended for highly active RRMS by NICE.

Publications and reports identified in the SLR were reviewed for data on patients with highly active RRMS. As the definition of high disease activity varied across studies, trials were selected for inclusion into the analysis based on their alignment with the definition used in the OPTIMUM trial (Section B.2.7.1). For all three efficacy outcomes, it was found that a network containing all relevant comparators would not be possible, due to a lack of reported subgroup data for some outcomes. To ensure full network connectivity, an assumption was made that the outcomes for the ITT population were equivalent to those of the highly active RRMS subgroup in these trials, similar to analyses presented in TA533.(205)

The resulting networks include all NICE-recommended second line DMTs, anchored via teriflunomide (ITT data from TEMSO and TOWER used for ARR only) and IFN beta-1a 44 µg SC TIW (ITT data from PRISMS used for all three outcomes). For the 3-month CDA network, data for the highly active subgroup was also unavailable for fingolimod and alemtuzumab. In order to facilitate the incorporation of fingolimod, a key comparator for our analysis, 6-month CDA outcome data from the pooled FREEDOMS I and II trials pertaining to highly active patients was used in place of 3-month CDA data.

Similar to the main NMAs, model fit statistics were used to determine that fixed effects (with vague prior distribution) provided the best fit for all three outcomes described below.

B.2.9.3.1 ARR: Highly active RRMS

The network for ARR in the highly active subgroup consisted of 11 trials and nine regimens (including placebo) representing all NICE-recommended highly active DMTs included in the final scope.

The NMA results are presented in forest plots (Figure 22) and in league tables (in Appendix D). Overall, ponesimod ranked [redacted] analysed, and was ranked [redacted] The analysis for ARR indicated that [redacted] probability at reducing ARR compared to [redacted].

Figure 22: Forest plot of the NMA for ARR in patients with highly active RRMS

24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; PBO = placebo; QD = every day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

B.2.9.3.2 3-month CDA: Highly active RRMS

The network for 3-month CDA in the highly active subgroup consisted of 11 trials and 8 regimens and included all NICE-recommended treatments for highly active RRMS, except for alemtuzumab.

The NMA results are presented in forest plots (Figure 23) and league tables (in Appendix D). The network contains all relevant NICE-recommended second line DMTs except [redacted]. Overall, ponesimod ranked [redacted], and was ranked [redacted]. The analysis shows that all [redacted] included in the analysis had [redacted] probabilities of reducing proportion of patients with 3-month CDA, compared to [redacted]

Figure 23: Forest plot of the NMA for 3-month CDA in patients with highly active RRMS

24W = every 24 weeks; CDA = confirmed disability accumulation; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; PBO = placebo; QD = every day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

B.2.9.3.3 6-month CDA: Highly active RRMS

The network for 6-month CDA in the highly active subgroup consisted of 10 trials and eight regimens (including placebo).

The NMA results are presented in forest plots (Figure 24) and league tables (in Appendix D.8). Overall, ponesimod ranked and was ranked All relevant second line DMTs were included in the analysis and probabilities of reducing the proportion of patients with 6-month CDA compared to

Figure 24: Forest plot of the NMA for 6-month CDA in patients with highly active RRMS

24W = every 24 weeks; ALE = alemtuzumab; CDA = confirmed disability accumulation; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; NMA = network meta-analysis; OCR = ocrelizumab; PBO = placebo; QD = every day; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

B.2.9.3.4 Treatment discontinuations: Highly active RRMS

A specific NMA for the highly active RRMS subgroup was not conducted for treatment discontinuations but results from the main analysis indicated that ponesimod was ranked lower than DMTs recommended for second-line treatment.

B.2.9.4 Subgroup analyses: RRMS (excluding patients with SPMS in OPTIMUM)

While the main NMAs included all trials with ≥80% RRMS patients, it also included four trials where the proportion of enrolled SPMS or progressive relapsing MS (PRMS) patients was unclear. Given the much higher prevalence of RRMS compared with SPMS or PRMS, the potential bias from these studies was considered minimal. However, additional analyses were conducted using trials that only included RRMS patients or reported subgroup data for RRMS patients separately from the RMS population (e.g., OPTIMUM) to check if there were any differences in the relative efficacy of ponesimod versus other DMTs compared with the base case analyses.

Thirty-one trials were identified from the original SLR that reported data for 100% RRMS populations. Forest plots describing these data are presented in Appendix D.8

The subgroup analyses in patients with RRMS showed consistent results with the base case analyses. Similar to the base case analysis, ponesimod was ranked [redacted] evaluated in the NMA for ARR and was ranked [redacted] Ponesimod was found to have a [redacted] probability of reducing relapses compared with [redacted] .

Subgroup analyses of the NMA for patients with RRMS for 3-month CDA and 6-month CDA showed consistent results with the base case analyses. For 3-month CDA, [redacted] probability at reducing the proportion of patients compared with [redacted] Ponesimod was ranked [redacted] For 6-month CDA, all DMTs [redacted] probability of disability accumulation as [redacted] had a higher probability of lower 6-month CDA scores compared to [redacted] In this analysis, ponesimod ranked [redacted] .

B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

A limitation of the NMA is uncertainty arising from heterogeneity between trials included in the networks, due to differences in study designs and patient characteristics. Although the majority of trials were double-blind or single-blind, three trials (GLACIER, INCOMIN and REFORMS) were open-label design. All but two trials (BEYOND and Mokhber 2015) reported modified or true intention-to-treat analyses. Although the majority of trials (n = 33) were conducted internationally, eight trials were conducted in single countries: Russia (Boiko 2018), Italy (INCOMIN), Japan (Ph2/NAT/Saida, Saida 2012), Iran (Mokhber 2015) and the US (COPOLYMER 1, GLACIER and REFORMS).

Variation in trial duration may act as a source of heterogeneity. Thirteen trials were less than one year long (the majority of which were phase 2) whereas most trials (n = 25) were one to two years long, and six trials were longer than two years. Patient enrolment spanned a very long timeframe, starting in 1991 and ending in 2018. As such, there is a large degree of heterogeneity in patient experiences, particularly with respect to prior DMT use, amongst the trials. Although most trials enrolled exclusively RRMS patients, there were nine trials which

included SPMS and/or PRMS patients, and three trials (OPERA I and II and RADIANCE A) where the proportion of enrolled SPMS or PRMS patients was unclear (populations were termed “relapsing multiple sclerosis”).

For the ARR analysis, all trials in the network except the Russian trial of glatiramer acetate (Boiko 2018) reported a clear definition of ARR. Similar proportions of trials used Poisson regression analyses and negative binomial regression analyses to analyse ARR. Where authors indicated a time requirement for relapse symptom persistence, either 24 hours or 48 hours was stated. The majority of trials (n = 33) specified that neurologic symptoms were required to define a relapse, and a large number of trials (n = 21) further specified that an EDSS increase of at least 0.5 points was required. There were no ARR definitions that were considered outliers.

For the CDA analyses, all trials in the network reported outcomes with definitions aligned with that used in the OPTIMUM trial. Terminology varied (e.g., progression, accumulation); however, the definitions were deemed equivalent in all cases. Per the PICOS criteria, all CDA definitions were based upon EDSS score changes alone, the thresholds for which were considered aligned. Several historic MS trials for established DMTs did not report the hazards for 6-month disability progression, (163, 169, 170, 172, 179, 184, 204, 206) an outcome that is now considered to be relevant for Health Technology Assessment (HTA). To ensure that these analyses remained robust and did not increase the uncertainty of outcomes, only trials with reported hazard ratios were included in the NMAs. As a result, the networks for both CDA outcomes did not include IFN β-1b (250 µg) and glatiramer acetate (40 mg), while the network for 6-month CDA additionally did not include IFN β-1a (22 µg). It was not anticipated that these missing data would affect the outcomes substantially, given that both networks included alternate beta interferons (IFN β-1a [30 µg], IFN β-1a [44 µg]) and an alternate dose for glatiramer acetate (20 mg). Our analyses are aligned with previous appraisals whereby the evidence networks for 3-month CDA contain more data and may be considered to consist of more reliable data as compared to 6-month CDA, given that a greater proportion of trials in the 3-month CDA network defined the outcome as either a primary or secondary endpoint. The 6-month CDA networks have a higher degree of uncertainty and the results should be interpreted with caution.

In the NMAs, ponesimod demonstrated favourable results against most comparators for the efficacy outcomes; however, it ranked lower with regards to premature treatment discontinuation. While this suggests that ponesimod has a less favourable profile than its comparators, the results of the long-term phase 2 extension study suggest otherwise.(49) Over a period of 9 years of continuous treatment, overall 39.3% of patients prematurely discontinued treatment. However, only [redacted] of patients randomised to ponesimod 20 mg in

the study discontinued due to an adverse event or tolerability issues and [redacted] due to lack of efficacy.(207) A limitation of the NMA is that it compares the discontinuation across trials with durations range from 16 weeks (186, 188) to 168 weeks (171), and sample sizes ranging from 69 patients (190) to 2,244 patients(171). When comparing discontinuation rates reported for DMTs in recent technology appraisals, the calculated rates for some comparators vary substantially (e.g. DMF 6.98% - 18.01%),(134, 135) highlighting the variability in results depending on the trials included in the SLR and the methods used. A sensitivity analysis within the model that assumes equivalent discontinuation rates results in an improved cost effectiveness of ponesimod versus first-line comparators. Another limitation of the analysis is the inclusion of DMTs such as alemtuzumab and cladribine within the same network. These DMTs are routinely prescribed as induction treatments and are taken over a couple of weeks every year over a two-year period. In comparison to the other DMTs, there is a relatively large “treatment-free” period for patients on these treatments, which may bias the results in favour of these treatments and influence the odds ratios of other DMTs within the network.

It should be noted that results of NMAs are largely dictated by the number of studies informing individual connections, and also by the number of connections between DMTs. For ponesimod in particular, comparisons to DMTs other than teriflunomide were often connected through key teriflunomide trials such as TOWER and TEMSO. For DMTs not investigated in a placebo-controlled trial, an additional connection was required to reach ponesimod. Considering the base case NMAs for CDA outcomes and all-cause treatment discontinuations, there was considerable variability in the data, which resulted in effect estimates with considerable overlap and prevented conclusions about the superiority of one agent over another.

B.2.9.5.1 Risk of bias of studies included in indirect or mixed treatment comparisons

Risk of bias was generally low across the included studies with respect to selection bias categories, though several studies did not report adequate detail regarding randomisation and allocation to determine the risk of bias (Appendix D.3). Potential for performance bias and other biases (defined here as balance of patient withdrawals between arms, and balance of patient baseline traits between arms) were more variable, largely due to the inclusion of single-blinded trials. Potential for attrition bias and reporting bias were generally low.

B.2.9.6 Sensitivity analyses

In addition to the primary and subgroup analyses described, sensitivity analyses were conducted for each outcome to test the sensitivity of the results to heterogeneity and varying methodology between trials. Sensitivity analyses and relevant results are presented in Appendix D.4 and Appendix D.9 and included the following:

- NMAs with random effects models and vague priors for ARR, 3-month CDA and 6-month CDA
- An NMA with fixed effects model for treatment discontinuations
- NMAs of the highly active RRMS subgroup with inclusion of ITT data for teriflunomide from the TEMSO and TOWERS RCTs for 3-month and 6-month CDA

For ARR, 3-month CDA and 6-month CDA, use of a random effects model with vague priors showed results that were consistent with the main analyses for these three outcomes, with the exception that [redacted] For treatment discontinuation, use of a fixed effects model was consistent with the main analysis, although [redacted]

A sensitivity analysis for 3-month and 6-month CDA in the highly active RRMS subgroup using ITT data from the TEMSO and TOWER trials showed consistent results with the main subgroup analysis (see B.2.9.3).

For further details on the results of sensitivity analyses please refer to Appendix D.9.

B.2.10 Adverse reactions

B.2.10.1 Pooled safety data from the ponesimod clinical program in MS

A total of [redacted] received at least one dose of ponesimod in phase 2 and phase 3 studies in MS.(47) Although results from the individual studies allowed for effective characterisation of safety, analyses of pooled data from these studies were conducted to identify any additional safety signals and to evaluate the long-term safety of ponesimod.

The long-term pooled analysis set included all [redacted] with MS who received double-blind or open-label treatment with ponesimod (10 mg, 20 mg or 40 mg) in phase 2 and phase 3 trials, including a total of [redacted] treated with ponesimod 20 mg.(47) An overview of exposure to ponesimod 20 mg in studies included in the long-term pooled analysis set is provided in Table 21.

Table 21: Exposure to ponesimod 20 mg in studies included in the long-term pooled analysis set

Study	n	Data cut-off date	Median treatment exposure (range)	Patient-years of exposure
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: Janssen Data on file (2020)(208)

B.2.10.2 Summary of adverse events from the OPTIMUM trial

Overall, the proportion of subjects who experienced at least 1 TEAE during the OPTIMUM trial was similar in the two treatment groups (Table 22). The proportions of subjects with severe AEs, drug-related AEs, and AEs leading to study drug discontinuation were higher in the ponesimod 20 mg group compared with the teriflunomide 14 mg group. The difference in the type of AEs leading to treatment discontinuation was mainly driven by anticipated class effects of S1P1 modulators on the respiratory system, macular oedema, and protocol-mandated study-specific criteria for study treatment discontinuation. No infections led to permanent study treatment discontinuation in the study. Two patients in the teriflunomide 14 mg group had a fatal AE; however, both events were considered not related to study drug by the investigator.(6)

Table 22 Overview of Treatment-Emergent Adverse Events, Safety Set(6)

	Ponesimod 20 mg N=565 n (%)	Teriflunomide 14 mg N=566 n (%)
Subject with at least one:		
AE	502 (88.8)	499 (8.2)
Severe AE	[redacted]	[redacted]
AE leading to study discontinuation	49 (8.7)	34 (6.0)
Serious AE	49 (8.7)	46 (8.1)
Fatal AE	0 (0.0)	2 (0.4)

AE=Adverse event

For detailed safety results from the OPTIMUM study, please refer to Appendix F.1.

B.2.10.3 TEAEs overall

An overview of TEAEs in the long-term pooled analysis is presented in Table 23.

Table 23: Summary of TEAEs (long-term pooled analysis set)(47)

TEAE	Ponesimod 20 mg [redacted] n (%)
Any TEAE	[redacted]
Severe TEAE	[redacted]
Serious TEAE	[redacted]
TEAE leading to discontinuation	[redacted]
TEAE leading to death	[redacted]

TEAE = treatment-emergent adverse event.

Most TEAEs were [redacted]. SAEs occurred in [redacted]

in the ponesimod 20 mg group in the long-term pooled analysis set. The most commonly reported serious AEs in the ponesimod 20 mg group were [redacted] and the following events that occurred in [redacted]

The most frequently reported ([redacted] ponesimod 20 mg group were [redacted].(47)

During the phase 2 and phase 3 studies in patients with MS no deaths were deemed by investigators as related to study treatment.(47)

B.2.10.4 TEAEs by preferred term

In the long-term pooled analysis set, [redacted] of patients [redacted] in the ponesimod 20 mg group reported at least one TEAE. The most frequently reported (≥10% of patients) TEAEs in the ponesimod 20 mg group included [redacted]. A summary of the most commonly reported TEAEs (≥5% of patients) by preferred term is provided in Table 24.(47)

Table 24: TEAEs occurring in ≥5% of patients in the ponesimod 20 mg group, by preferred term* (long-term pooled analysis set)(47)

TEAE	Ponesimod 20 mg, [redacted] n (%)
Nasopharyngitis	[redacted]
Alanine aminotransferase increased	[redacted]
Headache	[redacted]
Upper respiratory tract infection	[redacted]
Lymphopenia	[redacted]
Hypertension	[redacted]
Fatigue	[redacted]

TEAE	Ponesimod 20 mg, [redacted] n (%)
Back pain	[redacted]
Urinary tract infection	
Nausea	
Aspartate aminotransferase increased	

*Preferred Terms are based on MedDRA version 21.0 and are sorted by descending order of frequency.

B.2.10.5 Adverse events of special interest

Adverse events of special interest (AESIs) were identified based on events associated with MS comorbidities, preclinical assessment, and prior safety experience with ponesimod and other S1P receptor modulators. The following AESIs were assessed in the long-term pooled analysis set: hypertension, hepatobiliary disorders/liver enzyme abnormalities, pulmonary events, macular oedema, infection, herpetic infection, skin malignancy, non-skin malignancy, and seizure. Bradyarrhythmia and hypotension events also were AESIs but were assessed only at the study level. An overview of AESIs reported in the long-term pooled analysis set is provided in Table 25.(47)

Overall, the ponesimod safety profile was found to be in line with other S1P modulators.

Table 25: Adverse events of special interest (long-term pooled analysis set)(47)

Event	Narrative
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Event	Narrative
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

B.2.11 Ongoing studies

A summary of all completed and ongoing studies that should provide additional clinical evidence for ponesimod in RMS in the next 12 months are shown in Table 26.

Table 26: Clinical trials for the evaluation of ponesimod in patients with RMS

Study	Target indication/population	Key objectives	Phase	N	Description	Trial start date	Estimated primary completion date
AC-058B303 (OPTIMUM-LT)	Patients with RMS	• To describe the long-term safety and tolerability of ponesimod 20 mg QD • To describe the effects of re-initiation of ponesimod treatment after interruption • To describe the long-term disease control in patients receiving ponesimod 20 mg QD • To describe the effect of a switch from teriflunomide to ponesimod 20 mg QD on disease control	3	N=877	Long-term extension study of AC-058B301 (OPTIMUM)	July 2017	April 2022
AC-058B202	Patients with RRMS	• To investigate the long-term safety and tolerability of ponesimod • To investigate the long-term efficacy of ponesimod • To explore the dose-response relationship of ponesimod 10 mg, 20 mg, and 40 mg QD on lymphocyte count, MRI endpoints, ARR and safety endpoints	2b	TP1, n=353 TP2, n=305 TP3, n=228*	Long-term extension study of AC-058B201	May 2010	December 2021

ARR = annualised relapse rate; MRI = magnetic resonance imaging; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; TP = treatment period; QD = once daily
*The AC-058B202 study consists of 3 treatment periods

B.2.12 Long-term efficacy and safety of ponesimod

Evidence on the long-term efficacy and safety of treatment with ponesimod is available from the AC-058B202 and OPTIMUM-LT studies, as described below. For further details on the methodology of these studies, please refer to Appendix E.4.

B.2.12.1 Phase 2 AC-058B202 study

AC-058B202 is a phase 2, randomised, double-blind, multiple-dose, uncontrolled, parallel group extension study of patients with RRMS who completed the phase 2 dose-finding study AC-058B201.(147)

Safety analysis was conducted over the combined treatment period of AC-058B201 and AC-058B202 (Table 27). As of the 31 March 2019 cut-off date:(49)

- The cumulative exposure across all doses of ponesimod was 2372.5 patient-years
- The median exposure in the ponesimod 20 mg group was 8.0 (range: 0-9.4) years
- The most frequently reported TEAEs (≥10% of patients in any group) were nasopharyngitis, headache, URTI, ALT increased, influenza, dyspnoea, cough, and peripheral oedema(49)
- Ponesimod 20 mg demonstrated high levels of treatment persistence; after up to 9 years of follow-up, 52% of patients in the ponesimod 20 mg group were continuing treatment, 9% completed treatment and 39.3% had prematurely discontinued treatment.(209) Overall, treatment persistence over the 9 year period was reported in 61% of patients (Figure 25).(49)
- The most frequently cited reason for discontinuation of ponesimod 20 mg was patient decision (40.4%) due to pregnancy planning or issues with visiting study sites.(209)

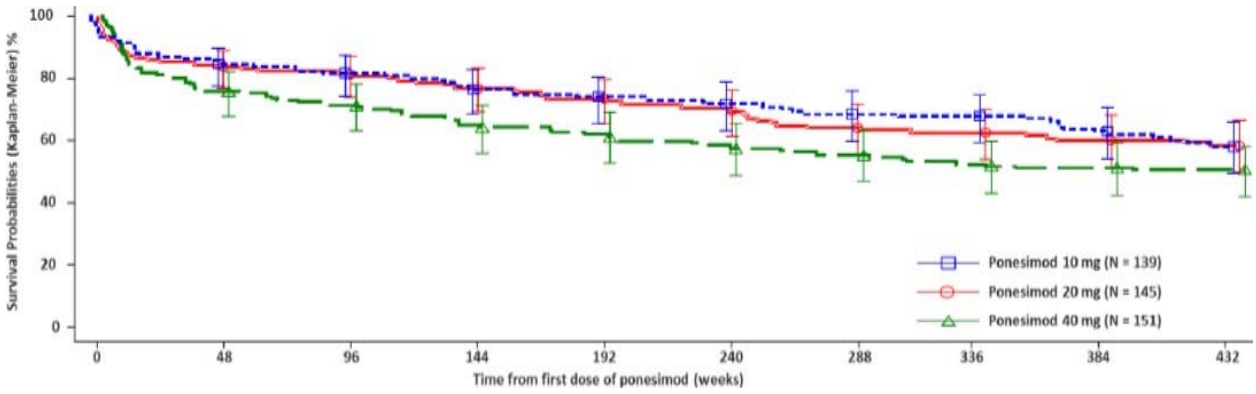
Table 27: Safety results from the ponesimod phase 2 core and extension studies(49)

Parameter, n (%)1	**Ponesimod (from core to 432 weeks)**			
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**	**Total (N=435)**
Patients with ≥1 TEAE	132 (95.0)	132 (91.0)	148 (98.0)	412 (94.7)
Patients with ≥1 serious TEAE	27 (19.4)	27 (18.6)	23 (15.2)	77 (17.7)
Patients with ≥1 TEAE leading to treatment discontinuation	20 (14.4)	16 (11.0)	34 (22.5)	70 (16.1)
Death	0	1 (0.7)	0	1 (0.2)

TEAE = treatment emergent adverse event

Source: Freedman, 2020(49)

Figure 25: Time to Premature Treatment Discontinuation in the AC-058B202 study



Note: Data are presented for the combined treatment period of AC-058B201 and AC-058B202
Source: Keenan 2020.(209)

Serious TEAEs and TEAEs leading to discontinuation were reported for 18.6% and 11.0% of patients treated with ponesimod 20 mg, respectively.(49) The overall safety profile of ponesimod was comparable to the OPTIMUM study, with no new safety concerns identified.(49)

A summary of the efficacy outcomes measured over the phase 2 core and extension studies in the analysis period AP3 (i.e., to the 31 March 2019 cut-off date) is presented in Table 28. Although Study B202 was not powered to test ARR or disability, there was a trend toward improvement with ponesimod treatment. The mean estimate of ARR for confirmed relapses using the ponesimod analysis set up to the end of AP3 for the 20 mg dose group was 0.15 [redacted]). (49, 207) The results in AP3 were consistent with the prior analysis periods, suggesting that the effect of ponesimod 20 mg in controlling MS disease were maintained over long-term treatment. The Kaplan-Meier estimate for the percentage of subjects who had experienced a confirmed relapse at Week 432 was 43.9% [redacted] in the 20 mg dose group.(49, 207)

Table 28 Efficacy results from the ponesimod phase 2 core and extension studies

	Ponesimod (from core to 432 weeks)		
	10 mg (n=139)	**20 mg (n=145)**	**40 mg (n=151)**
ARR (confirmed relapses), Mean	[redacted]	[redacted]	[redacted]
Number of Gd+ T1 lesions, mean/MRI timepoint	[redacted]	[redacted]	[redacted]
Patients free of new/enlarging T2 lesions, %	[redacted]	[redacted]	[redacted]
Time to 6-month CDA, %	[redacted]	[redacted]	[redacted]

ARR=annualized relapse rate; Gd+=gadolinium enhancing; MRI=magnetic resonance imaging; CDA=confirmed disability accumulation

Source: (49, 207)

Ponesimod also demonstrated favourable long-term effects for the outcome of 6-month CDA. The Kaplan-Meier estimate for the percentage of subjects in the ponesimod 20 mg dose group who had experienced a 24-week CDA at Week 432 was [redacted] (Figure 26)(207)

Figure 26 Time to first 24-week confirmed disability accumulation (Kaplan Meier curves) during AP3 study period in the AC-058B202 study(207)

[redacted]

B.2.12.2 Phase 3 OPTIMUM-LT study

OPTIMUM-LT (AC-058B303) is a phase 3, open-label, non-comparative, long-term extension study of OPTIMUM (AC-058B301).(146)

Efficacy and safety were assessed over the combined treatment period of OPTIMUM and OPTIMUM-LT over more than 4 years (240 weeks):(210)

- Ponesimod [redacted] ARR up to Week 240 compared with teriflunomide ([redacted]).
- Ponesimod was [redacted] to teriflunomide in extending time to first confirmed relapse, with [redacted] or patients experiencing an event in the ponesimod treatment group compared to [redacted] in the teriflunomide treatment group.
- Ponesimod [redacted] the number of CUALs on brain MRI compared with teriflunomide ([redacted] in the ponesimod treatment

group vs. [redacted] in the teriflunomide treatment group).

- Both 12-week and 24-week CDA endpoints were [redacted] for ponesimod compared with teriflunomide (% of patients with an event: [redacted] at 12-week, respectively; % of patients with an event: [redacted] at 24-week, respectively).
- Ponesimod [redacted] the number of new T1 Gd+ lesions ([redacted] in the ponesimod treatment group vs. [redacted] in the teriflunomide treatment group).

B.2.13 Innovation

Ponesimod provides a new treatment option for patients with RRMS, offering a balance between efficacy and safety, while having proven long-term tolerability and low rates of discontinuation.(46, 47, 49)

Key innovations relevant to patients include:

- **Balanced efficacy and safety**: Ponesimod showed significant and robust effects compared with teriflunomide across multiple endpoints, including reducing relapse rates, brain volume loss and the appearance of brain lesions.(6, 157) Safety data collected for up to 9 years of follow-up demonstrates high treatment persistence and consistent tolerability with ponesimod treatment.(46, 47, 49)
- **Convenience**: In line with patient preferences for MS treatment, ponesimod is convenient to use with once-daily dosing and oral administration.(12, 42-44)
- Additionally, as an oral treatment with rapidly reversible immunosuppressive effects, ponesimod offers flexibility during the ongoing COVID-19 pandemic, allowing people with MS to manage their treatments without worry of routine hospital appointments for infusion or additional monitoring, as is the case for some DMTs(50-53)
- **Reversibility**: The short half-life of ponesimod (terminal elimination half-life of ~30 hours) and subsequent rapid reversibility of its pharmacodynamic effects (elimination within 7 days of discontinuing treatment) may provide advantages in terms of safety and allows quick re-establishment of normal immune system function that may be especially beneficial in terms of

flexibility for pregnancy planning, serious infections, and vaccination.(142,

211, 212) In comparison, the lymphocyte count returned to normal ranges within 1-2 months of stopping treatment for fingolimod which has a terminal half-life of fingolimod is approximately 8 days.(6, 51)

- **Reduced monitoring burden**: First dose effects from fingolimod can decrease heart rate substantially, therefore patients should be monitored for 6 hours after first dose.(6, 51) In contrast, the gradual up-titration of ponesimod from Day 1 to Day 14 mitigates first-dose effects on heart rate and atrioventricular conduction. Therefore, no first dose cardiac monitoring is required in patients without history of cardiovascular risk.
- **Concomitant treatment**: The potential for DDIs with ponesimod is low because it has no active metabolites.(46) Therefore, choosing concomitant treatment to manage symptoms of MS is easier compared with some other DMTs.
- **Managing fatigue symptoms**: While fatigue is one of the most common symptoms reported by patients with RRMS, it is undertreated and considered a key unmet need from patients' perspective.(81, 213) OPTIMUM is the first study to implement a validated disease-specific fatigue measure as a prespecified endpoint, which suggested that ponesimod is the first DMT to demonstrate stabilisation of fatigue symptoms when compared with another oral DMT in a large pivotal trial.(46, 47)

B.2.14 Interpretation of clinical effectiveness and safety evidence

Despite the availability of a range of treatment options for RRMS, there remains an unmet need for a convenient efficacious treatment that reduces relapse frequency in patients with MS, manages disease symptoms and has a favourable long-term safety profile. Ponesimod provides a new treatment option for patients with RRMS, including patients with both active and highly active RRMS, meeting the unmet needs in the current treatment landscape.

OPTIMUM is the first controlled study with oral ponesimod that showed superior efficacy to the active comparator, teriflunomide, a first-line oral DMT recommended in England. The study had a high completion rate, with [redacted] of patients completing the trial according to the protocol, indicative of good tolerability and efficacy of study treatments.(6) The observed demographic and baseline characteristics of patients in OPTIMUM were consistent with the overall population of patients with RRMS and, given the common underlying

pathophysiology of the disease, the results of OPTIMUM can be extrapolated to the general RRMS patient population.(47)

Ponesimod provided a statistically significant reduction in annual relapses

Relapses are key drivers of reduced HRQoL in patients with RRMS, and the frequency of relapses is indicative of disease activity and a prognostic factor for disability progression; therefore, reducing the rate of relapse is a key treatment goal in MS.(23, 33-36) OPTIMUM demonstrated superior efficacy of ponesimod to a first-line oral DMT, teriflunomide, showing a clinically meaningful, statistically significant and robust effect with regards to the primary endpoint of ARR in patients with RMS, with a 30.5% reduction in relapse rates compared with teriflunomide (RR: 0.695; 99% CL: 0.536, 0.902; p=0.0003).(46, 157) The primary efficacy endpoint results were robust, and the results of supplementary and sensitivity analyses were consistent with the overall treatment effect.(6)

Ponesimod numerically decreased the risk of disability progression

Disability progression was assessed in the OPTIMUM trial as CDA which utilises worsening EDSS scores, in line with other trials in MS. The risk for a 12- and 24-week CDA was estimated to be 17% and 16% lower, respectively, with ponesimod compared with teriflunomide; the differences were not statistically significant, but the study was not powered for these endpoints.(6)

Other measures of disability (MSFC and EDSS) analysed individually, or as composite endpoints (exploratory or post hoc) showed a lower risk of disability worsening and a benefit on physical and cognitive impairment with ponesimod compared with teriflunomide. The change from baseline to EOS in the MSFC-Z score, which assessed physical and cognitive disability, was higher with ponesimod treatment than with teriflunomide treatment ([redacted]; higher scores correspond to a better outcome).(6, 47)

Ponesimod reduced inflammatory brain lesions and brain atrophy

Ponesimod was also superior to teriflunomide in reducing the number of inflammatory brain lesions (CUALs), indicative of disease activity and progression, by 56% (p<0.0001) between baseline and EOS, which is an established outcome measure of inflammatory MS disease activity.(6, 47)

Results of other exploratory endpoints complemented the results of the primary and the secondary endpoints. MRI-based analyses consistently demonstrated benefits with ponesimod over teriflunomide in terms of reducing brain volume loss and the appearance of new or enlarging lesions in the brain caused by MS.(6) Brain atrophy or brain volume loss in patients with RRMS is associated with worsening disability and disease progression.(106,

111) There was 34% less brain atrophy at EOS after ponesimod treatment than after teriflunomide treatment (p<0.0001).

Ponesimod showed a stabilising effect on MS-related fatigue symptoms

Fatigue is considered a key unmet need in RMS from the patients' perspective.(213) OPTIMUM is the first study to implement a validated disease-specific fatigue measure as a prespecified endpoint, which suggested that ponesimod is the first DMT to demonstrate stabilisation of fatigue symptoms when compared with another oral DMT in a large pivotal trial.(46, 47) In the main analysis on the FSIQ-RMS weekly symptoms score, the change from baseline to week 108 was statistically significantly lower with ponesimod compared with teriflunomide (LS mean difference: −3.57; p=0.0019).(46, 157) Of note, the assessment of FSIQ-RMS at week 108 was concomitant with the accelerated elimination procedure for teriflunomide with cholestyramine or activated charcoal. Although generally well tolerated, this procedure has often been associated with adverse effects such as dyspepsia, nausea and vomiting, which could impact the assessment of fatigue.(6) While the FSIQ-RMS is a validated tool, a limitation is that it was newly developed and as such has not been used in other studies in MS.(6) Since the majority of patients in OPTIMUM had no or mild fatigue at baseline, there may have been a limitation on the extent of any improvements.(6)

Ponesimod improved the proportion of patients achieving a disease-free state

Even when no relapses are apparent, new/enlarging MRI lesions due to inflammation may be developing in patients with MS.(20) This has led to the new treatment goal of total absence of disease activity, termed NEDA.(20, 41) In the OPTIMUM trial, ponesimod improved the proportion of patients achieving a disease-free state, as defined by NEDA-3 and NEDA-4, compared with teriflunomide.(6) Although regarded as exploratory, the OR for achieving NEDA status at EOS favoured ponesimod over teriflunomide for both NEDA-3 (OR: 1.70; 95% CL: 1.27, 2.28; p=0.0004) and NEDA-4 status (OR: 1.85; 95% CL: 1.24, 2.76; p=0.0026).(6, 47)

The benefits associated with ponesimod were consistent in highly active RRMS

Results in the subgroup of patients with highly active RRMS were consistent with those observed in the main analysis, indicating improvements in ARR, CDA, fatigue and inflammatory lesions on MRI with ponesimod compared to teriflunomide.(6) In line with previous clinical trials in MS, the definition of highly active RRMS employed during OPTIMUM was broad, incorporating patients with RES RRMS as defined by NHSE.(6, 7) Similar results were observed using the NICE definition of 'highly active' compared with the definition used in the OPTIMUM trial.(158)

The effect of ponesimod in controlling disease activity is maintained over long treatment periods

Although Study B202 was not powered to test ARR or disability, there was a trend toward improvement with ponesimod treatment. The mean estimate of ARR for confirmed relapses up to the end of the long-term study was consistent with the prior analysis periods over 9 years of treatment. Approximately [redacted] in the ponesimod 20 mg dose group experienced a 24-week CDA at Week 432 (~8.3 years) suggesting a favourable effect of ponesimod for this outcome.

Ponesimod is well-tolerated in the long-term with high treatment persistence

Given the chronic nature of MS, long-term tolerability is an important aspect of treatment. The safety profile of ponesimod is well characterised based on long-term data collected in phase 2 and 3 trials, and is in line with other S1P modulators.(47) The gradual up-titration of ponesimod, starting at a 2 mg dose, successfully mitigates its first-dose effects.(6) In the OPTIMUM trial, patients receiving ponesimod experienced a similar proportion of TEAEs (88.8% vs. 88.2%) or SAEs (8.7% vs. 8.1%) compared with teriflunomide, respectively.(46)

In the long-term pooled safety analysis, most TEAEs associated with ponesimod [redacted].(47)

Data from the phase 2 program demonstrates low levels of discontinuation and consistent tolerability with ponesimod treatment over up to 9 years of follow-up.(46, 47, 49)

Conclusion

Overall, the results of OPTIMUM demonstrate the robust clinical benefit of ponesimod in significantly reducing relapses and decreasing the risk of inflammatory brain lesions in patients with RMS, and show a safety profile consistent with the known safety profile of S1P receptor modulators.(6) Ponesimod meets the unmet need in the current RRMS treatment landscape by offering a balance between efficacy and safety, while having proven long-term tolerability and low rates of discontinuation.(46, 47, 49)

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In line with guidance from NICE, an SLR was conducted to identify cost-effectiveness studies in RMS relevant to the decision problem for ponesimod. Details of the methods used to identify and select the relevant studies are described in Appendix G. A total of 115 studies were identified, including 66 studies previously reported in NICE TA624 and 49 additional studies published since. Of the 49 additional studies identified, five were conducted in the UK and one study was conducted in Europe but included UK-specific data; these six studies are summarised in Table 29.

Table 29: Summary of cost-effectiveness studies in RMS in the UK (published since TA624)

Author, Year	Country	Summary of Model	Patient Population (Average Age in Years)	QALYs (Intervention, Comparator)	Costs (Currency) (Intervention, Comparator)	ICER (per QALY Gained)
Di Maio et al. (2020)(214)	UK	A Markov-state model based on 1-point spaced EDSS states (0-9) was used to estimate costs associated with disease progression.	RMS (NR)	NR	Costs, £ OCZ vs. DMF = 72,200,000 OCZ vs. NTZ = 27,900,000 OCZ vs. CLB = 18,700,000 Cost saving driven by informal care, £ OCZ vs. DMF = 27,900,000 OCZ vs. NTZ = 10,700,000 OCZ vs. CLB = 7,200,000 Cost savings driven by productivity, £ OCZ vs. DMF = 23,500,000 OCZ vs. NTZ = 9,200,000 OCZ vs. CLB = 6,100,000	NR
Giovannoni et al. (2018)(215)	UK	Continuous Markov model utilizing natural history data.	RMS (mean 30.2)	NR	NR	ICER, £ GA 10-year data = 17,841/QALY

Author, Year	Country	Summary of Model	Patient Population (Average Age in Years)	QALYs (Intervention, Comparator)	Costs (Currency) (Intervention, Comparator)	ICER (per QALY Gained)
Giovannoni et al. (2019)(216)	UK	Expected progression of disability: continuous Markov model with a time horizon of 10 years Separate model for cost-effectiveness: Markov model 50-year time horizon (with 50% treatment waning effect imposed at 10 years) using NHS list price of Copaxone (£513.95 per 28 days/£6,701 per annum).	RMS (GA cohort mean age = 30.2; BCMS cohort mean age = 29.2)	NR	NR	ICER, £ GA at Copaxone® list price during RSS study = 17,841/QALY GA costs from the UK MS Survey = 33,308/QALY
Harty et al. (2018)(217)	UK	An economic model, based on a UK perspective, published by Hettle et al (2018) was adapted to assume HRs of 1 for Confirmed Disability Progression and Annualized Relapse Rate, versus the comparators. The time horizon was 50 years	HA-RMS (NR)	Incremental QALY difference CLT = reference ALZ = 0.007 FNG = -0.004 NTZ = -0.003	Incremental savings, £ CLT = reference ALZ = -8,453 FNG = -199,635 NTZ = -234,430	NR
Phelps et al. (2018)(218)	UK	A cost-effectiveness Markov model	RRMS (NR)	NR	NR	ICER without modelling subsequent treatment cost or effects, £ NTZ vs. FNG = 29,500
Rock et al. (2019)(219)	Sweden, France, Germany, Italy, Spain, UK	Markov model with 10 health states (EDSS scores from 0 to 9) and death over a lifetime horizon using annual cycles. Model incorporates the ability to fail GA and switch to DMF.	RRMS (NR)	NR	Cost increases observed, £ In the UK = 56,949	NR

ALZ = alemtuzumab; BCMS = British Columbia multiple sclerosis database; CLB = cladribine; CLT = cladribine tablets; DMF = dimethyl fumarate; EDSS = expanded disability status scale; FNG = fingolimod; GA = glatiramer acetate; HA-RMS = highly active relapsing multiple sclerosis; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MS = multiple sclerosis; NHS = National Health Service; NR = not reported; NTZ = natalizumab; OCZ = ocrelizumab; QALY = quality adjusted life year; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; RSS = Risk-Sharing Scheme; UK = United Kingdom.

B.3.2 Economic analysis

Summary points

- A *de novo* cost-effectiveness model (CEM) was developed to assess the cost-effectiveness of ponesimod versus relevant NICE-recommended DMTs in active RRMS (the "ITT population") and in the subgroup of patients with highly active RRMS.
- The model uses a Markov-based cohort approach based on EDSS health states and is conducted from the perspective of the UK NHS and Personal Social Services over a 50-year time horizon.
- The results of the base-case analysis in the ITT population indicated:
  - [redacted]
  - The ICERs for ponesimod vs. interferon beta-1a (22 mcg) and peginterferon beta-1a were [redacted] the cost-effectiveness threshold accepted by NICE ([redacted] and [redacted], respectively).
  - [redacted]
- In the subgroup of patients with highly active RRMS:
  - [redacted]
  - [redacted]
  - Ponesimod was [redacted] and associated with [redacted] costs
- Results of the scenario analyses in the ITT population generally demonstrated consistency with the base-case results.
  - When the treatment effect of disease progression was based on 6-month data, ponesimod [redacted]
  - The ICER for ponesimod vs [redacted] was between the £20,000 and £30,000 cost-effectiveness threshold ([redacted])
  - In contrast to the base case, ponesimod was [redacted]
  - Since interferon beta-1b could not be included in the NMA network and was therefore evaluated through naïve comparison, the results for ponesimod vs. interferon beta-1b should be interpreted with caution.
- The annual discontinuation rate of ponesimod is among the top three model drivers of ICERs for ponesimod versus other treatments.
  - The odds ratios informing the discontinuation rates are based on a NMA comparing 43 trials with a large degree of heterogeneity and may overestimate the discontinuation rate of ponesimod. Indeed, when these rates are equalised across comparators in a scenario analysis, the cost effectiveness of ponesimod improves consistently versus all first-line comparators

The SLR described in Section B.3.1 did not identify any published studies reporting on the cost-effectiveness of ponesimod in patients with RRMS. Therefore, a *de novo* cost-effectiveness model was developed to assess the incremental cost-effectiveness of ponesimod versus relevant comparators in RRMS.

B.3.2.1 Patient population

In line with the decision problem summarised in Section B.1, the model allows for the analyses of two populations: firstly, the ITT population including male and female adults with diagnosed active RMS and EDSS scores between 0 and 6; secondly, a subgroup of patients with a higher frequency of relapses from the ITT population, referred to hereafter as the "ITT population" and "highly active subgroup," respectively.

- **The ITT population** (default base case): The ITT population in the model is based on the ITT population of the OPTIMUM clinical trial(6), with the following differences:

  - The ITT population in the OPTIMUM trial included 97.4% RRMS patients and 2.6% SPMS patients. Due to the wide confidence intervals of treatment-effect sizes for SPMS patients, the impact of SPMS patients on the overall trial results were estimated to be negligible and, for the purposes of this analysis, it is assumed that the clinical trial patient population characteristics and outcomes of the ITT population are reflective of those from the RRMS only subgroup.
  - The OPTIMUM trial included patients with EDSS scores from 0 to 5.5. However, the model structure is based on whole-number EDSS scores from 0 to 6. As a result, patients initially populating the EDSS score 5 state only include patients with an EDSS score of 5.0 to 5.5, which represents [redacted] of the OPTIMUM trial population. Since the same initial distribution was applied to all DMTs in the analysis, any overestimation of progression or relapse rates is expected to have negligible impact on incremental outcomes.

- **Highly active subgroup** (subgroup analysis): This group is based on a prespecified subgroup of patients in the OPTIMUM trial with high disease activity, and differs from the ITT population in the model in terms of the initial patient characteristics (mean age, percentage female, and EDSS score distribution), relevant treatments (initial and post-discontinuation), underlying RRMS disease natural history, annual relapse rates during periods of RRMS and SPMS, treatment effects on disease activity, and treatment effects on relapse rates.

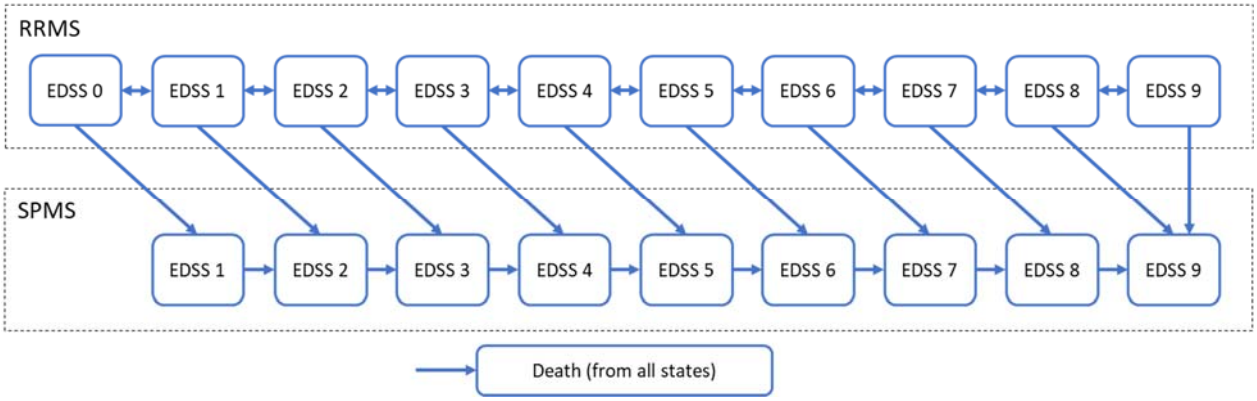
Population characteristics and clinical parameters are described in detail in Section B.3.3.1.

B.3.2.2 Model structure

B.3.2.2.1 Description of health states

The model uses a Markov-based cohort approach to estimate the cost effectiveness of ponesimod vs. NICE-recommended DMTs in a population of patients with RRMS. This model structure is similar to those used in most previous NICE technology appraisals to evaluate the cost-effectiveness of MS DMTs and consists of 20 health states based on EDSS scores: EDSS 0-9 for RRMS, EDSS 1-9 for SPMS, and death (equivalent to EDSS 10 for both RRMS and SPMS) (Figure 27). Health states were defined by the EDSS score because it is the primary measure used to define disease worsening in MS patients, and because EDSS scores are a critical factor in clinical care decision making (e.g. initiating and stopping DMTs and for determining progression to SPMS).(7) While patients with SPMS are not the target population for ponesimod, the model also captures disease progression from RRMS to SPMS to account for cost and utility differences that may occur along the disease pathway, with patients discontinuing active treatment and switching to best supportive care at conversion to SPMS. The model uses a cycle length of 1 year, with a half-cycle correction applied to all model outcomes that depend on the time spent in each state (e.g., life-years [LYs], quality-adjusted life-years [QALYs]). The 1-year cycle length was selected to be consistent with published natural history data used to inform the model.(220, 221)

Figure 27: Model Structure Diagram



EDSS=Expanded Disability Status Scale; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis.

Note: Although not shown in the diagram, EDSS changes of more than one level are permitted.

All patients are assumed to have an initial diagnosis of RRMS as they enter the model and are distributed across the RRMS health states. In each model cycle, patients with RRMS can experience disease improvement (modelled as transition to a health state with a lower EDSS score) or disease worsening (modelled as transition to a health state with a higher EDSS score or to an SPMS health state). Conversion from RRMS to SPMS within the model results in transition to an SPMS health state with an EDSS score of +1 vs. that in the RRMS

state. This assumption was based on an analysis by Mauskopf and colleagues (2016) of time-to-SPMS estimates generated from London Ontario data and has been applied in economic models from previous appraisals for NICE-recommended DMTs.(134, 222) Death may occur from any state.

The model considers relapses as events occurring within health states. To account for potential differences in relapse rates by EDSS score and between RRMS and SPMS, ARRs are considered separately for each of the EDSS health states. Treatments are assumed to reduce those rates; the degree of that effect varies by treatment option.

From a clinical perspective, disease worsening and treatment discontinuation depend on the occurrence and frequency of relapses; however, the EDSS-based structure of this model does not reflect the relationship between relapses and disease worsening or the clinical pathway of switching after multiple relapses. In other words, a reduced relapse rate does not translate to disease improvements in this model. As a result, the estimated health benefits from a reduced relapse rate due to DMTs are likely conservative.

B.3.2.2.2 Time horizon and model perspective

The time horizon observed can be varied from 1 to 70 years. The default base case analysis uses a lifetime horizon equivalent to 50 years, since patients entering the model are between 35 and 40 years regardless of which population (ITT population or highly active subgroup) or source for populating the inputs defining the characteristics of those populations. This assumption is in line with previous NICE submissions(133-135) and best practices from NICE (2013) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).(223, 224) The base case analysis was conducted from the perspective of the UK NHS and Personal Social Services.

B.3.2.2.3 Discounting and costs

Costs and health-related outcomes were discounted by 3.5% annually in line with the NICE reference case; an option for a scenario analysis with a 1.5% annual discount was included.(223) All costs are estimated in UK pounds (£) at 2019 currency levels. The cost-year was selected to be consistent with the year of the most recent published NHS costs, which are for 2018-2019.(225)

B.3.2.3 Comparators to ponesimod

The model compares the outcomes of a population whose initial treatment is ponesimod to one whose initial treatment is one of several NICE-recommended DMTs listed in the final scope (Table 30).(4) When the observed population is the ITT population, initial treatment

represents approved first-line treatments for RRMS as per the NHSE treatment algorithm; when the observed population is the highly active subgroup, initial therapy represents second-line treatments for RRMS.(7)

Table 30: Model Comparators to Ponesimod for the ITT Population and for the Highly Active RRMS Subgroup

Patient Population	Comparator	Brand Name	Associated NICE Appraisal
ITT population (RRMS)	Teriflunomide	Aubagio®	TA303(131)
	Dimethyl fumarate	Tecfidera®	TA320(132)
	Pegylated interferon beta-1a	Plegridy®	TA624(135)
	Glatiramer acetate	Copaxone®	TA527(133)
	Interferon beta-1a (22 mcg, 44 mcg)	Rebif®	TA527(133)
	Interferon beta-1a (30 mcg)	Avonex®	TA527(133)
	Interferon beta-1b	Extavia®	TA527(133)
	Ocrelizumab	Ocrevus®	TA533(134)
Highly active RRMS subgroup	Alemtuzumab	Lemtrada®	TA312(137)
	Cladribine	Mavenclad®	TA616(138)
	Fingolimod	Gilenya®	TA254(136)
	Ocrelizumab	Ocrevus®	TA533(134)

ITT = intent-to-treat; MS = multiple sclerosis; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis.

B.3.3 Clinical parameters and variables

B.3.3.1 Population characteristics

In all cases, the modelled population starts in RRMS health states only and is distributed across health states based on EDSS scores. The parameters used for the ITT population and highly active RRMS subgroup were sourced from OPTIMUM trial data (Table 31).(6)

The OPTIMUM trial included patients with RMS aged 18 to 55 years with an EDSS score of 0 to 5.5 at baseline (Section B.2.3.1.2).(6) Patients were treatment-naïve or had received prior treatment with IFN beta-1a, IFN beta-1b, glatiramer acetate, natalizumab, or dimethyl fumarate.(6)

Patients in OPTIMUM were defined as having highly active RRMS if they fulfilled one of the following criteria:(6)

- Any DMT for MS received within 12 months prior to randomisation and one or both of the following:
  - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions.

- Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for patients with at least one relapse within 2 years prior to study entry.

- ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.

Table 31: Initial population characteristics

Variable	Patients in the ITT population (RRMS)		Patients in the Highly active RRMS subgroup
	OPTIMUM Trial Population (Default)	UK MS RSS Population	OPTIMUM Trial Population
Mean age (years)	[redacted]	39.40	[redacted]
Female	[redacted]	74.19%	[redacted]
Baseline EDSS distribution			
EDSS (RRMS only[a])			
0	[redacted]	3.20%	[redacted]
1	[redacted]	16.30%	[redacted]
2	[redacted]	25.80%	[redacted]
3	[redacted]	23.00%	[redacted]
4	[redacted]	15.50%	[redacted]
5	[redacted]	10.50%	[redacted]
6	[redacted]	5.70%	[redacted]
7	[redacted]	0.00%	[redacted]
8	[redacted]	0.00%	[redacted]
9	[redacted]	0.00%	[redacted]

EDSS = Expanded Disability Status Scale; ITT = intent-to-treat; OWSA = one-way sensitivity analysis; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; RSS = Risk-Sharing Scheme.

Note: Median age, percentage female, and baseline EDSS distribution were not varied in the OWSA.

[a]All patients were assumed to start with RRMS.

Source: OPTIMUM trial populations: Janssen data on file(6, 158); UK MS RSS Population: NICE (2019)(135)

Alternatively, the characteristics of the patient population in the UK MS RSS can be used to define the initial characteristics of patients in the ITT population in a scenario analysis. The RSS population is offered to allow consideration of a patient population entirely from the UK(220), instead of the OPTIMUM trial, which was conducted in several international sites.(6) Patients were only included in the RSS data set if they met the ABN criteria for treatment with interferon or glatiramer acetate(135); therefore, a scenario analysis using the RSS population characteristics is not offered in the model for the highly active subgroup. As seen in Table 31, the OPTIMUM trial population was marginally younger (average 2.7 years), included more men (36.0% vs. 25.81%), and had a greater proportion of patients with low disease activity at baseline ([redacted] vs. 68.3% EDSS ≤ 3, [redacted] vs. 5.7% EDSS ≥ 6) than

the RSS population.(6) The observed differences in the age and initial disease stages of the population are expected, since OPTIMUM is a more recent trial where people with RRMS are treated earlier in their disease.

B.3.3.2 Natural history

B.3.3.2.1 EDSS transition probabilities for RRMS and SPMS

In the model, inputs for the EDSS transition matrix for the ITT population were obtained from the British Columbia MS database transition matrix (Table 32). This matrix is estimated from data on 898 patients with RRMS and SPMS, aged ≥28 years at onset, and obtained between 1980 and 1995. Transition probabilities were calculated using EDSS scores recorded at consecutive patient visits and were previously used in the UK MS RSS model developed by Palace et al.(220) In line with previous NICE appraisals in MS (TA493, TA527, TA533 and TA624) (134, 138), this database is the default source for the EDSS transition probabilities for the model and represents RRMS progression in a real-world setting.

Table 32: Natural history EDSS transition probabilities for patients with RRMS in the ITT population: the British Columbia multiple sclerosis database

Annual transition probabilities, by EDSS[a]										
(to)	0	1	2	3	4	5	6	7	8	9
(from) 0	0.695	0.203	0.073	0.022	0.004	0.001	0.002	0.000	0.000	0.000
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	0.116	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

EDSS = Expanded Disability Status Scale; ITT = intent-to-treat; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis.

[a]Nonzero transition probability rounded to 0.000. Additional precision is available in the Microsoft Excel (Microsoft Corporation; Redmond, Washington) model file. The natural history EDSS transition probabilities for RRMS were not varied in the OWSA. They were varied in the probability sensitivity analysis, utilizing the Dirichlet distribution and an assumed sample size of 100.
Source: Palace et al. 2014.(220)

The model allows a scenario analysis for the ITT population (first-line treatment), using the dimethyl fumarate and London, Ontario MS database transition matrix (Table 33). This matrix combines transition probability estimates from the placebo arms of the DEFINE and CONFIRM trials (for EDSS scores of 0 to 7) and from the London, Ontario MS database (for EDSS scores of 8 to 9), and thus represents RRMS progression in the controlled

environment of a clinical trial.(221) In contrast to the British Columbia dataset, this database provides data for SPMS conversion rates and disease progression transition probabilities for SPMS patients, thereby allowing the model to use a single source for all-natural history progression rates between health states.

Table 33: Natural history EDSS transition probabilities for patients with RRMS in the ITT population: the dimethyl fumarate trials and the London, Ontario database

Annual transition probabilities, by EDSS[a]										
(to)	0	1	2	3	4	5	6	7	8	9
(from) 0	0.312	0.289	0.312	0.070	0.016	0.001	0.000	0.000	0.000	0.000
1	0.178	0.232	0.419	0.127	0.039	0.004	0.001	0.000	0.000	0.000
2	0.060	0.130	0.494	0.215	0.088	0.011	0.002	0.000	0.000	0.000
3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0.000
4	0.005	0.017	0.127	0.251	0.410	0.121	0.048	0.014	0.007	0.000
5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0.000
6	0.000	0.001	0.009	0.034	0.123	0.257	0.329	0.190	0.056	0.001
7	0.000	0.000	0.003	0.013	0.057	0.169	0.309	0.256	0.189	0.004
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS = Expanded Disability Status Scale; ITT = intent-to-treat; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis.

[a] Natural history EDSS transition probabilities for RRMS were not varied in the OWSA. They were varied in the probability sensitivity analysis, utilizing the Dirichlet distribution and an assumed sample size of 100.
Source: Mauskopf et al. 2016.(221)

In line with the preference of previous NICE committees, a separate EDSS transition matrix for patients within the highly active subgroup is also included in the model (Table 34). This matrix is based on the transition probability matrix presented in NICE TA533, reflecting progression (excluding the effects of relapses[a]) of patients in the placebo arm of the AFFIRM phase 3 clinical trial with natalizumab.(226) Data for EDSS states 7 and beyond were imputed from the British Columbia MS database matrix (reported in Table 32).

Table 34: Natural history EDSS transition probabilities for patients with RRMS and highly active RRMS activity(220, 226)

Annual Transition Probabilities, by EDSS[a]										
(to)	0	1	2	3	4	5	6	7	8	9
(from) 0	0.2299	0.1670	0.4250	0.1040	0.0600	0.0120	0.0020	0.0001	0.0000	0.0000
1	0.0700	0.1084	0.5110	0.1560	0.1190	0.0280	0.0070	0.0005	0.0001	0.0000
2	0.0300	0.0860	0.4997	0.1730	0.1560	0.0420	0.0110	0.0017	0.0005	0.0000
3	0.0170	0.0600	0.3930	0.1619	0.2410	0.0820	0.0310	0.0103	0.0036	0.0003

[a] EDSS observations recorded within either 1, 3 or 6 months of a relapse were replaced with the next point that did not occur within 1, 3 or 6 months of a relapse respectively

Annual Transition Probabilities, by EDSS[a]										
(to)	0	1	2	3	4	5	6	7	8	9
4	0.0070	0.0320	0.2530	0.1710	0.2999	0.1360	0.0680	0.0258	0.0067	0.0006
5	0.0030	0.0120	0.1710	0.1480	0.3460	0.1254	0.1360	0.0388	0.0188	0.0010
6	0.0010	0.0070	0.0760	0.0930	0.2830	0.2210	0.1620	0.1090	0.0438	0.0042
7	0.0000	0.0002	0.0005	0.0025	0.0073	0.0039	0.1168	0.6927	0.1606	0.0156
8	0.0000	0.0000	0.0000	0.0003	0.0006	0.0005	0.0188	0.0557	0.9034	0.0207
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0018	0.0057	0.1741	0.8183

EDSS = Expanded Disability Status Scale; NICE = National Institute for Health and Care Excellence; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis.

[a] Natural history EDSS transition probabilities for RRMS were not varied in the OWSA. They were varied in the probability sensitivity analysis, utilizing the Dirichlet distribution and an assumed sample size of 100.
Source: NICE TA533(220, 226)

For patients who progress to SPMS in the model, a separate EDSS transition probability matrix was applied, for both the ITT population and highly active RRMS subgroup (Table 35). It was generated using the data from the London, Ontario MS database and used in preference over the British Columbia MS database, which does not distinguish between RRMS and SPMS.(221)

Table 35: Natural history EDSS transition probabilities for patients with SPMS(221)

Annual transition probabilities, by EDSS[a]									
(to)	1	2	3	4	5	6	7	8	9
(from) 1	0.769	0.154	0.077	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.636	0.271	0.062	0.023	0.008	0.000	0.000	0.000
3	0.000	0.000	0.629	0.253	0.077	0.033	0.003	0.006	0.000
4	0.000	0.000	0.000	0.485	0.350	0.139	0.007	0.018	0.000
5	0.000	0.000	0.000	0.000	0.633	0.317	0.022	0.026	0.002
6	0.000	0.000	0.000	0.000	0.000	0.763	0.190	0.045	0.002
7	0.000	0.000	0.000	0.000	0.000	0.000	0.805	0.189	0.006
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.926	0.074
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS = Expanded Disability Status Scale; OWSA = one-way sensitivity analysis; SPMS = secondary progressive multiple sclerosis.

[a] Natural history EDSS transition probabilities for SPMS were not varied in the OWSA. They were varied in the probability sensitivity analysis, utilizing the Dirichlet distribution and an assumed sample size of 100.
Source: Mauskopf et al. 2016.(221)

B.3.3.2.2 Conversion from RRMS to SPMS

The default annual transition probabilities of converting from RRMS to SPMS at each EDSS health state used in the model are presented in Table 36. These values were generated using the data from the London, Ontario MS database and were reported by Mauskopf et al. 2016.(221) The model assumes that all patients converting from RRMS to SPMS have their

EDSS score increased by 1 point, based on the expectation that the conversion to SPMS is associated with a change in disability level.

Table 36: Annual probability of converting from RRMS to SPMS(221)

Initial EDSS (RRMS)	Resulting EDSS (SPMS)	Probability[a]
0	1	0.000
1	2	0.003
2	3	0.032
3	4	0.117
4	5	0.210
5	6	0.299
6	7	0.237
7	8	0.254
8	9	0.153
9	9	1.000

EDSS = Expanded Disability Status Scale; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

[a] Annual probabilities for conversion from RRMS to SPMS were not varied in the OWSA. The beta distribution was used to model the uncertainty of the annual probability of conversion from RRMS to SPMS in the probabilistic sensitivity analysis; uncertainty parameters were based on an assumed sample size of 100. Source: Mauskopf et al. 2016.(221)

B.3.3.2.3 Relapse rates for RRMS and SPMS

Default annual relapse rates for RRMS and SPMS (Table 37) were sourced from Mauskopf et al.(221) These rates were estimated using patient data for relapse rates per person per year from a prospective study of MS patients conducted by Patzold and Pocklington (1982) and data for the population of patients with relapse from the burden of illness 2005 UK MS survey (reported by EDSS health state and time since diagnosis).(227)

Rates for patients with highly active RRMS were estimated based on the average relapse rates demonstrated in the placebo arm of the AFFIRM clinical trial, which were 1.98 times greater on average compared with the ITT population.(226, 228)

Table 37: Natural history ARR, by EDSS, for RRMS and SPMS(221, 228)

Population	Disease stage	Annual relapse rates by EDSS[a]									
		0	1	2	3	4	5	6	7	8	9
ITT (RRMS)	RRMS	0.710	0.730	0.680	0.720	0.710	0.590	0.490	0.510	0.510	0.510
	SPMS	NA	0.000	0.470	0.880	0.550	0.520	0.450	0.340	0.340	0.340
Highly active RRMS	RRMS	1.407	1.448	1.343	1.430	1.400	1.173	0.972	1.009	1.009	1.009
	SPMS	NA	0.000	0.923	1.738	1.803	1.041	0.900	0.676	0.676	0.676

ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; ITT = intent-to-treat; NA = not applicable; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

[a] Relapse rates were not varied in the OWSA. The lognormal distribution was used to model the uncertainty of the annual relapse rates in the probabilistic sensitivity analysis; uncertainty parameters were based on an assumed sample size of 100.
Source: Mauskopf et al. 2016; Biogen 2007.(221, 228)

B.3.3.3 Treatment effects and discontinuation

B.3.3.3.1 Treatment effects

By default, the model considers treatment effects on ARRs and rates of progression to higher EDSS scores compared to the natural history for these variables. Treatment-effect inputs for all comparators were obtained from Janssen's NMA results, as described in Section B.2.9.

The default effects of treatments on ARRs considered in the model are presented in Table 38.

Table 38: Treatment Effects on Annual Relapse Rates

Treatment	Rate Ratio for Relapse Rate (vs. Natural History) for the ITT Population[a]		Rate Ratio for Relapse Rate (vs. Natural History) for the Highly Active Subgroup[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on relapse rates for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

Source: Janssen NMA (further details in Section B.2.9)

The effect of treatment on progression to higher EDSS is determined by 3-month effects as default in the base case model. A scenario analysis using 6-month effects data can be modelled to examine the long-term effectiveness of each treatment. The input values applied in the model using these two data sources are reported in Table 39 for the ITT population

and in Table 40 for the highly active subgroup. Base-case effects were assumed to be the same for patients with RRMS and SPMS. However, those effects are relevant only if the base-case assumption of discontinuation at conversion to SPMS is not applied.

Table 39: Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the ITT Population

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]			
Dimethyl fumarate				
Glatiramer acetate				
Interferon beta-1a 22 mcg				
Interferon beta-1a 30 mcg				
Interferon beta-1a 44 mcg				
Interferon beta-1b				
Ocrelizumab				
Pegylated interferon beta-1a				
Teriflunomide				
Alemtuzumab				
Cladribine				
Fingolimod				
Natalizumab[b]				
Best supportive care[b]				

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] 6-month data assumed to be equal to 3-month data due to lack of data availability.

Source: Janssen NMA (further details in Section B.2.9) for all treatments except interferon beta-1b which was taken from Melendez-Torres, 2017.(229)

Table 40: Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the Highly active RRMS Subgroup

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]			
Dimethyl fumarate				
Glatiramer acetate				
Interferon beta-1a 22 mcg[c]				
Interferon beta-1a 30 mcg				
Interferon beta-1a 44 mcg				
Interferon beta-1b				

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

RRMS = relapsing-remitting multiple sclerosis; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] Data are assumed to be equal those for interferon beta-1a 44 mcg due to lack of data availability.

Source: Janssen NMA (further details in Section B.2.9)

B.3.3.3.2 Treatment waning

The model allows up to two stages of waning for treatment waning patterns specified by users. Effect of treatment waning can be assessed in three pre-programmed options:

- 0% reduction in years 1 and 2, 25% reduction in years 3 to 5, and 50% reduction from year 6 onwards (default base case)
- 0% reduction in years 1 to 10, 50% reduction in year 11 onwards
- No treatment waning

The default option was chosen as a conservative assumption in line with NICE TA624 (pegylated interferon beta-1a) as well as NICE TA320 (dimethyl fumarate).(132, 135)

B.3.3.3.3 Treatment discontinuation

The model considers treatment discontinuation for the following three reasons:

- When a patient's EDSS score equals or exceeds 7
- When a patient converts from RRMS to SPMS
- When a patient discontinues treatment prematurely for any reason

The first two reasons are based on clinical stopping rules and are applied in line with NHS guidance regarding treatment discontinuation for MS(7) and models included in previous NICE submissions (TA127, TA254, TA312, TA493, TA533 and TA624). (131, 133, 135, 136, 138, 226)

The third reason for treatment discontinuation is based on annualised treatment discontinuation risks which can vary between treatments. The default risks applied in the model were converted from the annual discontinuation rates (shown in Table 41), which were derived based on the estimated annual discontinuation rate for ponesimod and the relative risks of discontinuation for each treatment versus ponesimod. Relative risks were computed from the ORs informed by Janssen's NMA results (Section B.2.9) displayed in Table 41. These rates are calculated from the proportions of patients who discontinued for any reason during the duration of the trials included in the NMA. The discontinuation rate for ponesimod is calculated from a pooled discontinuation probability based on the OPTIMUM trial results (94 out of 565 patients experienced premature treatment discontinuation in safety set at 108 weeks)(6) and the ponesimod phase 2 trial results (patients experienced premature treatment discontinuation at 24 weeks)(142), and converted to annual discontinuation rate assuming a middle point of follow-up time estimation.

The model user can alternatively apply an assumption of a 5% annual treatment discontinuation for all treatments, to enable a scenario analysis in which treatments differ by costs and effects on disease progression and relapse rates only (and length of time on treatment when discontinuation occurs due stopping rules).

Table 41: Annual Treatment discontinuation Rates

Treatment	Odds Ratio: Ponesimod vs. Treatment[a]		Annual Discontinuation Rate[b]
	Value	Range	
Ponesimod			
Dimethyl fumarate			
Glatiramer acetate			
Interferon beta-1a 22 mcg			
Interferon beta-1a 30 mcg			
Interferon beta-1a 44 mcg			
Interferon beta-1b			
Ocrelizumab			
Pegylated interferon beta-1a			
Teriflunomide			
Alemtuzumab			
Cladribine			
Fingolimod			
Natalizumab[e]			
Best supportive care[e]			

NA = not applicable; NMA = network meta-analysis; OWSA = one-way sensitivity analysis.

[a] Odds ratios for ponesimod versus treatment for annual risk of discontinuation for all treatments except best supportive care and ponesimod were varied in the OWSA and in the probabilistic sensitivity analysis (the latter utilizing a lognormal distribution); ranges were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in NMA.

[b] Annual discontinuation rates for all treatments were calculated from the annual discontinuation rate of ponesimod times a relative risk of discontinuation for each treatment versus ponesimod, where the relative risk was calculated from the odds ratios.

[c] Annual discontinuation rate of ponesimod was varied in the OWSA and in the probabilistic sensitivity analysis (the latter using a beta distribution); the range was set to the bounds of the 95% confidence interval from the sampled distribution; that confidence interval was estimated assuming a sample size of 580, the sum of the clinical trial population sizes used for estimating the discontinuation rate of ponesimod in the NMA.

[d] For alemtuzumab and cladribine, this rate is applied only in years 1 to 5. They are both taken for two years and assumed to have no all-cause discontinuation after year 5.

[e] Considered in the model only as a post-discontinuation treatment.

Source: Janssen NMA (further details in Section B.2.9)

B.3.3.4 Post-discontinuation treatment

All patients who discontinue initial treatment with ponesimod or a comparator in the model will transition to best supportive care as post-discontinuation treatment by default. This approach allows the analysis to focus on the differences in treatment effects in the initial phase of treatment and is in line with models included in previous NICE submissions (TA312, TA533, TA320 and TA527).(132-134, 137) In addition to the base-case, the model offers a scenario for each population (ITT and highly active subgroup) to move to an alternative post-discontinuation treatment:

- 100% best supportive care (BSC) (base-case). By default, all patients in the ITT population as well as the highly active subgroup will switch to BSC. This option has been previously used in several models supporting the appraisals of NICE-recommended DMTs(132-134, 137) and allows the assessment of differences in treatment effects of the initial DMTs.
- 100% cladribine: The model offers a scenario whereby all patients in the ITT population (active RRMS) can switch to cladribine (as a highly active treatment option) instead of BSC. In a clinical setting, patients are more likely to switch treatment to a second DMT and cladribine was selected since it is unique to the second line setting and has a different mechanism of action compared to existing first-line DMTs. Moving all patients to the same treatment allows for a cleaner comparison of results, even though it is unlikely that all patients would move to cladribine in clinical practice.
- 100% natalizumab: The model also offers a scenario whereby all patients in the highly active group (second-line treatment) can switch to natalizumab (third-line treatment) instead of BSC, in line with recommended treatment options in the NHSE treatment algorithm.(7) Again, this allows for a cleaner comparison of results, although it is noted that in clinical practice all patients would not necessarily move to natalizumab.

B.3.3.5 Adverse events

In the model, AEs due to treatment are assumed to occur at defined rates, depending on the treatment, and result in direct costs and decrements in utility, as described in Sections B.3.5.3 and Section B.3.4.4, respectively.

The incidence rates for all AEs, excluding PML for natalizumab, were sourced from an SLR conducted by Janssen (as described in Section B.2.1) based on AE rates reported in relevant clinical trials. Any AEs with incidence <1% were assumed to be 0, as a conservative assumption. The incidence rates of PML for natalizumab and the percentage of PML cases estimated to be fatal were obtained from Hoepner et al. 2017.(230) The default annual incidence rates AEs of for all treatments considered by the model are shown in Table 42 and Table 43. The percentages of AEs that are serious were derived from the NMA conducted by Janssen (Section B.2.9) and are displayed in Table 44 and Table 45.

Table 42: Annual Incidence of Adverse Events, Part A (Alanine Aminotransferase Increased to Fatigue)

Treatment	ALT Increased	AST Increased	Alopecia	Back Pain	Depression	Diarrhea	Dizziness	Dyspnea	Fatigue
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Janssen = Janssen Pharmaceuticals, Inc.

Note: Annual incidence rates for each adverse event for each comparator were varied in one-way and probabilistic sensitivity analyses, the latter using a beta distribution, parameterised with sample sizes used to estimate serious adverse events incidence rates obtained from the Janssen SLR; sample sizes for interferon beta-1a 22mcg were assumed to be equal to those for interferon beta-1a 44mcg.

[a] Considered in the model only as a post-discontinuation treatment.

Source: Janssen NMA (Section B.2.9).

Table 43: Annual Incidence of Adverse Events, Part B (Headache to Upper Respiratory Tract Infection)

Treatment	Headache	Hypertension	Nausea	Naso-pharyngitis	Urinary Tract Infection	Upper Respiratory Tract Infection	PML, Nonfatal	PML, Fatal
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PML = progressive multifocal leukoencephalopathy.

Note: Annual incidence rates for each adverse event for each comparator were varied in one-way and probabilistic sensitivity analyses, the latter using a beta distribution, parameterised with sample sizes used to estimate serious adverse events incidence rates obtained from the Janssen SLR; sample sizes for interferon beta-1a 22mcg were assumed to be equal to those for interferon beta-1a 44mcg.

[a] Considered in the model only as a post-discontinuation treatment.

Source: Janssen NMA (Section B.2.9).

Table 44: Percentages of Adverse Events That Are Serious, Part A (Alanine Aminotransferase Increased to Fatigue)

Treatment	ALT Increased	AST Increased	Alopecia	Back Pain	Depression	Diarrhea	Dizziness	Dyspnea	Fatigue
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NMA = network meta-analysis

Note: The percentages of adverse events that are serious for each adverse event for each comparator were varied in one-way and probabilistic sensitivity analyses, the latter using a beta distribution.

[a] Considered in the model only as a post-discontinuation treatment.

[b] Incidence of serious events reported in NMA as "< 1%". Percentage of events that are serious is assumed to be 0, as a conservative assumption.

Source: Janssen NMA (Section B.2.9).

Table 45: Percentage of Adverse Events That Are Serious, Part B (Headache to Upper Respiratory Tract Infection)

Treatment	Headache	Hypertension	Nausea	Naso-pharyngitis	Urinary Tract Infection	Upper Respiratory Tract Infection	PML, Nonfatal	PML, Fatal
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PML = progressive multifocal leukoencephalopathy

Note: The percentages of adverse events that are serious for each adverse event for each comparator were not varied in sensitivity analyses, since adverse event incidence was already varied.

[a] Considered in the model only as a post-discontinuation treatment.

Source: Janssen NMA (Section B.2.9).

B.3.3.6 Mortality

All-cause mortality rates were based on the age- and gender-specific general mortality rates for the UK, obtained from UK life tables.(231) To account for the increased mortality risk associated with MS, general mortality rates were adjusted by a relative risk of mortality in each health state. Data were not available to support the differentiated risks of mortality due to SPMS versus RRMS, therefore an assumption was made that patients with RRMS and SPMS with the same EDSS score had the same relative risk of mortality, in line with previous NICE appraisals in MS (TA624).(135) This assumption is conservative in that it underestimates the mortality due to MS and, therefore, underestimates the benefits of treatments that prevent disease progression and relapse.

Default values in the model are estimated using linear interpolation of mortality ratios by severity from a Canadian study by Pokorski et al. (Table 46), in line with the methodology used for other recent NICE appraisals (TA624).(135, 232) While this source was recognised as being dated, more recent scientific literature was not available to inform the model. Linear interpolation was conducted to offer smoother increases in mortality risk by risk group; the use of this approach was endorsed by the Evidence Review Group in the evaluation of pegylated interferon beta-1a (TA624).(135) The model also offers a scenario analysis based on the raw mortality ratios by severity (without linear interpolation), listed in Table 47. These raw mortality ratios are included in the model for use in optional scenario analyses. Use of these relative risks for MS-related mortality would convey a mortality benefit to treatments and would keep patients in lower EDSS score levels.

Table 46: Relative Risk of Mortality by EDSS Scores (Linear Interpolation)(232)

Relative Risk of Mortality, by EDSS Score										
EDSS score	0	1	2	3	4	5	6	7	8	9
RRMS	1.00	1.30	1.60	1.68	1.76	1.84	2.71	3.57	4.44	5.31
SPMS	NA	1.30	1.60	1.68	1.76	1.84	2.71	3.57	4.44	5.31

EDSS = Expanded Disability Status Scale; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Note: The relative risk of mortality for both RRMS and SPMS was varied in the OWSA by ±10%.

Source: Pokorski et al. 1997.(232)

Table 47: Relative Risk of Mortality by EDSS Scores (Without Interpolation)(232)

Relative Risk of Mortality, by EDSS Score										
EDSS score	0	1	2	3	4	5	6	7	8	9
RRMS	1.60	1.60	1.60	1. 60	1. 84	1.84	1.84	4.44	4.44	4.44
SPMS	NA	1.60	1.60	1. 60	1. 84	1.84	1.84	4.44	4.44	4.44

EDSS = Expanded Disability Status Scale; NA = not applicable; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Note: The relative risk of mortality for both RRMS and SPMS was varied in the OWSA by ±10%.

Source: Pokorski et al. 1997.(232)

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 in the OPTIMUM trial. In line with the approach accepted by previous NICE committees for appraisals in MS, an SLR was undertaken to identify any relevant HRQoL data to inform the utility values included model. Further details of the SLR are provided in Section B.3.4.3 and Appendix H.

B.3.4.2 Mapping

Mapping analyses were not performed as EQ-5D data were sourced from scientific literature for the individual EDSS health states.

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

An SLR was conducted to identify health-related quality-of-life studies in RMS relevant to the decision problem for ponesimod. Details of the methods used to identify and select the relevant studies are described in Appendix H. A total of 31 studies were identified, including 29 studies previously reported in NICE TA624 and two additional studies published since. Of the two additional studies identified, one reported utility scores for RRMS patients in Iran, categorised by treatment and EDSS score, and is summarised in Table 48. It should be noted that this study considered in isolation may have limited relevance to the UK decision problem due to the geographical location, and that other studies previously reported in NICE TA624 may be more relevant.

In line with the approach accepted by previous NICE committees for appraisals in MS, the utility values in the CEM were informed by studies identified in previous NICE appraisals(131-137, 160, 226), which included: Orme et al (2007)(233), Gani et al (2008)(234) and Acaster et al (2013)(235); details on the HRQoL data used in the CEM are provided in the following sections.

Table 48: Summary of relevant health-related quality-of-life studies in RMS (published since TA624)

Author, Year	Country	Study Details	Method of Elicitation and Valuation	Health State Description	Mean (SD) Utility Estimate
Rezaee et al. 2019(236)	Iran, Fars Province (in 2016)	CEA and CUA Response rate: NR Selection and recruitment: related costs and outcomes data were collected for the studied patients on a cross-sectional basis. It was carried out on the patients referring to the MS Society and the Department of Special Diseases in Iran, Shiraz University of Medical Sciences. Inclusion/exclusion criteria: Patients using Fingolimod or Natalizumab for at least 1 year MS phenotype: RRMS Sex: female (81.47%) Age (years), mean (SD): FNG 35.22 (7.91) NTZ 35.55 (8.11) Sample size: 81 FNG 50 NTZ 31	Utility scores (calculated using the EQ-5D-3L questionnaire; original scores used to calculate utilities not provided) Instrument completed by: Patients	Different health statuses based on the EDSS score are: EDSS 0–2.5 (no limitation or slight limitation in mobility), EDSS 3–5.5 (moderate mobility limitation), EDSS 6–7.5 (walking with auxiliary equipment or using wheelchairs), EDSS 8–9.5 (limited to bed), death (natural causes or EDSS 10), relapse EDSS 0–2.5 (relapse or a change in disability EDSS 0–2.5), and relapse EDSS 3–5.5 (relapse or a change in disability EDSS 3–5.5)	For NTZ, EDSS 0.0-2.5: 0.68 (0.19) EDSS 3.0-5.5: 0.46 (0.12) For FNG, EDSS 0.0-2.5: 0.75 (0.1) EDSS 3.0-5.5: 0.42 (0.19)

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; EDSS = expanded disability status scale; EQ = EuroQol; FNG = fingolimod; MS = multiple sclerosis; NR = not reported; NTZ = natalizumab; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation.

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

In the model, patient utility can be affected by three factors: distribution of patients across health states, decrements due to relapses and decrements due to AEs from treatment.

Utilities are calculated across all modelled patients in each time step, then accrued over the model time horizon. In each model time step, patient utilities are calculated as a weighted average of utility for patients across the health states. The resulting number is reduced by subtraction to reflect decrements due to relapses and AEs. Decrements due to relapses and AEs are calculated as the number of each of those associated events occurring in the time step multiplied by the utility decrement associated with each of the events.

The default values for health-state utilities for each EDSS health state and the utility decrement per relapse were based on a published regression of quality-of-life responses from the 2005 UK MS burden-of-illness survey of patients and caregivers of patients with MS as reported by Orme et al.(233) This is in line with most previous NICE appraisals in MS (TA127, TA254, TA312, TA320, TA303, TA493, TA527 TA533, TA624).(131-137, 160, 226) Values were assessed using the EQ-5D utility scoring system, where respondent domain scores were converted to a single utility weight, using the UK value set.(233)

Patients who are in SPMS health states were assumed to have utility values that are 0.045 less than the utility values for patients with RRMS with the same EDSS score, based on the study by Orme et al.(233) The utility decrement of 0.071 per relapse reflects utility reductions for all patients with recent relapses and is assumed to remain constant across all health states.(233)

Health-state utilities for each EDSS score health state and the utility decrement per relapse are reported in Table 49 for RRMS and SPMS.

Table 49: Utility values and relapse utility decrements, by EDSS score(233)

Utility without relapse											**Utility decrement per relapse**
EDSS score	0	1	2	3	4	5	6	7	8	9	0-9
RRMS	0.870	0.799	0.705	0.574	0.610	0.518	0.460	0.297	−0.049	−0.195	0.071
SPMS	NA	0.754	0.660	0.529	0.565	0.473	0.415	0.252	−0.094	−0.240	0.071

Note: Utility values without relapse and the relapse utility decrements were varied in the OWSA by ±10%

EDSS = Expanded Disability Status Scale; NA = not applicable; OWSA = one-way sensitivity analysis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis
Source: Orme et al. 2007

B.3.4.4.1 Adverse event utility decrements

Utility decrements for AEs were calculated as weighted averages of decrements for serious and non-serious AEs (Table 50). The default utility decrements per AE were calculated as the utility decrement per day of each event multiplied by the number of days in a year in which the event reduces utility. Where available, inputs were based on previous NICE appraisals (TA441, TA533 and TA624).(134, 135, 237) The default annual utility decrements for diarrhoea and nausea were sourced from Mauskopf et al. (2016).(221) Those for dyspnoea and hypertension were sourced from Soini et al. (2017) and Paracha et al. (2018), respectively.(238, 239) The default annual utility decrement for alopecia was derived from a disutility from TA303 and a duration assumption from Travis et al. (2018).(131, 240) The annual utility decrement of increased AST was assumed to be equal to that of increased ALT.

Table 50: Adverse Event Utility Decrements(131-133, 237-240)

Adverse Event	Serious Adverse-Event Utility Decrement	Nonserious Adverse-Event Utility Decrement
ALT increased	0.0000	0.0000
AST increased	0.0000	0.0000
Alopecia	0.0037	0.0000
Back pain	0.0336	0.0072
Depression	0.5600	0.0339
Diarrhoea	0.0000	0.0000
Dizziness	0.0000	0.0000
Dyspnoea	0.0003	0.0000
Fatigue	0.0000	0.0000
Headache	0.0331	0.0040
Hypertension	0.0300	0.0000
Nausea	0.0000	0.0000
Nasopharyngitis	0.0000	0.0000
Urinary tract infection	0.0014	0.0014
Upper respiratory tract infection	0.0077	0.0038
PML, nonfatal	0.3000	0.3000
PML, fatal	1.0000	1.0000

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NICE = National Institute for Health and Care Excellence; PML = progressive multifocal leukoencephalopathy.

Note: The utility decrements for adverse events were varied in the sensitivity analysis, using a beta distribution and an assumed sample size of 100.

Sources: NICE TA320, NICE TA303, NICE TA 441, TA527; Soini et al. (2017); Paracha et al. (2018); Travis et al. (2018).(131-133, 237-240)

B.3.4.4.2 Caregiver disutilities

To reflect the considerable burden of MS on caregivers (as described in Section B.1.3.1.6), the model also includes caregiver disutilities by EDSS score for RRMS and SPMS, in line with previous NICE appraisals (TA624, TA527).(133, 135) Default caregiver disutilities for all EDSS scores for both RRMS and SPMS are presented in Table 51 by EDSS score level.(235) The findings from the Acaster et al. (2013) publication were used as the source for caregiver disutilities as this study was the most recent and relevant source.(235) In this study, the caregiver utility values were estimated from a regression, which in turn was estimated from data obtained from cross-sectional observational study of 200 caregivers of patients with MS and matched controls.(235) This source was used in several recent NICE evaluations of MS therapies (TA624, TA527).(133, 135) The sample size obtained from Acaster et al. (2013) was used to model the uncertainty of these inputs in the probabilistic sensitivity analysis. Caregiver disutility associated with each EDSS score was conservatively assumed to be the same for RRMS vs. SPMS, given a lack of data supporting differentiated values; this assumption is in line with previous MS NICE submissions (TA624).(135)

Table 51: Caregiver Utility Decrements by EDSS Scores, From Acaster et al. (2013)(235)

Caregiver Utility Decrements										
EDSS score	0	1	2	3	4	5	6	7	8	9
RRMS	0.002	0.002	0.045	0.045	0.142	0.160	0.173	0.030	0.095	0.095
SPMS	NA	0.002	0.045	0.045	0.142	0.160	0.173	0.030	0.095	0.095

EDSS = Expanded Disability Status Scale; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Note: Caregiver utility decrements were varied in the sensitivity analysis, using a beta distribution and a sample size of 200.
Source: Acaster et al. 2013(235)

Alternative values from Gani et al. (2008) are provided for the scenario analysis (Table 52) and were used in a previous economic evaluation of natalizumab.(234) Disutilities reported in Gani et al. (2008) were derived from a maximum caregiver disutility of 0.14 taken from a NICE Alzheimer's disease (AD) health technology assessment (HTA) and weighted across EDSS score levels using hours of unpaid care from the 2005 UK MS burden-of-illness survey. Carer disutility values for AD are based on a publication by Neumann et al. 1999 and were cited in the NICE appraisal for AD treatments.(241) These values were first used in the natalizumab submission (TA127)(226) and then in the daclizumab submission (TA441).(237) At the time, no systematic study had been done in carers of MS patients but it was assumed that there is a similar level of caregiver burden in both cases. Carer disutility values for the CEM were calculated as follows:

- For every EDSS level, the number of hours of care per day required by caregivers of patients with MS was taken from the UK MS study of 2005. Patients at EDSS 9 needed 14.8 hours of care per day this was set to 100% of the maximum time needed.
- Based on mean caregiver utility of 0.86 in AD from the publication, a maximum disutility of 0.14 was assumed when caring for people with MS in the worst health state (EDSS 9)
- The number of hours of care for each EDSS was then multiplied by a utility value of 0.14

Table 52: Caregiver Utility Decrements, by EDSS Scores, From Gani et al (2008)

Caregiver Utility Decrements										
EDSS score	0	1	2	3	4	5	6	7	8	9
RRMS	0.00	0.00	0.00	0.01	0.01	0.02	0.03	0.05	0.11	0.14
SPMS	NA	0.00	0.00	0.01	0.01	0.02	0.03	0.05	0.11	0.14

EDSS = Expanded Disability Status Scale; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Note: Caregiver utility decrements were varied in the sensitivity analysis, using a beta distribution and an assumed sample size of 100

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

A SLR was conducted to identify cost and healthcare resource use studies in RMS relevant to the decision problem for ponesimod. Details of the methods used to identify and select the relevant studies are described in Appendix I. A total of 124 studies were identified, including 114 studies previously reported in NICE TA624 and 10 additional studies published since. Of the 10 additional studies identified, none reported UK-specific resource utilisation or costs in patients with MS; however, one international cross-sectional study included the UK alongside France, Germany, Italy, Spain and the US, and is summarised in Table 53.

In line with the approach accepted by previous NICE committees for appraisals in MS, the cost and healthcare resource use values in the CEM were informed by studies identified in previous NICE appraisals(132, 135); details on the cost data used in the CEM are provided in the following sections.

Table 53: Summary of relevant cost and healthcare resource utilisation studies in RMS (published since TA624)

Author, Year	Country	Patient Population	Study Period	Year and Currency Reported	Study Design/Approach Used, and Setting	Direct Costs (Medical and Non-medical)	Indirect Costs	Total Costs and Cost Drivers
Acosta et al. 2020(242)	France, Germany, Italy, Spain, UK and US	Age: NR Sex: NR Sample size: 1L NTZ: 79 Delayed NTZ: 189 MS Phenotype: RRMS	2014 - 2018	NR	International cross-sectional study	1L NTZ was associated with fewer hospitalisations (5 vs. 38 among 100 person-years; p=0.004) and fewer hospitalisation days (6 vs. 16 among 100 person-years; p=0.023).	The use of 1L NTZ (n=79) vs. delayed (n=189) was associated with significantly fewer professional caregiver hours (0.00 vs. 0.06 per week; p=0.001). An exploratory analysis associated 1L NTZ (n=29) vs. delayed (n=101) with lower work productivity activity impairment (25.3% vs. 40.1%; p=0.003).	Delayed NTZ use is associated with greater downstream HCRU use and work productivity activity impairment.

1L = first-line; HCRU = healthcare resource utilisation; MS = multiple sclerosis; NR = not reported; NTZ = natalizumab; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; UK = United Kingdom; USA = United States.

B.3.5.1 Intervention and comparators' costs and resource use

Direct treatment costs (acquisition, administration, and monitoring costs) are reported in Table 54. Those costs are differentiated by the first year and subsequent years, to account for differences in the frequencies and health care resource use required for administration and monitoring during the treatment initiation period and for differences in the treatment maintenance period for some treatments. They are considered independent of the costs of disease management, relapse, and AEs.

The acquisition costs for treatments were obtained from the British National Formulary(243) when available. The model allows for discount rates to be applied (in all years) to acquisition costs of each treatment; these discount rates are specific to each treatment option. However, in the default setting, no discount is applied for any treatments. Because cladribine and alemtuzumab are primarily administered over 2 years, the acquisition and administration costs for those treatments were calculated using modified methods. Further details on the methods used to calculate the costs of alemtuzumab and cladribine are provided in Section B.3.5.1.1.

Oral DMTs (ponesimod, teriflunomide, cladribine, and dimethyl fumarate) and best supportive care were assumed to have no administration costs because they can be taken by patients at home, without incurring additional health care resources. Estimates for annual treatment administration costs for all other treatments were calculated by combining treatment-specific resource utilisation frequencies (e.g., nurse and physician visits, infusions, MRIs, lab tests) with standard UK unit costs published by the Personal Social Services Research Unit(244) and the NHS Reference Costs 2018-2019.(225) Resource use for administration of pegylated interferon, glatiramer acetate, interferon beta-1a, and interferon beta-1b were taken from Table 41 of TA624.(245) Resource use for administration of alemtuzumab, ocrelizumab, and fingolimod were taken from Table 47 of TA533.(205)

Estimates for annual monitoring costs for treatments were calculated by combining treatment-specific resource use measures with unit costs (Table 54). Default values for resource unit costs were taken from the UK list prices in the British National Formulary.(243) Resource use for each treatment was consistent with those used in TA533(205) for all treatments except ponesimod and cladribine, neither of which were included in the NICE report. Monitoring costs for ponesimod were assumed to be 30% of the monitoring costs of fingolimod in year 1 only, based on (a) 30% of patients requiring first-dose observation, which was based on an estimated 18.5% of OPTIMUM patients assessed as "being at risk for symptomatic bradycardia (i.e., HR <55 bpm, first or second degree atrioventricular [AV] block or cardiac disorders in medical history)" and then inflated, since certain cardiovascular

conditions were excluded from the trial; (b) per-patient costs of first-dose monitoring for ponesimod, which were assumed to be equal to the per-patient first-dose monitoring costs of fingolimod; and (c) no monitoring in year 2. Cladribine monitoring costs were taken from the committee papers for TA493 (TA493 was later replaced by TA616),(160) as it was not included as a comparator in TA533.(205)

The annual cost of ponesimod used in the economic model was [redacted], due to rounding across a full 365.25 days in the year.

Table 54: Annual Treatment Costs

Treatment	Acquisition		Administration		Monitoring	
	Year 1	Years 2+	Year 1	Years 2+	Year 1	Years 2+
Ponesimod	[redacted]	[redacted]	£0.00	£0.00	£123.44	£0.00
Dimethyl fumarate	£17,910.29	£17,910.29	£0.00	£0.00	£454.88	£222.25
Glatiramer acetate	£6,704.29	£6,704.29	£165.00	£0.00	£275.24	£223.84
Interferon beta-1a 22 mcg	£8,003.15	£8,003.15	£165.00	£0.00	£322.20	£244.18
Interferon beta-1a 30 mcg	£8,531.20	£8,531.20	£165.00	£0.00	£315.92	£244.18
Interferon beta-1a 44 mcg	£10,608.03	£10,608.03	£165.00	£0.00	£322.20	£244.18
Interferon beta-1b	£7,263.97	£7,263.97	£165.00	£0.00	£315.92	£244.18
Ocrelizumab	£19,160.00	£19,160.00	£1,865.66	£1,251.05	£293.88	£229.41
Pegylated interferon	£8,531.20	£8,531.20	£165.00	£0.00	£315.92	£244.18
Teriflunomide	£13,538.25	£13,538.25	£0.00	£0.00	£307.72	£209.60
Alemtuzumab[a]	£35,225.00	£21,135.00	£3,131.92	£1,902.68	£731.76	£663.91
Cladribine[a]	£24,566.88[b]	£24,566.88[b]	£0.00	£0.00	£604.61	£190.26
Fingolimod	£19,175.63	£19,175.63	£614.62	£0.00	£411.48	£228.82
Natalizumab[b]	£14,740.45	£14,740.45	£8,017.47	£8,017.47	£562.85	£375.27/ £511.45[c]
Best supportive care[b]	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00

NHS = National Health Service; NICE = National Institute for Health and Care Excellence.

Sources: British National Formulary (2020); Curtis and Burns (2019); NHS (2020); NICE TA624, NICE TA533, NICE TA493.(160, 205, 225, 243-245)

[a] Cladribine and alemtuzumab are given to most patients for 2 years only. Therefore, annual acquisition costs in years 3 to 5 are equal to weighted averages of costs for the portions of patients receiving retreatment and no costs for all other patients; details are provided in Section B.3.5.1.1.

[b] Considered in the model only as a post-discontinuation treatment.

[c] Reflects monitoring costs for years 2 and years 3 and beyond, respectively. When natalizumab is applied as a post-discontinuation treatment for the highly active subgroup, natalizumab's year 3 and beyond monitoring costs are used instead of year 2 and beyond. This was because monitoring costs of patients on that treatment differ between year 2 and year 3 onwards, and year 3 costs better represent those patients' long-term costs.

B.3.5.1.1 Direct costs for alemtuzumab and cladribine

Alemtuzumab and cladribine are both administered over two years and, for most patients, not administered in following years. The acquisition and administration costs for both of these treatments were applied as calculated for year 1 and year 2. For years 3 through 5, however, the model's costs were calculated to capture the costs of those patients who received an additional course in each of those years. The cost for each of those treatments was equal to a weighted average of no cost and the year 2 cost applied to 28.0%, 11.0%, and 1.0%, respectively, of alemtuzumab patients and 9.3%, 4.2%, and 3.2%, respectively, of cladribine patients.(160) The NICE committee on daclizumab (TA441) favoured a maximum of four treatment courses;(246) therefore, no re-treatment after year 5 was assumed. After this time, patients on alemtuzumab no longer incurred drug acquisition or administration costs but continued to benefit from the effectiveness of the treatments until they transitioned to subsequent treatment or best supportive care. The monitoring costs were applied every year after treatment initiation until patient discontinuation.

B.3.5.1.2 Direct costs for post-discontinuation treatment

The base case post-discontinuation treatment is best supportive care, which incurs no specific treatment costs. Direct costs are incurred only for post-discontinuation treatment in those scenario analyses that consider post-discontinuation DMTs and cladribine for the ITT population and natalizumab for the highly active subgroup.

The model allows for consideration of a post-discontinuation DMT if the user chooses not to apply the default setting in which all patients who discontinue treatment begin best supportive care. The model calculates the costs of the post-discontinuation treatment based on the costs for year 2 and beyond for acquisition, administration, and monitoring of the DMT, with the following exceptions:

- Monitoring costs for natalizumab in year 3 and beyond are applied in post-discontinuation treatment cost calculations, since monitoring costs of patients on that treatment differ between year 2 and year 3 onwards, and year 3 costs better represent those patients' long-term costs.
- The acquisition and administration costs of cladribine in post-discontinuation treatment costs are calculated from weighted annual averages across a 5-year period, given expected retreatment rates. This was because the model does not individually track patients' post-discontinuation treatment, or the number of years patients are receiving a post-discontinuation treatment. As a result, costs for treatments that vary by year required assumptions so that they could be reflected accurately in the model structure.

B.3.5.2 Health-state unit costs and resource use

The default annual direct management costs, and cost per relapse for RRMS and SPMS, by EDSS score health state (Table 55), were obtained from Table 43 of TA624.(245) These costs were inflated from previously reported values in TA320(132) published by Tyas et al. (2007).(247) Costs were inflated to 2019 currency levels using the Hospital and Community Health Services index from the 2019 Personal Social Services Research Unit.(244)

Disease management costs include health care cost (e.g., inpatient care, day admissions, consultations, tests, and non-DMT medications) and costs for community services (e.g., nurse visit, home helper) and major investments (e.g., purchase of a wheelchair, transform the house or car).

Table 55: Annual Direct Management and Relapse Costs, by EDSS Score

EDSS Score	RRMS	SPMS
Management costs		
0	£998.74	NA
1	£1,039.11	£1,386.86
2	£760.70	£1,108.45
3	£4,165.75	£4,512.46
4	£2,018.19	£2,364.90
5	£3,422.64	£3,771.42
6	£4,569.38	£4,916.10
7	£12,027.36	£12,374.08
8	£29,293.73	£29,641.48
9	£23,439.95	£23,788.74
Relapse costs		
0-9	£2,243.81	£2,243.81

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; NA = not applicable; NICE = National Institute for Health and Care Excellence; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Note: The direct management costs by EDSS score and relapse costs for both RRMS and SPMS were varied using the gamma distribution and an assumption that the standard error of the mean is 25% of the mean in the sensitivity analysis. Disease management costs include health care costs (e.g., inpatient care, day admissions, consultations, tests, and non-DMT medications) and costs for community services (e.g., nurse visit, home helper) and major investments (e.g., purchase of a wheelchair, transform the house or car).

Sources: NICE TA624, NICE TA320; Curtis and Burns (2019); Tyas et al. (2007).(132, 244, 245, 247)

B.3.5.3 Adverse reaction unit costs and resource use

The direct costs per serious and nonserious AEs were estimated by combining resource utilisation frequencies reported in NICE technology appraisals(205, 237, 245) with the

standard UK unit costs(225, 244) (see Table 56). Resource utilisation assumptions were needed to estimate costs for the following adverse reactions:

- Costs associated with increased aspartate aminotransferase (AST) were assumed to be the same as those for increased alanine aminotransferase (ALT.)
- Alopecia was assumed to have no associated costs, an assumption based on Travis et al. (2018).(240)
- Serious diarrhoea, dyspnoea, and hypertension all were assumed to be associated with one hospital admission, with the rationale that serious versions of those events would warrant inpatient care.
- Serious nausea events were assumed to incur the costs of cyclizine 50 mg.

Table 56: Adverse Event Costs

Adverse Event	Costs per Nonserious Event	Costs per Serious Event
ALT increased	£0.00	£210.60
AST increased	£0.00	£210.60
Alopecia	£0.00	£0.00
Back pain	£0.00	£912.14
Depression	£2,873.26	£12,110.80
Diarrhoea	£0.00	£1,770.94
Dizziness	£0.00	£168.33
Dyspnoea	£0.00	£1,196.31
Fatigue	£0.00	£249.40
Headache	£0.00	£220.24
Hypertension	£0.00	£1,849.29
Nausea	£0.00	£5.78
Nasopharyngitis	£0.00	£39.00
Urinary tract infection	£2.11	£1,254.62
Upper respiratory tract infection	£39.00	£39.00
PML, fatal	£19,391.18	£19,391.18
PML, nonfatal	£19,391.18	£19,391.18

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NICE = National Institute for Health and Care Excellence; PML = progressive multifocal leukoencephalopathy.

Note: The adverse-event costs were varied using the gamma distribution and an assumption that the standard error of the mean is 25% of the mean in the sensitivity analysis.

Sources: NICE TA441, NICE TA533, NICE TA624; Curtis and Burns (2019); Travis et al. (2018); Thompson et al. (2017).(79, 205, 237, 240, 244, 245)

B.3.6 Summary of model features

A summary of the model features discussed in the previous sections is presented in Table 57, alongside a comparison with models included in previous NICE appraisals of treatments for RMS/RRMS.

Table 57: Features of the economic analysis(135)

Factor	Previous appraisals								Current appraisal*	
	TA254	TA303	TA312	TA320	TA493	TA527	TA533	TA624	Chosen values	Justification
Source of natural history EDSS	London, Ontario	Trial placebo arm for EDSS 0-6 London Ontario for EDSS 7-9 Committee considered EDSS improvements more appropriate	Trial placebo arm for EDSS 0-6 London Ontario for EDSS 7-9 Committee considered EDSS improvements more appropriate	Trial placebo arm for EDSS 0-7 London Ontario for EDSS 8-9	BCMS	BCMS	BCMS	BCMS for transitions across EDSS for patients with RRMS London Ontario for transitions from RRMS to SPMS and during SPMS	BCMS for transitions across EDSS levels for patients with RRMS London Ontario for transitions from RRMS to EDSS	In line with the majority of previous submissions
Source of natural history relapse	Patzold et al. (1982)(227) combined with UK MS survey data	Held et al. (2005)(248) combined with Orme et al. (2007)(233) data, divided by assumption about hospitalised vs. non-hospitalised	Held et al. (2005)(248) combined with Orme et al. (2007)(233) data, divided by assumption about hospitalised vs. non-hospitalised	Patzold et al. (1982)(227) combined with UK MS survey data	CLARITY trial(249) and Tremlett et al. (2010)(250)	UK MS survey	Patzold et al. (1982)(227) combined with UK MS survey data	Patzold et al. (1982)(227) combined with UK MS survey data	Patzold et al. (1982)(227) combined with UK MS survey data	In line with the majority of previous submissions

Factor	Previous appraisals								Current appraisal*	
	TA254	**TA303**	**TA312**	**TA320**	**TA493**	**TA527**	**TA533**	**TA624**	**Chosen values**	**Justification**
Source of MS mortality multiplier	Pokorski (1997)(232)	Pokorski (1997)(232), extrapolated for EDSS states	Pokorski (1997)(232), extrapolated for EDSS states	Pokorski (1997)(232), extrapolated for EDSS states	Jick et al. (2014)(251)	Not applied	Pokorski (1997)(232), extrapolated for EDSS states	Pokorski (1997)(232), extrapolated for EDSS states	Pokorski (1997)(232), extrapolated for EDSS states	In line with the majority of previous submissions
Application of treatment effect	• ARR • CDP6M	• ARR • CDP6M • SPMS transition	• ARR • CDP6M • SPMS transition	• ARR • CDP6M	• ARR • CDP6M	• ARR • CDP6M • SPMS transition	• ARR • CDP6M • SPMS transition	• ARR • CDP6M • SPMS transition	• ARR • CDA3M	In line with previous submissions
Model structure	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS and 1 death state	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS and 1 death state	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS and 1 death state	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS and 1 death state	11 states based on 10 EDSS states representing RR and secondary-progressive forms of MS and 1 death state	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS and 1 death state	21 states (31 when RRMS DMT and RRMS BSC states are considered separately) based on 10 EDSS states for each of RRMS, DMT, RRMS BSC, and SPMS BSC and death	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS and 1 death state	20 states based on 10 EDSS states for RRMS, 9 EDSS states for SPMS and 1 death state	Use of EDSS states is in line with previous submissions

Factor	Previous appraisals								Current appraisal*	
	TA254	TA303	TA312	TA320	TA493	TA527	TA533	TA624	Chosen values	Justification
Time horizon	50 years	50 years	50 years	30 years	50 years	50 years	50 years	50 years	50 years	Reflects a lifetime horizon as patients starting in the model are aged 35 to 40 years. This is in line with previous NICE submissions and recommended best practices from NICE and ISPOR
Treatment waning effect?	50% waning after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years, time-dependent rate of treatment	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	In line with the majority of previous submissions
Application of treatment withdrawal	Trial data (discontinuation due to AEs), constant annualised rates	Trial data (treatment discontinuation), constant annualised rates for year 1-2, 50% for year ≥2	Trial data (treatment discontinuation), constant annualised rates for year 1-2, 50% for year ≥2	Trial data (treatment discontinuation), constant annualised rates	Trial data (treatment discontinuation), constant annualised rates	UK MS survey, Tappenden et al. (2001)	Trial data (treatment discontinuation), constant annualised rates	Trial data (treatment discontinuation), constant annualised rates	Trial data (treatment discontinuation), constant annualised rates	In line with the majority of previous submissions

Factor	Previous appraisals								Current appraisal*	
	TA254	TA303	TA312	TA320	TA493	TA527	TA533	TA624	Chosen values	Justification
Stopping rule	• EDSS ≥7 • SPMS transition (scenario)	• EDSS ≥7 • SPMS transition (scenario)	• EDSS ≥7 • SPMS transition (scenario)	• EDSS ≥7 • SPMS transition (scenario)	• EDSS ≥7 • SPMS transition (scenario)	• By individual treatment	• EDSS ≥7 • SPMS transition (scenario)	• EDSS ≥7 • SPMS transition	• EDSS ≥7 • SPMS transition	In line with the majority of previous submissions
Source of patient utilities	Orme et al. (2007)(233)	Trial data and Orme et al. (2007)(233)	Trial data and Orme et al. (2007)(233)	Trial data and Orme et al. (2007)(233)	Trial data, Hawton et al. (2016)(80), and Orme et al. (2007)(233)	Orme et al. (2007)(233)	Trial data and Orme et al. (2007)(233)	Trial data and Orme et al. (2007)(233)	Orme et al. (2007)(233)	In line with the majority of previous submissions
Source of relapse disutilities	Orme et al. (2007)(233)	Orme et al. (2007)(233) (non-hospitalised) and Prosser et al. (2003) (hospitalised)	Orme et al. (2007)(233) (non-hospitalised) and Prosser et al. (2003) (hospitalised)	UK MS survey (2005) (later published by Orme et al. (2007)	Orme et al. (2007)(233)	Not applied	Orme et al. (2007)(233)	Orme et al. (2007)(233)	Orme et al. (2007)(233)	In line with the majority of previous submissions
Source of caregiver disutilities	Loveman et al. (2006)(252) and UK MS survey data	Loveman et al. (2006)(252) and UK MS survey data	Loveman et al. (2006)(252) and UK MS survey data	Loveman et al. (2006)(252) and UK MS survey data	No caregiver disutilities	Acaster et al. (2013)(235)	Loveman et al. (2006)(252) and UK MS survey data	Acaster et al. (2013)(235)	Acaster et al. (2013)(235)	The most recent and relevant source was used and is in line with TA527 and TA624

Factor	Previous appraisals								Current appraisal*	
	TA254	TA303	TA312	TA320	TA493	TA527	TA533	TA624	Chosen values	Justification
Source of EDSS costs	UK MS survey (2005), direct medical and non-medical (NHS & PSS) (later published by Tyas et al. [2007])	Tyas et al. (2007)(247) (direct medical and midpoint of non-medical)	Tyas et al. (2007)(247) (direct medical only)	UK MS survey (2005) (NHS & PSS)	Kobelt et al. (2000), direct costs for EDSS 0-7, direct & indirect costs for EDSS 8-9	Tyas et al. (2007)(247)	Tyas et al. (2007)(247)	UK MS survey (2005) (direct medical only), inflated to 2019	Tyas et al. (2007)(247) inflated to 2019 for direct medical costs only	In line with previous submissions
Source of relapse costs	Tyas et al. (2007)(247)	Dee et al. (2012)(253)	Dee et al. (2012)(253)	UK MS survey (2005)	Not reported	Tyas et al. (2007)(247)	Tyas et al. (2007)(247)	Tyas et al. (2007)(247)	Tyas et al. (2007)(247) inflated to 2019	In line with TA624 submission

*Only default parameters for the ITT model are reported.

AE = adverse event, ARR = annualized relapse rate, BCMS = British Columbia Multiple Sclerosis, CDP6M = confirmed disability progression sustained for 6 months, EDSS = Expanded Disability Status Scale, ISPOR = International Society for Pharmacoeconomics and Outcomes Research, MS = multiple sclerosis, NHS = National Health Service, NICE = National Institute for Health and Care Excellence, PSS = personal social services, RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis, TA = technology appraisal, UK = United Kingdom.

Source: The values for previous appraisals are based on the NICE committee papers of TA624 (Company submission, Table 26).

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

Table 58: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Population characteristics			
Age	36.7 years	Scenario analysis	B.3.3.1
Gender (female)	64.02%		B.3.3.1
Baseline EDSS distribution	OPTIMUM trial		B.3.3.1
Model structure			
Time horizon	50 years	Fixed	B.3.2.2.2
Cycle length	1 year	Fixed	B.3.2.2.1
Discount rates for costs and outcomes	3.5% for costs and health outcomes	Scenario analysis	B.3.2.2.3
Half cycle correction	Yes	Fixed	B.3.2.2.1
Transition probabilities			
Baseline Relapse Rates for RRMS and SPMS	Values based on Patzold et al. (Table 37)	Lognormal	B.3.3.2.3
Baseline EDSS transitions for RRMS	Values based on British Columbia dataset (Table 32)	Dirichlet; Scenario analysis	B.3.3.2.1
Baseline conversion to SPMS	Values based Mauskopf et al. (Table 36)	Beta	B.3.3.2.2
Baseline EDSS Transitions for SPMS	Values based on London Ontario dataset (Table 35)	Dirichlet	B.3.3.2.1
Relative mortality risk	Values based on Pokorski et al. 1997; with linear interpolation (Table 46)	Lognormal; Scenario analysis	B.3.3.6
Treatment effect			
Relapse rate (relative risk vs natural history)	Values based on Janssen's NMA (Table 38)	Lognormal	B.3.3.3.1
Disability progression (hazard ratio vs natural history)	Values based on Janssen's NMA (Table 39 for ITT) (Table 40 for highly active)	Lognormal; Scenario analysis	B.3.3.3.1
Annual discontinuation risk for ponesimod	OPTIMUM trial; Ponesimod phase 2 trial	Beta; Scenario analysis	B.3.3.3.3
Annual discontinuation risk for comparators (relative risk vs ponesimod)	Values based on Janssen's NMA (Table 41)	Lognormal; Scenario analysis	B.3.3.3.3
Utilities			
Utility values and relapse utility decrements by EDSS score	Values based on by Orme et al. 2007 (Table 49)	Normal	B.3.4.4
Utility decrements due to AEs	Values based on previous NICE appraisals and publications (Table 50)	Beta	B.3.4.4.1

Caregiver disutility	Caregiver disutility included based on Acaster et al (Table 51)	Normal; Scenario analysis	B.3.4.4.2
Adverse events			
Annual incidence of AEs	Based on a SLR conducted by Janssen (Table 42, 43, 44, 45)	Beta	B.3.3.5
Costs			
Direct treatment costs	Table 54	Fixed	B.3.5.1
Direct management costs by EDSS	Values based on previous NICE appraisals and publications (Table 55)	Gamma	B.3.5.2
Direct relapse cost	Values based on previous NICE appraisals and publications (Table 55)	Gamma	B.3.5.2
AE costs	Values based on previous NICE appraisals and publications (Table 56)	Gamma	B.3.5.3

ARR = annualised relapse rate; CDA = confirmed disability progression; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NHS = National Health Service; IFN = interferon; QALY = quality-adjusted life year; RRMS = relapsing-remitting multiple sclerosis, SLR = systematic literature review; SPMS = secondary progressive multiple sclerosis; UK = United Kingdom; WTP = willingness-to-pay.

B.3.7.2 Assumptions

Table 59 outlines the assumptions made in the model.

Table 59: Model assumptions and justification

Model Aspect	Assumptions	Justification
Model structure	Although clinical disease progression and treatment discontinuation depend on the occurrence and frequency of relapses, the EDSS-based model structure does not reflect the relationship between relapses and disease progression or the clinical pathway of switching after multiple relapses.	This same model structure, however, has been widely accepted in the majority of previous models of MS treatments, including those submitted to NICE and described in the published literature (see summary Table 57)
	Transitions between health states are observed on an annual basis, and progression between health states is solely dependent on the current health state. Therefore, health states do not consider disease history or length of time spent in that state.	Transitions occur on an annual basis and are dependent only on current health states, to match published disease progression and relapse risk rates(220, 221, 227)
	Within a model cycle, patients with RRMS who do not convert to SPMS and patients with SPMS may transition to an EDSS score health state that is more than 1 point higher than their current EDSS score health state.	This assumption is consistent with the progression observed in analyses of the dimethyl fumarate trials and London Ontario data (Mauskopf et al., 2016)(221) and the British Columbia MS database (220) It also is aligned with previous NICE submissions (e.g., TA533 and TA624)(205,

Model Aspect	Assumptions	Justification
		245) and other MS models (Gani et al., 2008; Mauskopf et al., 2016).(221, 234)
	Patients who convert from RRMS to SPMS automatically transition to an EDSS score health state that is 1 point higher than their EDSS score health state before they had converted to SPMS.	This assumption was based on an analysis by Mauskopf and colleagues (2016) of time-to-SPMS estimates generated from London Ontario data (Scalfari et al., 2010)(222) and is applied in previous MS models (205, 221, 234)
Utilities	Caregiver disutility associated with each EDSS score was assumed to be the same for RRMS vs. SPMS.	There is a lack of data supporting differentiation. This assumption is conservative in that it underestimates the disutility due to MS and, therefore, underestimates the benefits of treatments that prevent disease progression and relapse. It is an assumption that is in line with the peginterferon NICE submission. (see summary Table 57)
AEs	Incidence rates of AEs were assumed to be constant over time.	Those rates were assumed to be constant over time, to capture varying incidences of AEs that may rise and fall over a treatment duration, given natural tendencies of some AEs to occur at different times in a treatment cycle or after prolonged use of therapies. This approach is necessary, given the Markovian structure of the model.
Treatment discontinuation	Discontinuation from treatment occurs only in the following circumstances: constant annual treatment discontinuation rates, EDSS score (when EDSS score is ≥ 7), or conversion to SPMS.	These discontinuation rules are in line with the clinical guidance for MS (NHS, 2019) and the majority of the models submitted previously to NICE. (see summary Table 57)
	Treatment discontinuation rates were assumed to be constant over time.	Those rates were assumed to be constant over time, to capture fluctuations in rates from multiple sources, each of which may vary over a treatment duration, given natural tendencies of some sources to occur at different times in a treatment cycle, such as discontinuation due to AEs or nonresponse that may be more likely to occur at treatment start or discontinuation due to drug resistance after prolonged use of a therapy. This approach is consistent with the approach used in several previous appraisals (see summary Table 57). The one exception to this assumption is for alemtuzumab and cladribine, which are taken for two years and assumed to have no discontinuation unless due to stopping rules after year 5.

Model Aspect	Assumptions	Justification
Mortality	Risk of death due to MS is primarily dependent on the level of disability.	Pokorski (1997) demonstrated that the risk of death is primarily dependent on the level of disability.(232)
	Treatment indirectly affects mortality by reducing rates of disability progression.	No evidence has been published to support a direct treatment effect on mortality, but clinical trials are not of sufficient duration to capture such an effect. Pokorski (1997) demonstrated that the risk of death is primarily dependent on the level of disability. This assumption is in line with other NICE submissions for MS therapies. (see summary Table 57)
	Patients with RRMS and SPMS with the same EDSS score have the same relative risk of mortality (where risk was from Pokorski, 1997).	This assumption is conservative in that it underestimates the mortality due to MS and, therefore, underestimates the benefits of treatments that prevent disease progression and relapse. It is an assumption that is in line with previous MS NICE submissions. (see summary Table 57)

AE = adverse event; ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis

B.3.8 Results of the base-case incremental cost-effectiveness analysis

The clinical and economic outcomes for the base-case analysis comparing ponesimod with the comparator treatments in ITT population are presented in Table 60.

Overall, ponesimod efficacy, as observed by its phase 3 trial results, translated to fewer lifetime relapses than teriflunomide, interferon beta-1a (22mcg, 30mcg and 40mcg) and peginterferon beta-1a; higher life-years and higher QALYs than all the comparators, except for ocrelizumab.

[redacted]

(annual cost of [redacted] for ponesimod versus [redacted] for glatiramer acetate, respectively). However, [redacted]

[redacted]

Base case results indicate that [redacted] The ICERs for ponesimod versus [redacted] the cost-effectiveness threshold that is accepted by NICE ([redacted] and [redacted], respectively). Compared [redacted], ponesimod had [redacted] Consequently, in a proportion of eligible patients with active RRMS, ponesimod offers a cost-effective use of resources. Moreover, patients receiving ponesimod spent [redacted] in the RRMS state and [redacted] receiving other treatments except for [redacted] (i.e., [redacted] with ponesimod, versus a range of [redacted] years with other comparators; [redacted]).

A summary of the analysis results comparing ponesimod with other treatments is shown in Table 60.

Table 60: CEM base-case results for the ITT Population

	Ponesimod	Teriflunomide	Dimethyl fumarate	Glatiramer acetate	IFN beta-1a 22 mg	IFN beta-1a 30 mg	IFN beta-1a 44 mg	IFN beta-1b	Ocrelizumab	Peginterferon beta-1a
Economic outcomes										
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes										
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness										
ICER, ponesimod vs. comparator (£ per QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CEM = cost-effectiveness model; ICER = incremental cost-effectiveness ratio; IFN = interferon; ITT = intent-to-treat; NA = not applicable; QALY = quality-adjusted life-year.

[a] Number of relapses outcomes are undiscounted.

B.3.9 Results of the highly active subgroup incremental cost-effectiveness analysis

The clinical and economic outcomes for the subgroup analysis comparing ponesimod with the comparator treatments in highly active population are presented in Table 61.

In patients with highly active RRMS, ponesimod was [redacted] Compared with [redacted] ponesimod was [redacted]

[redacted]

Treatment with ponesimod [redacted]

[redacted]

Ponesimod was associated with incremental QALYs of [redacted] compared to [redacted] Furthermore, ponesimod led to [redacted] compared to [redacted]. Similar to the results of the ITT population, ponesimod [redacted] in a small proportion of eligible patients.

Overall, ponesimod offers an [redacted], with its similar mode of action and [redacted]. Ponesimod is [redacted] for patients who [redacted] and who prefer a DMT with [redacted].

Table 61: CEM base-case results for the highly active RRMS subgroup

	Ponesimod 20mg PO	Ocrelizumab 600mg IV	Alemtuzumab 12mg IV	Cladribine 3.5mg/kg PO	Fingolimod 0.5mg PO
Economic outcomes					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes					
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness					
ICER, ponesimod vs. comparator (£ per QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CEM = cost-effectiveness model; ICER = incremental cost-effectiveness ratio; IFN = interferon; NA = not applicable; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

[a] Number of relapses outcomes are undiscounted.

B.3.10 Sensitivity analyses

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted to better understand the robustness of the cost-effectiveness estimates, given uncertainty about model input values. All model input values were varied except initial patient characteristics; treatment waning rates; treatment acquisition, monitoring, and administration costs; and background mortality rates. Ranges around all inputs were defined by the 95% CI, if available. When that interval was not available, parameter uncertainties were estimated from published means and an assumed sample size of 100, and ranges approximating 95% CIs were generated. Dirichlet, lognormal, beta, or gamma distributions were applied to each input, as appropriate. 5,000 sampled sets of inputs were generated. In Table 62, total costs and total QALYs from the PSA for each treatment are presented by mean (with 95% CI lower and 95% CI upper range), as well as a comparison of cost-effectiveness results (i.e., ICER) with deterministic results. The corresponding scatterplot with incremental costs by incremental QALYs for ponesimod vs. the comparators, and cost-effectiveness acceptability curves (CEAC) are presented in Figure 28 and Figure 29, respectively.

The scatter plot shown in Figure 28 illustrates the uncertainty in the ITT population surrounding the estimates of expected incremental cost and expected incremental effect (QALYs gained) when comparing ponesimod versus other treatments. The [redacted] the incremental cost-effectiveness [redacted] when comparing to [redacted] However, the spread of the points in the vertical and horizontal planes suggests there is some uncertainty regarding the magnitude of the costs and effects. Despite the [redacted]. As shown in Figure 29, ponesimod is [redacted] treatment at a willingness-to-pay threshold of both £20,000 and £30,000. For ponesimod versus [redacted], the curves intersect at the [redacted] at a willingness-to-pay threshold (x-axis) of around [redacted] that is [redacted]).

The scatter plot shown in Figure 30 illustrates the uncertainty in the highly active subgroup population and the estimates of expected incremental cost and effect when comparing ponesimod to highly active treatments. The location of the incremental cost-effectiveness results [redacted]. Against [redacted] there is some [redacted] as the spread of the [redacted]. The spread of points in the vertical and horizontal planes suggests [redacted].

Table 62: PSA results (mean) compared with deterministic results (ITT population)

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30mcg IM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ICER = incremental cost-effectiveness ratio; ITT = intent-to-treat; IM = intramuscular; IV = intravenous; PO = *per os* (oral); PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SC = subcutaneous

Figure 28: Cost-effectiveness scatter plot (ITT population)

ITT = intent-to-treat; IM = intramuscular; IV = intravenous; PO = *per os* (oral); QALY = quality-adjusted life-year; SC = subcutaneous

Figure 29: Cost-effectiveness acceptability curve (ITT population)

ITT = intent-to-treat; IM = intramuscular; IV = intravenous; PO = *per os* (oral); QALY = quality-adjusted life-year; SC = subcutaneous

Table 63: PSA results (mean) compared with deterministic results (highly active subgroup)

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 30: Cost-effectiveness scatter plot (highly active subgroup)

Figure 31: Cost-effectiveness acceptability curve (highly active subgroup)

B.3.10.2 Deterministic sensitivity analysis

A one-way sensitivity analysis was conducted to better understand the impact of individual inputs on the cost-effectiveness estimates. All model input values were varied in the one-way sensitivity analysis, except initial patient characteristics, natural disease (EDSS score) progression probabilities for RRMS and SPMS, post-discontinuation treatment mix, treatment waning rates, treatment acquisition, monitoring, and administration costs and background mortality rates. Ranges around all inputs were defined by the 95% CI, if available. When that interval was not available, parameter uncertainties were estimated from published means and an assumed sample size of 100, and ranges approximating 95% CIs were generated. Model input values were varied to the lower and upper bounds of their defined range.

Tornado charts are used to illustrate the parameters that have the biggest impact on the results. The top 12 drivers (ranked by influence on ICER per QALY) for ponesimod versus teriflunomide and fingolimod are presented in Figure 32 and Figure 33 respectively. Results for all other comparators are presented in Appendix L.

As expected, the results were most sensitive to annual treatment discontinuation rate for ponesimod and treatment effect of EDSS progression during RRMS (for both ponesimod and comparators). All other parameters have only modest impact on the results, including direct management costs by EDSS, relative mortality risks by EDSS, treatment effect of relapse rates, and baseline utility by EDSS during SPMS. Similar findings were seen in highly active subgroup, with an exception that baseline conversion to SPMS is a key driver for ponesimod compared to fingolimod.

Figure 32: Ponesimod versus teriflunomide: ICER per QALY results of OWSA (ITT population)

EDSS = expanded disability status scale; ICER = incremental cost-effectiveness ratio; ITT = intent-to-treat; OWSA = one-way sensitivity analysis; PO = *per os* (oral); QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Figure 33: Ponesimod versus Fingolimod: ICER per QALY results of OWSA (highly active RRMS subgroup)

EDSS = expanded disability status scale; ICER = incremental cost-effectiveness ratio; ITT = intent-to-treat; OWSA = one-way sensitivity analysis; PO = *per os* (oral); QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

B.3.10.3 Scenario analysis

Scenario analyses were conducted to estimate the cost-effectiveness of ponesimod compared to comparators under key alternate assumptions, evaluate how the model outcomes varied in relation to changes in key model parameters, and to examine whether the model results were robust to those variations. Scenarios were conducted in ITT population according to the base case analysis (Section B.3.8), as well as in highly active subgroup (details provided in Section B.3.9):

The following key scenarios were considered, and a full list is shown in Table 64:

- Apply mean age, sex distribution, and EDSS score distribution values from the UK MS RSS population reported in the TA624 for the model's ITT population characteristics.(245) This scenario can be chosen by the user to consider a UK MS patient population, rather than the patient population from the OPTIMUM trial, which was conducted in multiple countries and continents.(6)
- Apply EDSS transition matrix values reported in Mauskopf et al. 2016 and derived from the dimethyl fumarate trials and London, Ontario MS database transition matrix for patients with RRMS in the ITT population.(221) This data source has the advantage of also providing data for SPMS conversion rates and disease progression transition probabilities for SPMS patients. Because it is the source for the SPMS conversion and SPMS disease progression inputs in the current model, applying it for RRMS patients as well means that one source is used for all-natural history progression rates between health states.
- Apply no treatment waning assumption and 50% loss after 10 years assumption, rather than the base-case assumption where treatment effect remains 0% loss up to year 2, followed by 25% loss after year 2 and 50% loss after year 5.
- After discontinuation of the initial treatment, patients transition to post-discontinuation treatment of cladribine (ITT population) or natalizumab (highly active subgroup), rather than to the base-case assumption of transitioning to post-discontinuation treatment of best supportive care only.
- Apply caregiver utility decrement values reported by Gani et al. 2008, rather than on the base-case values reported by Acaster et al. 2013.(234, 235) This alternative source was considered because it was based on responses to the

UK MS Survey 2005 and had been used for estimating the cost-effectiveness of natalizumab.(234)

- Apply relative risk of mortality by EDSS score values reported by Pokorski 1997, without interpolation rather than by the base-case values reported by the same source, but with interpolation.(232) This alternate assumption was used to understand the impact of the interpolation of the data used in the base-case analysis.
- Apply a 5% annual treatment discontinuation rate for all treatments, rather annual treatment discontinuation rates that differ by treatment, as estimated in the NMA. This scenario allows the user to study the differences in outcomes between treatments when those treatments differ by costs and effects on disease progression and relapse rates only (and by length of time on treatment when discontinuation occurs due stopping rules). This scenario was also considered in several previous appraisals of MS therapies because it reflects observed discontinuation rates in the UK RSS.(245)

Table 64: Description of the scenario analysis

No.	Parameter	Base case	Scenario
ITT population			
S1	Discounting	3.5% for both costs and outcomes	1.5% for both costs and outcomes
S2	Population characteristics	OPTIMUM trial source	UK Risk Sharing Scheme source
S3	Natural history transition matrix between EDSS states	British Columbia	Dimethyl fumarate and London Ontario data source
S4	Disease progression to higher EDSS	Treatment effect based on 3-month data	Treatment effect based on 6-month data
S5a	Treatment waning effect	0% loss up to year 2, 25% loss after year 2, 50% loss after year 5	1. No waning effect
S5b			2. 50% loss after 10 years
S6	Caregiver disutilities	Caregiver disutility included based on Acaster et al. 2013	Disutility included based on Gani et al. 2008
S7	Mortality	Pokorski et al. 1997 with interpolation	Pokorski et al. 1997 without interpolation
S8	Treatment discontinuation	Annual rates of discontinuation sourced from Janssen NMA	5% of discontinuation for all treatments
S9	Post-treatment discontinuation	100% best-supportive care treatment	100% move to post treatment discontinuation of cladribine
Highly active RRMS population			
S10	Population	NA	Highly active RRMS subgroup
S11	Disease progression to higher EDSS	Treatment effect based on 3-month data	Treatment effect based on 6-month data
S12a	Treatment waning effect	0% loss up to year 2, 25% loss after year 2, 50% loss after year 5	1. No waning (backed up with phase 2 long-term data)
S12b			2. 50% loss after 10 years
S13	Treatment discontinuation	Annual rates of discontinuation sourced from Janssen NMA	5% of discontinuation for all treatments
S14	Post-treatment discontinuation	100% best-supportive care treatment	100% move to post treatment discontinuation of natalizumab

EDSS = expanded disability status scale; ITT = intent-to-treat; NA = not applicable; NMA = network meta-analysis; RRMS = relapsing-remitting multiple sclerosis; UK = United Kingdom

Results of the scenario analyses in ITT population demonstrated consistency with the base-case results where ponesimod dominated [redacted]

Compared with interferon beta-1a (22mcg), ponesimod either dominated or had an ICER ranging from [redacted] (when mortality was based on Pokorski without interpolation) to [redacted] (when using treatment effect of disease progression to higher EDSS was based on 6-month data). Compared with [redacted] or with an ICER ranging from

[redacted]_which was mainly driven by the assumptions explored for treatment discontinuation and post-discontinuation treatment.

With the scenario where treatment effect of disease progression was based on 6-month data, ponesimod [redacted] Given that the interferon beta-1b was not included in the NMA network and therefore evaluated through naïve comparison, the uncertainties in its clinical outcomes should be interpreted with caution. The evidence networks for the 3-month CDA informing the base case of the model included more data and was more connected with a larger number of closed loops and may be considered to consist of more reliable data as compared to 6-month CDA, given that a greater proportion of trials in the 3-month CDA network defined the outcome as either a primary or secondary endpoint. 6-month CDA was more rarely defined as a primary or secondary endpoint across the identified trials.

Results of the scenario analyses conducted among the highly active subgroup also demonstrated consistency with the base case results where ponesimod was [redacted] in all explored scenarios. With the scenario where 100% patients discontinued treatment will switch to natalizumab, ponesimod was [redacted]

Detailed scenario analysis results are presented in Table 65 (ITT population) and Table 66 (highly active RRMS subgroup).

Table 65: Scenario analysis results (ITT population)

Scenario	Outcome	Ponesimod 20mg PO	Teriflunomide 14mg PO	Dimethyl fumarate 240mg PO	Glatiramer acetate 20mg SC	IFN beta-1a 22mcg SC	IFN beta-1a 30mcg IM	IFN beta-1a 44mcg SC	IFN beta-1b 250mcg SC	Ocrelizumab 600mg IV	Peginterferon beta-1a 125mcg SC
Base case	QALY	[redacted]									
	Costs										
	ICER										
S1											
	QALY										
	Costs										
	ICER										
S2											
	QALY										
	Costs										
	ICER										
S3											
	QALY										
	Costs										
	ICER										
S4											
	QALY										
	Costs										
	ICER										
S5a	QALY										

Scenario	Outcome	Ponesimod 20mg PO	Teriflunomide 14mg PO	Dimethyl fumarate 240mg PO	Glatiramer acetate 20mg SC	IFN beta-1a 22mcg SC	IFN beta-1a 30mcg IM	IFN beta-1a 44mcg SC	IFN beta-1b 250mcg SC	Ocrelizumab 600mg IV	Peginterferon beta-1a 125mcg SC
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5b	QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S6	QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7	QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8	QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S9	QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome	Ponesimod 20mg PO	Teriflunomide 14mg PO	Dimethyl fumarate 240mg PO	Glatiramer acetate 20mg SC	IFN beta-1a 22mcg SC	IFN beta-1a 30mcg IM	IFN beta-1a 44mcg SC	IFN beta-1b 250mcg SC	Ocrelizumab 600mg IV	Peginterferon beta-1a 125mcg SC
										[redacted]	

ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; ITT = intent-to-treat; IV = intravenous; QALY = quality-adjusted life-year; PO = *per os* (oral); SC = subcutaneous

Table 66: Scenario analysis results (highly active RRMS subgroup)

Scenario	Outcome	Ponesimod 20mg PO	Ocrelizumab 600mg IV	Alemtuzumab 12mg IV	Cladribine 3.5mg/kg PO	Fingolimod 0.5mg PO
S10	QALY					
	Costs					
	ICER					
S11	QALY					
	Costs					
	ICER					
S12a	QALY					
	Costs					
	ICER					
S12b	QALY					
	Costs					
	ICER					
S13	QALY					
	Costs					
	ICER					
S14	QALY					
	Costs					
	ICER					

ICER = incremental cost-effectiveness ratio; IV = intravenous; PO = *per os* (oral); QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis

B.3.10.4 Summary of sensitivity analyses results

Detailed in section B.3.9, it has been demonstrated that the results of the CEM are robust and not sensitive to changes in important parameters or assumptions. The scenario analyses show that the presented base-case ICER is conservative.

B.3.11 Validation

B.3.11.1 Internal validation of cost-effectiveness analysis

The model was subjected to a thorough quality-check process to minimise the risk of errors in the model's logical structure, equations, and programming. This process was performed by a researcher not involved in the original model design or programming and included the following tasks:

- Conducted a comprehensive series of diagnostic tests to assess the correctness of the model code, calculations, and mechanics
- Reviewed one-way sensitivity analysis results to ensure that all model inputs were appropriately influencing key model outcomes
- Checked the values applied for each model input to ensure that they matched their referenced source material
- Checked the appearance of the model for consistency and text of the model for clarity and accuracy

Any identified errors were corrected; those corrections then were quality checked as well.

B.3.11.2 External validation of cost-effectiveness analysis

A technical review of the economic model was performed in February 2021.(254) The model was independently reviewed by health economists not involved with the development of the economic model.(254) The following steps were taken:

- Review of model functionality and presentation
- Inspection of the model inputs
- Cross-check of model inputs vs. source data where possible
- Logical scenarios and checks
- Manual inspection of formulae
- Comparison of model outputs to other analyses.

Considering these aspects, the independent reviewers concluded that the model was designed and presented appropriately, with suitable inputs for the base case and appropriate setup of formulae.(254)

B.3.12 Interpretation and conclusions of economic evidence

A *de novo* CEM was developed to assess the cost-effectiveness of ponesimod versus relevant NICE-recommended DMTs in active RRMS (the "ITT population") and in the subgroup of patients with highly active RRMS. The model uses a Markov-based cohort approach based on EDSS health states and is conducted from the perspective of the UK NHS and Personal Social Services over a 50-year time horizon. The model structure and inputs were informed by previous NICE appraisals in MS and published data on costs and clinical outcomes.

In the ITT analysis ponesimod [redacted] The ICERs for ponesimod vs. [redacted] cost-effectiveness threshold accepted by NICE [redacted], respectively). Compared with [redacted], ponesimod was [redacted]). For patients who are eligible for medium efficacy treatments and a lower side effect profile, ponesimod offers a cost-effective use of resources. Cost effectiveness results in the subgroup of patients with highly active RRMS demonstrate that [redacted] in multiple sclerosis in patients who are eligible for ponesimod treatment.

Disaggregated results from the CEM (Appendix J) were in line with expectations, as illustrated by disease management costs for the SPMS disease stage being considerably higher than those for RRMS.

Scenario analyses were conducted to evaluate the robustness of the model results in relation to changes in key model parameters. Results of the scenario analyses in the ITT population generally demonstrated consistency with the base-case results. When treatment effect of disease progression was based on 6-month data, ponesimod [redacted] However, it should be noted that the NMAs informing the 6-month CDA based scenario are not as robust as the 3-month networks, firstly because there were fewer trials that reported

this outcome, and among these it was usually reported as a secondary efficacy endpoint, and the trials were not powered to detect differences between interventions. Based on the eligibility criteria of the NMA, interferon beta-1b was not represented in the NMA network and was therefore evaluated through naïve comparison. Therefore, the results for ponesimod vs. interferon beta-1b should be interpreted with caution. It should be noted that clinical trial data from the phase 2 long-term study has shown that approximately four of five patients did not experience a 6-month CDA over a 9-year period of treatment suggesting a favourable effect of ponesimod for this outcome over several years.

The annual discontinuation rate of ponesimod is among the top three model drivers of ICERs for ponesimod versus other treatments. While the uncertainty with treatment discontinuation estimation is within expectation, different assumptions and selection of data sources could lead to a relatively wide range for these inputs. Although the estimations of annual discontinuation risk for ponesimod and other treatments were verified comparing against previous NICE appraisals (e.g. TA533)(205) and deemed reasonably aligned, there was no strong consensus on whether the estimations were plausible, and slightly different estimations were provided in another previous NICE appraisal (TA624).(135) Indeed, in a scenario exploring equal discontinuation rates of DMTs, [redacted] compared to the base case of the model. While the 24-week core phase 2 ponesimod study was included in the NMA, data from the long-term extension study was not eligible for inclusion in the NMA due to the lack of a comparator. However, it should be noted that treatment persistence with ponesimod was 61% over 9 years, and overall, only a small proportion of patients randomised to ponesimod 20 mg discontinued due to adverse events ([redacted]) or lack of efficacy ([redacted]).

Overall, cost-effectiveness analysis demonstrates that ponesimod is likely to be cost-effective at £20,000 per QALY [redacted]. In the second line, [redacted] and hence offers a cost-effective [redacted] patients. Sensitivity analysis confirms that it is highly likely that ponesimod is cost-effective in all reasonable structural and parameter variations.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Clarification questions

April 2021

File name	Version	Contains confidential information	Date
[ID1393 Ponesimod_ERG Clarification questions 29.04.2021_v1	1	Yes	29 April 2021

Tables

Figures

Section A: Clarification on effectiveness data

Systematic review methods

A1. Please confirm whether any authors from trials included in the network meta-analysis (NMA) were contacted and if any additional data not included in the publications was provided.

Company response: No authors from the trials included in the NMA were contacted. All data included in the NMAs were extracted from publications and reports identified in the SLR described in Section B.2.1 of the Company submission (CS). Inputs for all NMAs have now been provided in the response to A4.

Clinical effectiveness evidence

A2. Priority question. We note that at the time of submission, ofatumumab and ozanimod were still undergoing NICE appraisal, However, NICE have asked us to consider both in our appraisal of ponesimod. Consistent with other comparators in the company submission (CS), please provide relevant methodological information and clinical efficacy results for trials evaluating both treatments in populations relevant to ponesimod. This should include updating the NMA to include ofatumumab and considering both ofatumumab and ozanimod in your response to all clarification queries.

Company response: As requested by the ERG, Janssen have updated the NMAs to include all eligible trials for ofatumumab and ozanimod in the analyses. Janssen would like to note that the PICOS for the original analyses were designed to consider only NICE-recommended treatment options and therefore, excluded ofatumumab and ozanimod which are still undergoing NICE appraisal at the time of responding to clarification questions and not yet considered as standard of care. In response to the draft NICE scope, ozanimod had been included in the original NMAs but not reported for the reasons stated above, and these results are now fully reported. For ofatumumab, all citations pertaining to RCTs of ofatumumab 20 mg dose, every 4 weeks subcutaneously) (Q4W) were identified and retained from the original searches, in line

with the PICOS criteria. The search strategy employed on the Cochrane Central Register of Controlled Trials, Embase and MEDLINE included ofatumumab as a treatment option (described in CS Appendix D, Table 1). For grey literature searches, not all original sources were reviewed due to time constraints; however, a targeted search of clinicaltrials.gov and the MSVirtual 2020 conference (ECTRIMS-ACTRIMS) was deemed appropriate to identify the most recent data from any other RCTs to include in the analyses. Clinicaltrials.gov was searched using the following criteria, with the advanced search function:

- Condition or disease: Multiple sclerosis
- Other terms: ofatumumab
- Study type: Interventional Studies (Clinical Trials)
- Eligibility criteria: Adult (18-64)

The MSVirtual 2020 conference abstracts published in the Multiple Sclerosis Journal (Volume 26, December 2020) were reviewed using the search keyword “ofatumumab”.

From the results of these searches, we identified three eligible RCTs (APOLITOS, ASCELPIOS I, and ASCELPIOS II) describing clinical effectiveness of ofatumumab in RRMS (Table 1).

Table 1 RCTs included in the updated NMAs

Trial Name or Identifier	Full Citation	Record Type
ASCLEPIOS I	Hauser, S.L., Bar-Or, A., Cohen, J.A., Comi, G., Correale, J., et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020 Aug 6;383(6):546-557. doi: 10.1056/NEJMoa1917246.	Primary publication
	https://clinicaltrials.gov/ct2/show/NCT02792218	Trial registry
ASCLEPIOS II	Hauser, S.L., Bar-Or, A., Cohen, J.A., Comi, G., Correale, J., et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020 Aug 6;383(6):546-557. doi: 10.1056/NEJMoa1917246.	Primary publication
	https://clinicaltrials.gov/ct2/show/NCT02792231	Trial registry

APOLITOS	Kita, J.I., Nakahara, J., Sazonov, D.V., Kurosawa, T., Tsumiyama, I., et al. Efficacy and safety of ofatumumab versus placebo in relapsing multiple sclerosis patients in Japan and Russia: results from the phase 2 APOLITOS study. Multiple Sclerosis. 2020 December; 26(3):219	Early abstract

Details of the study summaries, eligibility criteria and NMA inputs are presented in Table 2, Table 3, and Table 4 respectively.

Table 2: Summary of ofatumumab studies included in the updated NMAs

Author, Publication Date	Trial Name/ Identifier	Phase	Blinding	Enrolment Period	Number of Sites; Location	Primary Time point (weeks)[a]	Treatment		Sample Size (N)
							1	2	
Hauser, 2020	ASCLEPIOS I	3	Double	Oct 2016-Mar 2018	385 sites, international	72	Ofatumumab 20 mg SC, 4W	Teriflunomide 14 mg PO, QD	927 1: 465 2: 462
	ASCLEPIOS II					76.8			955 1: 481 2: 474
Kira, 2020	APOLITOS	2	Double	Mar 2018 - UC	14 sites, Japan and Russia	24	Ofatumumab 20 mg SC, 4W	Placebo	64 1: 43 2: 21

[a] Median time in trial was reported for ASCLEPIOS I and II in years (1.5 years and 1.6 years respectively) and was converted to weeks, where 1 year was set equal to 48 weeks (aligned with the majority of other trials which were verified to be either 48 weeks or 96 weeks long

4W = every 4 weeks; Ph = phase; PO = orally; QD = every day; SC = subcutaneous

Table 3 Eligibility criteria of ofatumumab studies included in the updated NMAs

Trial name/ Identifier	Key inclusion criteria	Key exclusion criteria
ASCLEPIOS I and II	• 18 to 55 vears • Diagnosis of MS (2010 revised McDonald criteria) with a relapsing–remitting course or a secondary progressive course with disease activity • EDSS score of 0 to 5.5 • ≥1 relapse in the year before screening, ≥2 relapses in the 2 years before screening, or ≥1 Gd+ T1 lesion in the year before randomisation • neurologically stable condition for at least 1 month before randomisation	• Diagnosis of PPMS or SPMS without disease activitv or meeting the criteria of neuromyelitis optica • Patients with an active chronic disease of the immune system other than MS • Patients at risk of developing or having reactivation of hepatitis • Patients with active systemic infections or with neurological findings consistent with PML Other protocol-defined inclusion/exclusion criteria may apply
APOLITOS	• 18–55 years of age • Diagnosis of MS (2010 revised McDonald criteria),	• Primary progressive MS or SPMS without disease activity

	• At least 1 appearance of a new neurological abnormality or worsening of pre-existing neurological abnormality during the previous 2 years prior to Screening AND an MRI activity (Gd+ T1 lesions or new or enlarging T2 lesions) in brain during the previous 1 year prior to randomization • EDSS score of 0–5.5	• Patients with an active chronic disease of the immune system other than MS • Patients at risk of developing or having reactivation of hepatitis • Patients with active systemic infections or with neurological findings consistent with PML Other protocol-defined inclusion/exclusion criteria may apply

Abbreviations: EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 4 Input data for ofatumumab

Trial Name/ Identifier	Treatment	n	ARR		3-month CDA		6-month CDA		Discontinuation	Treatment Duration (weeks)
			Mean ARR	Standard deviation	Hazard ratio	95% CI	Hazard ratio	95% CI	Events	
ASCLEPIOS I	Ofatumumab 20 mg SC, Q4W	465	0.11	0.28	0.65	0.45 – 0.96	0.61	0.40 – 0.93	64	72*
	Teriflunomide 14 mg PO, QD	462	0.22	0.44					98	72*
ASCLEPIOS II	Ofatumumab 20 mg SC, Q4W	481	0.1	0.28	0.66	0.45 – 0.97	0.76	0.49 – 1.17	97	76.8*
	Teriflunomide 14 mg PO, QD	474	0.25	0.50					103	76.8*
APOLITOS	Ofatumumab 20 mg SC, Q4W	43	0.264	NR	NR		NR		0†	24
	Placebo	21	0.6286	NR					0†	24

*Median duration of treatment, converted from years to weeks (considering one year equal to 48 weeks)
†APOLITOS trial was not incorporated in NMAs of treatment discontinuations due to the zero event rates in each arm.

Results of the updated base case network meta-analyses

ARR

There were 44 RCTs and 18 regimens (including placebo) included in the network for ARR (Figure 1). All DMTs specified in the PICOS and at licenced dosages in the UK were represented in the network, with most connections supported by one or two trials. With the exception of alemtuzumab, all DMTs were anchored directly to the placebo node.

Figure 1: Network diagram for the updated base case NMA of ARR (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The results of the ARR analysis in the ITT populations of the trials are presented in a forest plot (Figure 2) and a league table (Figure 3). Overall, ponesimod ranked [redacted] out of the [redacted] regimens evaluated in the NMA for ARR in patients with RRMS and was ranked [redacted] than all NICE-recommended first-line treatments for active RRMS, except [redacted] Ponesimod was found to have a [redacted] probability of reducing relapses compared with [redacted] and performed similarly to [redacted]. In line with the analyses presented in their company submissions to NICE, [redacted] performed better than [redacted] for this outcome.(1, 2)

Figure 2: Forest plot of ponesimod versus comparators in the updated base case NMA for ARR (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

[redacted]

Figure 3: League table for the updated base case NMA of ARR (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

3-month CDA

There were 23 RCTs and 16 regimens (including placebo) included in the network for 3-month CDA (Figure 4). All DMTs specified in the PICOS, and all UK approved regimens except [redacted] were represented in the network.

Figure 4: Network diagram for the updated base case NMA of 3-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The relative efficacy of ponesimod versus other treatments for 3-month CDA based on the NMA in the ITT populations of the trials are presented in a forest plot (Figure 5) and a league table (Figure 6). Most DMTs in the network had a [redacted]probability at reducing the proportions of patients with 3-month CDA compared to best supportive care (placebo), except for [redacted]. Overall, ponesimod ranked [redacted]and was higher than [redacted]

Figure 5: Forest plot of ponesimod versus comparators in the updated base case NMA for 3-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Figure 6: League table for the updated base case NMA of 3-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

6-month CDA

There were 22 RCTs and 15 regimens (including placebo) included in the network for 6-month CDA (Figure 7) for the ITT population. All DMTs specified in the PICOS and all UK approved regimens except were represented in the network. Heterogeneity in trial duration was also noted, although all trials included in the NMA were of more than 1 year in duration.

Figure 7: Network diagram for the updated base case NMA of 6-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The results of the NMA in the ITT populations of the trials are presented in a forest plot (Figure 8) and a league table (Figure 9). Ponesimod [redacted] in the network for this outcome. Overall, ponesimod ranked [redacted]out of 15 regimens (including placebo), ranking [redacted] n 6-month CDA for active RRMS except [redacted].

Figure 8: Forest plot of ponesimod versus comparators in the updated base case NMA for 6-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Figure 9: League table for the updated base-case NMA of 6-month CDA (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Treatment discontinuations

There were 45 RCTs and 18 regimens (including placebo) included in the network for treatment discontinuations in the ITT populations of the trials (Figure 10). All DMTs specified in the PICOS and all UK approved regimens were represented in the network.

Figure 10: Network diagram for the updated base case NMA of treatment discontinuation (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The results of the NMA for treatment discontinuations are described in a forest plot (Figure 11) and a league table (Figure 12). Ponesimod performed similarly to [redacted] for this outcome. [redacted] probability of low treatment discontinuations compared with [redacted]. Overall, ponesimod was ranked [redacted] out of the 18 regimens included in the analysis and ranked [redacted] the following. [redacted]

Figure 11: Forest plot of ponesimod versus comparators in the updated base case NMA for treatment discontinuations (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Figure 12: League table for the updated base case NMA for treatment discontinuations (ITT Population)

2W = every 2 weeks; 4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CLA = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB-1a = interferon beta-1a; IFNB-1b = interferon beta-1b IM = intramuscular; ITT = intention-to-treat; NAT = natalizumab; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PEG = peginterferon; PON = ponesimod; QD = every day; QOD = every other day; QW = weekly; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Results of NMAs in highly active RRMS

The efficacy of ponesimod versus NICE recommended DMTs in patients with highly active RRMS was evaluated separately as a subgroup analysis in line with the decision problem (section B.1.1). For this analysis, the comparators were restricted to NICE-recommended treatments for highly active RRMS (i.e., alemtuzumab, cladribine, fingolimod, ocrelizumab and ofatumumab) and other DMTs (i.e., teriflunomide, interferon beta-1a 30 µg IM and interferon beta-1a 44 µg SC) were only included if they were essential for connecting the network. Ozanimod was also included in the analyses since it is currently undergoing appraisal as a treatment option for this population. Natalizumab was excluded from this analysis since it is not recommended for highly active RRMS by NICE.

Publications and reports identified in the SLR were reviewed for data on patients with highly active RRMS. As the definition of high disease activity varied across studies, trials were selected for inclusion into the analysis based on their alignment with the definition used in the OPTIMUM trial (described in Section B.2.7.1 of the CS and also in company response to A5). For all three efficacy outcomes, it was found that a network containing all relevant comparators would not be possible, due to a lack of reported subgroup data for some outcomes. To ensure full network connectivity, an assumption was made that the outcomes for the ITT population were equivalent to those of the highly active RRMS subgroup in these trials, similar to analyses presented in TA533.(1)

The resulting networks include all NICE-recommended second line DMTs and ozanimod, anchored as needed via teriflunomide (ITT data from TEMSO and TOWER used for ARR only), IFN beta-1a 30 µg intramuscular (IM) (ITT data from BRAVO used for 6-month CDA only) or IFN beta-1a 44 µg SC TIW (ITT data from PRISMS used for all three outcomes). For ofatumumab (ASCLEPIOS I, ASCLEPIOS II) and ozanimod (RADIANCE A, RADIANCE B and SUNBEAM), data for the ITT population of relevant trials was used in all three NMAs since outcome data for people with highly active disease is not publicly available. For the 3-month CDA network, data for the highly active subgroup was also unavailable for fingolimod and alemtuzumab. In order to facilitate the incorporation of fingolimod, a key comparator for our analysis, 6-month CDA outcome data from the pooled FREEDOMS I and II trials pertaining to highly active patients was used in place of 3-month CDA data.

Random effects models as well as fixed effect models were used to conduct analyses, where the model with better fit based on the deviance information criterion (DIC) was selected for the base case analysis. The model used for the base case analysis was also used for subgroup or sensitivity analyses of common outcomes.

ARR: Highly active RRMS

The network for ARR in the highly active subgroup consisted of 17 trials and 11 regimens (including placebo) representing all NICE-recommended second line DMTs included in the final scope (Figure 13).

Figure 13: Network diagram for the updated NMA of ARR in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The NMA results are presented in a forest plot (Figure 14) and a league table (Figure 15). Overall, ponesimod ranked [redacted] out of the 11 regimens analysed, and was ranked [redacted] The analysis for ARR indicated that [redacted] probability at [redacted].

Figure 14: Forest plot of the updated NMA for ARR in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; CrI = credible interval; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Figure 15: League table for the updated NMA for ARR in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; ARR = annualised relapse rate; BID = twice daily; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

3-month CDA: Highly active RRMS

The network for 3-month CDA in the highly active subgroup consisted of 14 trials and 10 regimens and included all NICE-recommended treatments for highly active RRMS, except for alemtuzumab (Figure 16).

Figure 16: Network diagram for the updated NMA of 3-month CDA in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The NMA results are presented in a forest plot (Figure 17) and a league table (Figure 18). The network contains all relevant NICE-recommended highly active treatments, in addition to ozanimod and ofatumumab, which are currently ongoing appraisals. Alemtuzumab is excluded from the results due to a lack of reported data for this outcome. Overall, ponesimod ranked [redacted] out of the 10 regimens analysed, and was ranked [redacted] The analysis shows that all [redacted] included in the analysis had [redacted] probabilities of reducing proportion of patients with 3-month CDA, compared to best supportive care (placebo).

Figure 17: Forest plot of the updated NMA for 3-month CDA in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; CrI = credible interval; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Figure 18: League table for the updated NMA for 3-month CDA in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

6-month CDA: Highly active RRMS

The network for 6-month CDA in the highly active subgroup consisted of 15 trials and 11 regimens (including placebo) (Figure 19).

Figure 19: Network diagram for the updated NMA of 6-month CDA in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

The NMA results are presented in a forest plot (Figure 20) and a league table (Figure 21). Overall, ponesimod ranked [redacted] out of the 11 regimens analysed, and was ranked [redacted]. All relevant second line DMTs were included in the analysis and [redacted] for this outcome and had [redacted] probabilities of reducing the proportion of patients with 6-month CDA compared to best supportive care (placebo).

Figure 20: Forest plot of the updated NMA for 6-month CDA in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; CrI = credible interval; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Figure 21: League table for the updated NMA for 6-month CDA in people with highly active RRMS (subgroup analysis)

4W = every 4 weeks; 24W = every 24 weeks; ALE = alemtuzumab; BID = twice daily; CDA = confirmed disability accumulation; CLA = cladribine; FIN = fingolimod; IFNB-1a = interferon beta-1a; IM = intramuscular; NMA = network meta-analysis; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PBO = placebo; PON = ponesimod; QD = every day; RRMS = relapsing remitting multiple sclerosis; SC = subcutaneous; TER = teriflunomide; TIW = three times per week

Note: Ozanimod was included in the NMA based on the final scope but is not recommended by NICE for the treatment of patients with RRMS at the time of responding to the clarification questions

Treatment discontinuations: Highly active RRMS

A separate NMA for treatment discontinuations was not conducted for the highly active RRMS subgroup due to a lack of available data for this subgroup. However, results from the main analysis indicated that ponesimod was ranked lower than all DMTs recommended for second-line treatment.

Conclusions from the updated NMAs

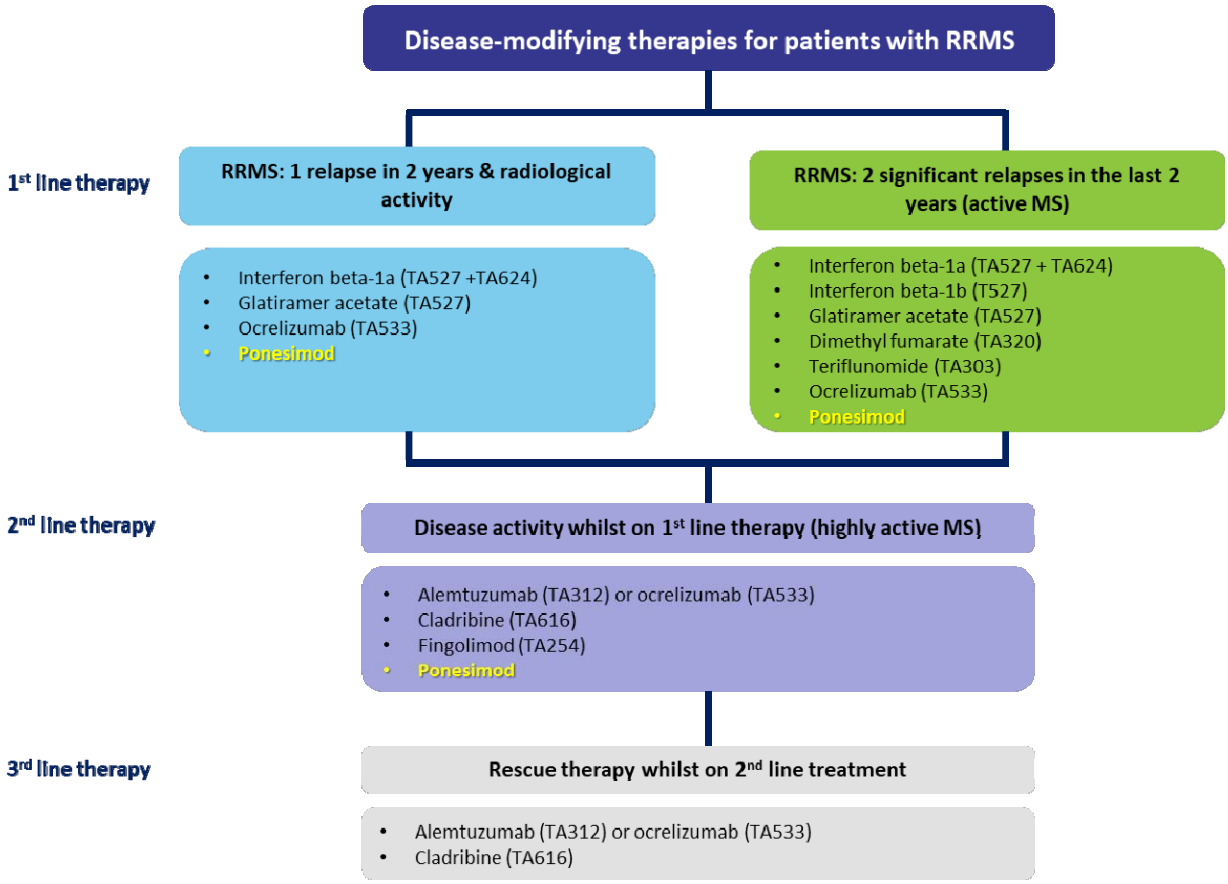
Overall, the results of the updated NMAs are consistent with those presented in the initial company submission, with ponesimod demonstrating a clinical effectiveness profile that is [redacted]. For the highly active subgroup, ponesimod performed [redacted] for the efficacy outcomes. Inclusion of RCT data for ofatumumab appears to have minimal or no impact in the effect sizes between ponesimod and other DMTs and

therefore, did not impact the relative rankings of the DMTs presented in the original submission.

A3. Please confirm that the intended population for ponesimod in the UK treatment pathway does not include people with rapidly evolving severe (RES) MS, as defined within the UK.

Company response: As indicated in Figure 4 of the company submission (reproduced below as Figure 22), Janssen has presented evidence supporting the positioning of ponesimod in people with active RRMS and people with highly active RRMS with disease activity whilst on first line therapy, as defined in the NHS England treatment algorithm. As described in the CS Section B.2.9, the evidence for ponesimod as an effective treatment option in these two populations is based on NMAs, informed by the ITT population and the pre-defined highly active subgroup of the OPTIMUM trial.

Figure 22: NHSE treatment algorithm for DMTs in RRMS with proposed positioning of ponesimod (yellow)



N.B. the most recent version of the NHSE treatment algorithm (updated in March 2019) does not reflect revisions required following a European Medicines Agency safety review in November 2019 that resulted in a change to the marketing authorisation indication for alemtuzumab with new warnings and precautions for use.
Note: Treatments for RES MS are not shown.
DMT = disease modifying treatment; JCV = John Cunningham Virus; IFN = interferon; MS = multiple sclerosis; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis.
Adapted from: NHSE 2019(3)

Janssen would like to note that, in comparison to the NHS England definition of highly active RRMS, the pre-specified subgroup of patients with highly active disease in the OPTIMUM trial was defined more broadly and therefore contains a population more closely aligned to the NICE definition of both highly active and RES RRMS. The OPTIMUM definition is as follows:

1. Any DMT for MS received within 12 months prior to randomisation and one or both of the following:

    - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions

    - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for patients with at least one relapse within 2 years prior to study entry.

2) ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.

RES RRMS was not prespecified as a distinct subgroup in OPTIMUM; however, post hoc analysis revealed that [redacted] of patients from the overall ITT population or [redacted] of patients in the highly active disease subgroup meet the NICE criteria for RES RRMS.

The results of post-hoc analyses for patients with RES RRMS (as defined by NICE) for the key efficacy outcomes showed a numerical benefit for the ponesimod group vs teriflunomide group, which is consistent with the results for the prespecified ITT population and the highly active subgroup (Table 5). As expected, the confidence intervals grow wider as the subgroup size decreases, particularly since the original trial was powered only to detect differences in the overall ITT population, and the RES subgroup are a subset of the highly active patient group.

In all three populations, ponesimod demonstrated a favourable effect over teriflunomide, and a numerical benefit in relapse reduction was apparent even in patients with high disease activity. The hazard ratios for the two CDA outcomes showed a benefit in the populations with higher disease activity, indicating the effectiveness of ponesimod at managing long-term disability. As these analyses were conducted post-hoc, the results should be interpreted with caution. Given the limitations encountered when conducting the NMAs for the highly active subgroup, additional NMAs comparing RES subgroups across trials were deemed inappropriate due to greater lack of comparative data for this subgroup. In the recent appraisal for ofatumumab, the committee agreed that the RES

RRMS subgroup should not be considered separately and would be evaluated as part of the whole RRMS population.

Table 5 Post hoc analysis of OPTIMUM trial (RES RRMS subgroup)

	ITT population (prespecified)		HA subgroup (prespecified)		RES subgroup (post-hoc)	
	PON	**TER**	**PON**	**TER**	**PON**	**TER**
Annualised relapse rate up to EOS						
N	567	566	202	200	34	40
Mean rate (99% CL)	0.202 (0.165, 0.246)	0.290 (0.244, 0.345)	0.310 (0.234, 0.411)	0.401 (0.310, 0.518)	0.467 (0.259, 0.841)	0.491 (0.285, 0.845)
RR (99% CL)	0.695 (0.536, 0.902)		0.774 (0.529, 1.132)		0.950 (0.427, 2.116)	
Time to 3-month CDA up to EOS						
N	57	70	22	31	3	5
HR	0.83 (0.58, 1.18)		0.72 (0.41, 1.24)		0.69 (0.17, 2.91)	
Time to 6-month CDA up to EOS						
Number of events	46	56	19	29	3	5
HR (95% CI)	0.84 (0.57, 1.24)		0.66 (0.37, 1.17)		0.69 (0.17, 2.90)	

A4. Priority question. It is not clear where the data for the NMA were obtained in some trial publications. This is especially the case with confirmed disability accumulation (CDA) at 3 and 6 months. Please provide breakdown of the effect estimates used in each NMA, including the subgroup analyses. This may be presented as a separate table for each analysis, similar to Table 20 of the submission (Doc B), with effect estimates replacing the ticks.

Company response: Details of input data for the base case NMAs described in the company submission are presented in Table 6 to Table 9, while those for the subgroup analyses are presented in Table 10 to Table 12.

Table 6 Input Data for Main NMA of ARR

Trial Name or Identifier	Treatment	n	Mean ARR	Standard deviation	Treatment Duration (weeks)
ADVANCE(4)	placebo	500	0.397	0.87	48
ADVANCE(4)	peginterferon 125 µg 2W	512	0.256	0.65	48
AFFIRM(5)	placebo	315	0.73	1.60	120
AFFIRM(5)	natalizumab 300 mg 4W	627	0.23	0.41	120
APEX Part I(6)	placebo	113	0.65	NR	24
APEX Part I(6)	dimethyl fumarate 240 mg bid	111	0.45	NR	24
ASSESS(7)	glatiramer acetate 20 mg qd	324	0.26	0.64	48
ASSESS(7)	fingolimod 0.5 mg qd	345	0.15	0.47	48
BEYOND(8)	glatiramer acetate 20 mg qd	374	0.34	NR	110.4*
BEYOND(8)	interferon β-1b 250 µg qod	784	0.36	NR	110.4*
Boiko 2018 (GA)(9)	placebo	28	0.17857	0.39	48
Boiko 2018 (GA)(9)	glatiramer acetate 20 mg qd	61	0.09836	0.35	48
BRAVO	Placebo	450	0.34	0.64	96
BRAVO	interferon beta-1a 30 ug intramuscular qw	447	0.26	0.42	96
CAMMS223(10)	interferon β-1a 44 µg subcutaneous tiw	111	0.36	0.40	144
CAMMS223(10)	alemtuzumab 12 mg qd	112	0.11	0.22	144
CARE-MS I(11)	interferon β-1a 44 µg subcutaneous tiw	187	0.39	0.84	96
CARE-MS I(11)	alemtuzumab 12 mg qd	376	0.18	0.49	96
CARE-MS II(12)	interferon β-1a 44 µg subcutaneous tiw	202	0.52	0.91	96
CARE-MS II(12)	alemtuzumab 12 mg qd	426	0.26	0.63	96
CLARITY(13)	placebo	437	0.33	0.48	96
CLARITY(13)	cladribine 3.5 mg/kg qd	433	0.14	0.27	96
CombiRx(14)	interferon β-1a 30 µg intramuscular qw	250	0.16	0.37	144
CombiRx(14)	glatiramer acetate 20 mg qd	259	0.11	0.21	144
CONFIRM(15)	placebo	363	0.4	0.78	96
CONFIRM(15)	dimethyl fumarate 240 mg bid	359	0.22	0.48	96

Trial Name or Identifier	Treatment	n	Mean ARR	Standard deviation	Treatment Duration (weeks)
CONFIRM(15)	glatiramer acetate 20 mg qd	350	0.29	0.57	96
COPOLYMER 1 (16)	placebo	126	0.84	NR	96
COPOLYMER 1 (16)	glatiramer acetate 20 mg qd	125	0.59	NR	96
DEFINE(17)	placebo	408	0.36	0.72	96
DEFINE(17)	dimethyl fumarate 240 mg bid	410	0.17	0.36	96
Eur/Can GA(18)	placebo	120	1.21	NR	36
Eur/Can GA(18)	glatiramer acetate 20 mg qd	119	0.81	NR	36
EVIDENCE(19)	interferon β-1a 44 µg subcutaneous tiw	339	0.54	NR	48
EVIDENCE(19)	interferon β-1a 30 µg intramuscular qw	338	0.64	NR	48
FREEDOMS(20)	placebo	418	0.4	0.68	96
FREEDOMS(20)	fingolimod 0.5 mg qd	425	0.18	0.37	96
FREEDOMS II(21)	placebo	355	0.4	0.67	96
FREEDOMS II(21)	fingolimod 0.5 mg qd	358	0.21	0.39	96
GALA(22)	placebo	461	0.505	1.05	48
GALA(22)	glatiramer acetate 40 mg tiw	943	0.331	0.88	48
GATE(23)	placebo	84	0.38	1.03	36
GATE(23)	glatiramer acetate 20 mg qd (generic)†	353	0.31	1.34	36
GATE(23)	glatiramer acetate 20 mg qd (brand name)	357	0.4	1.74	36
IFNB-MS(24)	placebo	123	1.27	0.88	96
IFNB-MS(24)	interferon β-1b 250 µg qod	124	0.84	0.71	96
INCOMIN(25)	interferon β-1a 30 µg intramuscular qw	92	0.7	0.9	96
INCOMIN(25)	interferon β-1b 250 µg qod	96	0.5	0.7	96
MSCRG(26)	placebo	143	0.82	NR	104
MSCRG(26)	interferon β-1a 30 µg intramuscular qw	158	0.67	NR	104
OPERA I(27)	interferon β-1a 44 µg subcutaneous tiw	411	0.29	0.62	96
OPERA I(27)	ocrelizumab 600 mg 24W	410	0.16	0.41	96
OPERA II(27)	interferon β-1a 44 µg subcutaneous tiw	418	0.29	0.68	96
OPERA II(27)	ocrelizumab 600 mg 24W	417	0.16	0.42	96
OPTIMUM(28)	teriflunomide 14 mg qd	566	0.29	0.47	108
OPTIMUM(28)	ponesimod 20 mg qd	567	0.202	0.38	108
Ph2/EVO/Montalban(29)	Placebo	53	0.37	NR	24
Ph2/EVO/Montalban(29)	dimethyl fumarate 240 mg bid	54	0.2	NR	24
Ph2/NAT/Saida(30)	placebo	47	1.73	2.15	24
Ph2/NAT/Saida(30)	natalizumab 300 mg 4W	47	0.53	1.22	24
Ph2/OCR/Kappos(31)	placebo	54	0.636	0.96	24
Ph2/OCR/Kappos(31)	interferon β-1a 30 µg intramuscular qw	54	0.364	0.72	24
Ph2/OCR/Kappos(31)	ocrelizumab 600 mg 24W	55	0.125	0.45	24
Ph2/PON/Olsson(32)	placebo	121	0.525	1.16	24
Ph2/PON/Olsson(32)	ponesimod 20 mg qd	114	0.417	1.05	24
PRISMS(33)	placebo	187	1.49	1.50	48
PRISMS(33)	interferon β-1a 22 µg subcutaneous tiw	189	1.01	1.16	48

Trial Name or Identifier	Treatment	n	Mean ARR	Standard deviation	Treatment Duration (weeks)
PRISMS(33)	interferon β-1a 44 µg subcutaneous tiw	184	0.92	1.07	48
RADIANCE A(34)	placebo	88	0.5	2.39	24
RADIANCE A(34)	ozanimod 1 mg qd	83	0.24	1.16	24
RADIANCE B(35)	interferon β-1a 30 µg intramuscular qw	441	0.28	0.48	96
RADIANCE B(35)	ozanimod 1 mg qd	433	0.17	0.37	96
Saida 2012 Fin(36)	placebo	57	0.99	1.50	24
Saida 2012 Fin(36)	fingolimod 0.5 mg qd	57	0.5	1.12	24
SUNBEAM(37)	interferon β-1a 30 µg intramuscular qw	448	0.35	0.87	54*
SUNBEAM(37)	ozanimod 1 mg qd	447	0.18	0.59	54.4*
TEMSO(38)	placebo	363	0.54	0.73	108
TEMSO(38)	teriflunomide 14 mg qd	358	0.37	0.63	108
TENERE(39)	interferon β-1a 44 µg subcutaneous tiw	104	0.22	0.81	60.1*
TENERE(39)	teriflunomide 14 mg qd	111	0.26	0.78	64.2*
TER-MS(40)	placebo	61	0.81	1.22	36
TER-MS(40)	teriflunomide 14 mg qd	57	0.55	1.12	36
TOWER(41)	placebo	388	0.5	0.75	83*
TOWER(41)	teriflunomide 14 mg qd	370	0.32	0.54	84*
TRANSFORMS(42)	interferon β-1a 30 µg intramuscular qw	431	0.33	0.85	48
TRANSFORMS(42)	fingolimod 0.5 mg qd	429	0.16	0.48	48

*Mean or median treatment duration was used for analysis input since trial used variable follow-up.
†Generic glatiramer acetate was considered equivalent to brand name glatiramer acetate for the purposes of these analyses.

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ARR = annualized relapse rate, BID = twice daily, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

Table 7 Input Data for Main NMA of 3-month CDA

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
ADVANCE(4)	placebo	500	0.62	0.4	0.97	48
ADVANCE(4)	peginterferon 125 µg 2W	512				48
AFFIRM(5)	placebo	315	0.58	0.43	0.77	120
AFFIRM(5)	natalizumab 300 mg 4W	627				120
BRAVO(43)	placebo	450	0.74	0.51	1.09	96
BRAVO(43)	interferon β-1a 30 µg intramuscular qw	447				96
CAMMS223 + CARE-MS I + II(44)	interferon β-1a 44 µg subcutaneous tiw	500	0.66	0.49	0.87	96-144
CAMMS223 + CARE-MS I + II(44)	alemtuzumab 12 mg qd	914				96-144
CLARITY(45)	placebo	437	0.67	0.48	0.93	96
CLARITY(45)	cladribine 3.5 mg/kg qd	433				96
CONFIRM(15)	placebo	363	0.79	0.52	1.19	96
CONFIRM(15)	dimethyl fumarate 240 mg bid	359				96
CONFIRM(15)	placebo	363	0.93	0.63	1.37	96
CONFIRM(15)	glatiramer acetate 20 mg qd	350				96
DEFINE(17)	placebo	408	0.62	0.44	0.87	96

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
DEFINE(17)	dimethyl fumarate 240 mg bid	410				96
EVIDENCE(19)	interferon β-1a 44 µg subcutaneous tiw	338	0.87	0.58	1.31	48
EVIDENCE(19)	interferon β-1a 30 µg intramuscular qw	339				48
FREEDOMS(20)	placebo	418	0.7	0.52	0.96	96
FREEDOMS(20)	fingolimod 0.5 mg qd	425				96
FREEDOMS II(21)	placebo	355	0.83	0.61	1.12	96
FREEDOMS II(21)	fingolimod 0.5 mg qd	358				96
OPERA I(27)	interferon β-1a 44 µg subcutaneous tiw	411	0.57	0.37	0.9	96
OPERA I(27)	ocrelizumab 600 mg 24W	410				96
OPERA II(27)	interferon β-1a 44 µg subcutaneous tiw	418	0.63	0.42	0.92	96
OPERA II(27)	ocrelizumab 600 mg 24W	417				96
OPTIMUM(28)	teriflunomide 14 mg qd	566	0.83	0.58	1.18	108
OPTIMUM(28)	ponesimod 20 mg qd	567				108
PRISMS(46)	placebo	187	0.68*	0.48	0.98	96
PRISMS(46)	interferon β-1a 22 µg subcutaneous tiw	189				96
PRISMS(46)	placebo	187	0.62*	0.43	0.91	96
PRISMS(46)	interferon β-1a 44 µg subcutaneous tiw	184				96
RADIANCE B + SUNBEAM(35)	interferon β-1a 30 µg intramuscular qw	889	0.95	0.68	1.33	48-120
RADIANCE B + SUNBEAM(35)	ozanimod 1 mg qd	880				48-120
TEMSO(38)	placebo	363	0.7	0.51	0.97	108
TEMSO(38)	teriflunomide 14 mg qd	359				108
TOWER(41)	placebo	388	0.68	0.47	1	48-173
TOWER(41)	teriflunomide 14 mg qd	370				48-173
TRANSFORMS(42, 47)	interferon β-1a 30 µg intramuscular qw	431	0.71	0.42	1.21	48
TRANSFORMS(42, 47)	fingolimod 0.5 mg qd	429				48

*Primary publication for the PRISMS trial reported as relative risk, and this was deemed sufficiently comparable to hazard ratio for incorporation in the analysis(46)
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, BID = twice daily, CDA = confirmed disability accumulation, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

Table 8 Input Data for Main NMA of 6-month CDA

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
ADVANCE(48)	Placebo	500	0.59	0.38	0.9	48
ADVANCE(48)	Peginterferon 125 µg 2W	512				48
AFFIRM(5)	placebo	315	0.46	0.33	0.64	120
AFFIRM(5)	natalizumab 300 mg 4W	627				120
BRAVO(43)	placebo	450	0.73	0.47	1.14	96
BRAVO(43)	interferon β-1a 30 µg intramuscular qw	447				96
CAMMS223(10)	interferon β-1a 44 µg subcutaneous tiw	111	0.25	0.11	0.57	144
CAMMS223(10)	alemtuzumab 12 mg qd	112				144
CARE-MS I(11)	interferon β-1a 44 µg subcutaneous tiw	187	0.7	0.4	1.23	96
CARE-MS I(11)	alemtuzumab 12 mg qd	376				96
CARE-MS II(12)	interferon β-1a 44 µg subcutaneous tiw	202	0.58	0.38	0.87	96
CARE-MS II(12)	alemtuzumab 12 mg qd	426				96
CLARITY(45)	placebo	437	0.68	0.47	0.97	96
CLARITY(45)	cladribine 3.5 mg/kg qd	433				96
CONFIRM(15)	placebo	363	0.62	0.37	1.03	96
CONFIRM(15)	dimethyl fumarate 240 mg bid	359				96
CONFIRM(15)	placebo	363	0.87	0.55	1.38	96
CONFIRM(15)	glatiramer acetate 20 mg qd	350				96

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
DEFINE(49)	placebo	408	0.77	0.52	1.14	96
DEFINE(49)	dimethyl fumarate 240 mg bid	410				96
EVIDENCE(19)	interferon β-1a 30 µg subcutaneous tiw	338	0.7	0.39	1.25	48
EVIDENCE(19)	interferon β-1a 44 µg intramuscular qw	339				48
FREEDOMS(20)	placebo	418	0.63	0.44	0.9	96
FREEDOMS(20)	fingolimod 0.5 mg qd	425				96
FREEDOMS II(21)	placebo	355	0.72	0.48	1.07	96
FREEDOMS II(21)	fingolimod 0.5 mg qd	358				96
OPERA I(27)	interferon β-1a 44 µg subcutaneous tiw	411	0.57	0.34	0.95	96
OPERA I(27)	ocrelizumab 600 mg 24W	410				96
OPERA II(27)	interferon β-1a 44 µg subcutaneous tiw	418	0.63	0.4	0.98	96
OPERA II(27)	ocrelizumab 600 mg 24W	417				96
OPTIMUM(28)	teriflunomide 14 mg qd	566	0.84	0.57	1.24	108
OPTIMUM(28)	ponesimod 20 mg qd	567				108
PRISMS(50)	placebo	187	0.67	0.5	0.9	96
PRISMS(50)	interferon β-1a 44 µg subcutaneous tiw	184				96
RADIANCE B + SUNBEAM(35)	interferon β-1a 30 µg intramuscular qw	889	1.41	0.92	2.17	48-120
RADIANCE B + SUNBEAM(35)	ozanimod 1 mg qd	880				48-120
TEMSO(51)	placebo	363	0.749	0.505	1.111	108
TEMSO(51)	teriflunomide 14 mg qd	358				108
TOWER(51)	placebo	388	0.843	0.533	1.334	48-173
TOWER(51)	teriflunomide 14 mg qd	370				48-173

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, CDA = confirmed disability accumulation, BID = twice daily, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

Table 9 Input Data for Main NMA of Treatment Discontinuations

Trial Name or Identifier	Treatment	N*	Events**	Treatment Duration (weeks)
ADVANCE(4)	placebo	500	44	48
ADVANCE(4)	peginterferon 125 µg 2W	512	75	48
AFFIRM(5)	placebo	312	46	120
AFFIRM(5)	natalizumab 300 mg 4W	627	76	120
APEX Part I(6)	placebo	113	11	24
APEX Part I(6)	dimethyl fumarate 240 mg bid	111	12	24
ASSESS(7)	glatiramer acetate 20 mg qd	342	115	48
ASSESS(7)	fingolimod 0.5 mg qd	352	68	48
BEYOND(8)	glatiramer acetate 20 mg qd	445	71	96-168
BEYOND(8)	interferon β-1b 250 µg qod	888	104	96-168
Boiko 2018 (GA)(9)	placebo	31	4	48
Boiko 2018 (GA)(9)	glatiramer acetate 20 mg qd	63	8	48
BRAVO(43)	placebo	450	91	96
BRAVO(43)	interferon β-1a 30 µg intramuscular qw	447	69	96
CAMMS223(10)	interferon β-1a 44 µg subcutaneous tiw	107	41	144
CAMMS223(10)	alemtuzumab 12 mg qd	108	14	144
CARE-MS I(11)	interferon β-1a 44 µg subcutaneous tiw	187	23	96
CARE-MS I(11)	alemtuzumab 12 mg qd	376	14	96
CARE-MS II(12)	interferon β-1a 44 µg subcutaneous tiw	202	44	96
CARE-MS II(12)	alemtuzumab 12 mg qd	426	27	96
CLARITY(13)	placebo	437	57	96
CLARITY(13)	cladribine 3.5 mg/kg qd	433	35	96
CombiRx(14)	interferon β-1a 30 µg intramuscular qw	250	56	144
CombiRx(14)	glatiramer acetate 20 mg qd	259	36	144
CONFIRM(15)	placebo	363	129	96
CONFIRM(15)	dimethyl fumarate 240 mg bid	359	106	96

Trial Name or Identifier	Treatment	N*	Events**	Treatment Duration (weeks)
CONFIRM(15)	glatiramer acetate 20 mg qd	350	87	96
COPOLYMER 1(16)	placebo	126	17	96
COPOLYMER 1(16)	glatiramer acetate 20 mg qd	125	19	96
DEFINE(17)	placebo	408	144	96
DEFINE(17)	dimethyl fumarate 240 mg bid	410	129	96
Eur/Can GA(18)	placebo	120	7	36
Eur/Can GA(18)	glatiramer acetate 20 mg qd	119	7	36
EVIDENCE(19)	interferon β-1a 44 µg subcutaneous tiw	339	25	48
EVIDENCE(19)	interferon β-1a 30 µg intramuscular qw	338	21	48
FREEDOMS(20)	placebo	418	201	96
FREEDOMS(20)	fingolimod 0.5 mg qd	425	136	96
FREEDOMS II(21)	placebo	355	223	96
FREEDOMS II(21)	fingolimod 0.5 mg qd	358	202	96
GALA(22)	placebo	461	31	48
GALA(22)	glatiramer acetate 40 mg tiw	943	84	48
GATE(23)	placebo	84	3	36
GATE(23)	glatiramer acetate 20 mg qd (generic)†	353	29	36
GATE(23)	glatiramer acetate 20 mg qd (brand name)	357	33	36
GLACIER(52)	glatiramer acetate 20 mg qd	101	3	16
GLACIER(52)	glatiramer acetate 40 mg tiw	108	7	16
IMPROVE(53)	Placebo	60	3	16
IMPROVE(53)	interferon β-1a 44 µg subcutaneous tiw	120	8	16
INCOMIN(25)	interferon β-1a 30 µg intramuscular qw	92	19	96
INCOMIN(25)	interferon β-1b 250 µg qod	96	11	96
Mokhber 2015(54)	interferon β-1b 250 µg qod	23	4	48
Mokhber 2015(54)	interferon β-1a 30 µg intramuscular qw	23	3	48
Mokhber 2015(54)	interferon β-1a 44 µg subcutaneous tiw	23	2	48
OPERA I(27)	interferon β-1a 44 µg subcutaneous tiw	409	69	96
OPERA I(27)	ocrelizumab 600 mg 24W	408	42	96
OPERA II(27)	interferon β-1a 44 µg subcutaneous tiw	417	97	96
OPERA II(27)	ocrelizumab 600 mg 24W	417	57	96
OPTIMUM(28)	teriflunomide 14 mg qd	566	93	108
OPTIMUM(28)	ponesimod 20 mg qd	565	94	108
Ph2/EVO/Montalban(29)	Placebo	54	5	24
Ph2/EVO/Montalban(29)	dimethyl fumarate 240 mg bid	54	2	24
Ph2/NAT/Saida(30)	placebo	47	4	24
Ph2/NAT/Saida(30)	natalizumab 300 mg 4W	47	1	24
Ph2/OCR/Kappos(31)	placebo	54	0	24
Ph2/OCR/Kappos(31)	interferon β-1a 30 µg intramuscular qw	54	3	24
Ph2/OCR/Kappos(31)	ocrelizumab 600 mg 24W	55	4	24
Ph2/PON/Olsson(32)	placebo	121	11	24
Ph2/PON/Olsson(32)	ponesimod 20 mg qd	114	15	24
PRISMS(46)	placebo	187	17	96
PRISMS(46)	interferon β-1a 22 µg subcutaneous tiw	189	22	96
PRISMS(46)	interferon β-1a 44 µg subcutaneous tiw	184	19	96
RADIANCE A(34)	placebo	88	3	24
RADIANCE A(34)	ozanimod 1 mg qd	83	1	24
RADIANCE B(35)	interferon β-1a 30 µg intramuscular qw	441	65	96
RADIANCE B(35)	ozanimod 1 mg qd	433	45	96
REFORMS(55)	interferon β-1a 44 µg subcutaneous tiw	65	9	12
REFORMS(55)	interferon β-1b 250 µg qod	64	1	12
Saida 2012 Fin(36)	placebo	57	6	24
Saida 2012 Fin(36)	fingolimod 0.5 mg qd	57	9	24
SUNBEAM(37)	interferon β-1a 30 µg intramuscular qw	448	36	48-120
SUNBEAM(37)	ozanimod 1 mg qd	447	29	48-120
TEMSO(38)	placebo	363	104	108
TEMSO(38)	teriflunomide 14 mg qd	358	95	108
TENERE(39)	interferon β-1a 44 µg subcutaneous tiw	101	30	48-118
TENERE(39)	teriflunomide 14 mg qd	111	22	48-118
TER-MS(40)	placebo	61	4	36
TER-MS(40)	teriflunomide 14 mg qd	57	12	36
TOWER(41)	placebo	388	125	48-173
TOWER(41)	teriflunomide 14 mg qd	370	126	48-173

Trial Name or Identifier	Treatment	N*	Events**	Treatment Duration (weeks)
TRANSFORMS(42)	interferon β-1a 30 µg intramuscular qw	431	57	48
TRANSFORMS(42)	fingolimod 0.5 mg qd	429	57	48

*Total number of patients considered all patients who received treatment. If unavailable, the total number of randomized patients was used.
**Total number of events considered discontinuations from clinical studies, as well as discontinuations of treatment (where clearly reported and mutually exclusive from study discontinuations).
†Generic glatiramer acetate was considered equivalent to brand name glatiramer acetate for the purposes of these analyses.

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, BID = twice daily, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

Table 10 Input Data for Highly Active Disease Subgroup NMA of ARR

Trial Name or Identifier	Treatment	n	Mean ARR	Standard deviation	Treatment Duration (weeks)
AFFRIM ǂ	placebo	61	1.46	NR	96
AFFRIM ǂ	natalizumab 300 mg 4W	148	0.28	NR	96
CARE-MS II	interferon β-1a 44 µg subcutaneous tiw	69	0.68	0.70	96
CARE-MS II	alemtuzumab 12 mg qd	131	0.22	0.38	96
CLARITY	placebo	149	0.47	0.31	96
CLARITY	cladribine 3.5 mg/kg qd	140	0.16	0.33	96
FREEDOMS I and II	placebo	257	0.46	0.65	96
FREEDOMS I and II	fingolimod 0.5 mg qd	249	0.24	0.44	96
OPERA I + II	interferon β-1a 44 µg subcutaneous tiw	140	0.313	NR	96
OPERA I + II	ocrelizumab 600 mg 24W	143	0.099	NR	96
OPTIMUM	teriflunomide 14 mg qd	200	0.41	0.75	108
OPTIMUM	ponesimod 20 mg qd	202	0.31	0.64	108
PRISMS **	placebo	187	1.49	0.73	48
PRISMS **	interferon β-1a 44 µg subcutaneous tiw	184	0.92	0.63	48
TEMSO **	placebo	363	0.54	0.75	108
TEMSO **	teriflunomide 14 mg qd	358	0.37	0.54	108
TOWER **	placebo	388	0.5	0.75	83*
TOWER **	teriflunomide 14 mg qd	370	0.32	0.64	84*
TRANSFORMS	interferon β-1a 30 µg intramuscular qw	192	0.506	NR	48
TRANSFORMS	fingolimod 0.5 mg qd	187	0.249	NR	48

*Mean or median treatment duration was used for analysis input, since trial used variable follow-up.
** Data from PRISMS/TEMSO/TOWER trials for highly active disease population was unavailable; data for the ITT population was utilized.
ǂ AFFIRM was only incorporated within sensitivity analyses.
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ARR = annualized relapse rate, BID = twice daily, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

Table 11 Input Data for Highly Active Disease Subgroup NMA of 3-month CDA

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
AFFIRM ǂ	placebo	61	0.47	0.24	0.93	96
AFFIRM ǂ	natalizumab 300 mg 4W	148				96
CLARITY	placebo	149	0.28	0.15	0.54	96
CLARITY	cladribine 3.5 mg/kg qd	140				96
FREEDOMS I & II	placebo	257	0.5*	0.34	0.9	96

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
FREEDOMS I & II	fingolimod 0.5 mg qd	249				96
OPERA I & II	interferon β-1a 44 µg subcutaneous tiw	140	0.47	0.23	0.95	96
OPERA I & II	ocrelizumab 600 mg 24W	143				96
OPTIMUM	teriflunomide 14 mg qd	200	0.72	0.41	1.24	108
OPTIMUM	ponesimod 20 mg qd	202				108
PRISMS**	placebo	187	0.62	0.43	0.91	96
PRISMS**	interferon β-1a 44 µg subcutaneous tiw	184				96
TEMSO ǂ ǂ	placebo	363	0.7	0.51	0.97	108
TEMSO ǂ ǂ	teriflunomide 14 mg qd	359				108
TOWER ǂ ǂ	placebo	388	0.68	0.47	1	48-173
TOWER ǂ ǂ	teriflunomide 14 mg qd	370				48-173
TEMSO and TOWER	placebo	NR	0.535	NR	NR	Varied
TEMSO and TOWER	teriflunomide 14 mg qd	NR				Varied
TRANSFORMS	interferon β-1a 30 µg intramuscular qw	149	LogHR = -0.5	0.26	1.41	48
TRANSFORMS	fingolimod 0.5 mg qd	160				48

* 6-month CDA outcome data for highly active patients was leveraged, since 3-month CDA outcome data for highly active patients was not available in the form of a hazard ratio.
**Data from PRISMS trials for highly active disease population was unavailable; data for the ITT population was utilized.
ǂ AFFIRM was only incorporated within sensitivity analyses.
ǂ ǂ Outcome data pertaining to the ITT population of TEMSO and TOWER was incorporated within a sensitivity analysis.
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, BID = twice daily, CDA = confirmed disability accumulation, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

Table 12 Input Data for Highly Active Disease Subgroup NMA of 6-month CDA

Trial Name or Identifier	Treatment	n	Hazard ratio	95% confidence interval		Treatment Duration (weeks)
				Lower	Upper	
AFFIRM ǂ	placebo	61	0.36	0.17	0.76	96
AFFIRM ǂ	natalizumab 300 mg 4W	148				96
CARE-MS II	interferon β-1a 44 µg subcutaneous tiw	69	0.41	0.19	0.85	96
CARE-MS II	alemtuzumab 12 mg qd	131				96
CLARITY	placebo	149	0.18	0.07	0.43	96
CLARITY	cladribine 3.5 mg/kg qd	140				96
FREEDOMS I & II	placebo	257	0.5	0.34	0.9	96
FREEDOMS I & II	fingolimod 0.5 mg qd	249				96
OPERA I & II	interferon β-1a 44 µg subcutaneous tiw	140	0.5	0.23	1.09	96
OPERA I & II	ocrelizumab 600 mg 24W	143				96
OPTIMUM	teriflunomide 14 mg qd	200	0.66	0.37	1.17	108
OPTIMUM	ponesimod 20 mg qd	202				108
PRISMS**	placebo	187	0.62	0.43	0.91	96
PRISMS**	interferon β-1a 44 µg subcutaneous tiw	184				96
TEMSO ǂ ǂ	placebo	363	0.749	0.505	1.111	108
TEMSO ǂ ǂ	teriflunomide 14 mg qd	358				108
TOWER ǂ ǂ	placebo	388	0.843	0.533	1.334	48-173
TOWER ǂ ǂ	teriflunomide 14 mg qd	370				48-173
TEMSO and TOWER	placebo	NR	0.598	NR	NR	Varied
TEMSO and TOWER	teriflunomide 14 mg qd	NR				Varied

** Data from PRISMS trials for highly active disease population was unavailable; data for the ITT population was utilized.
ǂ AFFIRM was only incorporated within sensitivity analyses.
ǂ ǂ Outcome data pertaining to the ITT population of TEMSO and TOWER was incorporated within a sensitivity analysis.
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, BID = twice daily, CDA = confirmed disability accumulation, qd = once daily, qod = every other day, qw = once weekly, TIW = three times per week.

A5. The eligibility criteria in many of the trials included in the NMA likely resulted in a heterogeneous mix of active, highly active, and rapidly evolving severe relapsing-remitting multiple sclerosis (RRMS), as defined within the UK. Several of these trials conducted subgroup analyses based on lesion load, number of gadolinium-enhancing (Gd+) lesions or number of relapses at baseline. Please specify the approach to including these participants in the highly active subpopulation for the NMA.

Company response: In the OPTIMUM trial, patients were considered to have highly-active disease if one or both of the following conditions were fulfilled(28):

1) Any DMT for MS received within 12 months prior to randomisation and one or both of the following:

    - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions

    - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for patients with at least one relapse within 2 years prior to study entry.

2) ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.

Broadly, the OPTIMUM definition could be considered to include patients with active RRMS as well as highly active and RES RRMS (as defined by NHS England), within parts (1) and (2) of the highly active OPTIMUM definition respectively). Please see response to question A3.

For all other trials, literature was reviewed to identify prespecified subgroups of patients with highly active disease. Datasets corresponding to pre-specified populations aligned with parts (1) and (2) or part (1) only of the OPTIMUM definition were selected for the NMAs. Datasets corresponding to populations aligned with part (2) of the OPTIMUM definition alone were not considered.

The definitions of highly active disease within the subgroup networks were as follows:

Table 13 Trials and Regimens Included in Subgroup Networks for Highly Active Disease

Trials incorporated	Regimens incorporated	Definition of highly active selected	Notes	Source
CARE-MS II	• IFNB-1a 44 SC TIW • ALE 12 QD	• Ayant eu au moins une poussée sous traitement (interféron β ou acétate de glatiramère) au cours de l'année précédente avec presence d'une ou plusieurs lésion(s) réhaussée(s) par le Gadolinium à l'inclusion.	Definition did not include RES patients. Data not available for 3-month CDA	Haute Autorité de Santé submission (alemtuzumab)(44)
CLARITY	• PBO • CLA 3.5 mg/kg QD	• Subjects with ≥1 relapse in previous year while on DMD therapy and ≥1 T1 Gd+ or ≥9 T2 lesions AND/OR • Subjects with ≥2 relapses in previous year regardless of treatment status	Definition aligned with OPTIMUM	EMA Public Assessment Report(45)
FREEDOMS I+II*	• PBO • FIN 0.5 QD	• Patients who had high disease activity despite previous DMT, according to the following criteria: (1) 1 relapse in the previous year and either 1 gadolinium (Gd) enhancing T1 lesion or 9 T2 lesions at baseline and/or (2) As many or more relapses in the year before baseline as in the previous year.	Definition did not include RES patients	Derfuss et al. 2015(56)
OPERA I+II	• IFNB-1a 44 SC TIW • OCR 600 24W	• Highly Active Inadequate Responders: treated with interferon or glatiramer acetate for at least 1 year and: – had at least one relapse in the previous year AND – had at least nine T2 hyperintense lesions or at least one T1 Gd-enhancing lesion at baseline	Definition did not include RES patients	NICE Submission (ocrelizumab)(57)
OPTIMUM	• PON 20 QD • TER 14 QD	• Any DMT for MS received within 12 months prior to randomization and one or both of the following: a) ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions b) Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for subjects with at least one relapse within 2 years prior to study entry. AND/OR • ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion	Definition combined RES and HA patients	OPTIMUM clinical study report(28)

Trials incorporated	Regimens incorporated	Definition of highly active selected	Notes	Source
PRISMS**	• PBO • IFNB-1a 44 SC TIW	• Data unavailable for ARR, 3-month CDA	ITT data used for ARR, 3-month CDA	Traboulsee et al. 2018(33) Ebers et al. 1998(46) Wong et al. 2018(50)
TEMSO & TOWER*	• PBO • TER 14 QD	• ARR: Data unavailable	ITT data used for ARR	O'Connor et al. 2011 (TEMSO)(38) and Confavreux et al. 2014 (TOWER)(41)
		• CDA: Subgroup B: Patients with disease modifying therapy use in the prior 2 years and either ≥1 relapse in the year before study entry of ≥1 Gd+ lesion on baseline MRI	Definition did not include RES patients. Relapse activity or lesion activity included.	NICE Submission (ocrelizumab)(57)
TRANSFORMS	• IFNB-1a 30 IM QW • FIN 0.5 QD	• ARR: Group 2b: patients who received any DMT during the year before study enrolment and had ≥1 relapse in the previous year plus ≥1 Gd-enhancing T1 lesion or ≥9 T2 lesions at baseline	Definition did not include RES patients	Cohen et al. 2013(58)
		• 3-month CDA: Interferon non-responder, at least 1 relapse/year and ≥9 T2 lesions or presence of Gd-enhancing lesion	Definition did not include RES patients	NICE Submission (ocrelizumab)(57)

*6-month CDA outcome data incorporated for the 3-month CDA network, given that 3-month CDA outcome data was not reported as a hazard ratio.
**ITT data incorporated as stated above, given that HA subgroup data was unavailable.
KEY: 4W: =every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, ARR = annualized relapse rate, CLA = cladribine, FIN = fingolimod, IFNB-1a = interferon beta-1a, IM = intramuscular, NAT= natalizumab, OCR = ocrelizumab, PBO = placebo, PON = ponesimod, SC = subcutaneous, TER = teriflunomide, TIW = three times per week, QD = every day.

A6. Please explain the general approach to using outcome data reported at multiple time points within the same trial.

Company response: Outcome data from only a single time point (i.e., the trial endpoint) of a given trial was used as inputs for the NMAs reported in the company submission. No trial data was used from interim or intermediate timepoints. Four of the 41 trials in the ARR network had published data for follow-up periods exceeding the core trial periods (CombiRx Extension(59), COPOLYMER 1 Extension(60), IFNB-MS long-term(61) and PRISMS-4(62)).

The most mature data, reflective of the originally assigned (randomised) treatment arm was considered in a sensitivity analysis where the long-term data replaced core trial data for the respective trials (presented in the original CS appendices Figure 16).

A7. Several trials included in the NMA reported sensitivity analyses and covariate-adjusted analyses in addition to the primary analyses of outcomes.

(a) Please explain the general approach in selecting analyses for inclusion.

(b) In the BEYOND trial [reference 171], were intention-to-treat (ITT) or per protocol results used? If ITT data were used, were primary or covariate-adjusted data included? If per protocol data were used, was analysis A or B selected?

Company response:

(a) Only the results of primary analyses (usually a primary or secondary endpoint) described in the publications were selected for inclusion in the base case NMAs. No other sensitivity analyses or covariate-adjusted analyses informed the NMAs described in the company submissions.

Data for the intention-to-treat (ITT) or modified ITT analyses were selected over per protocol analyses to ensure alignment with the OPTIMUM trial. The only exception was the BEYOND trial since our literature review only identified publications reporting per protocol analyses. For the base case NMAs of 3-month and 6-month CDA, only those trials reporting a HR were included in the network to reduce any potential uncertainty that could bias the economic analyses.

(b) Based on the results of our literature reviews, the primary publication and the trial registry records for the BEYOND trial did not report outcome data for an ITT population. In Table 2 of reference 171, the outcome of 'relapse risk' was reported for 2 distinct per-protocol populations; however, ARR was not similarly reported. Data for ARR were obtained from Table 3 of reference 171 and it is unclear from the reference if these are reported based on analysis A or B.

A8. Some trials reported outcomes of interest in multiple ways.

(a) Please explain the general approach to selecting the most appropriate outcome.

(b) In the trial by Boiko et al 2018 [reference 172], relapses were reported as exacerbations without magnetic resonance imaging (MRI) evidence and exacerbations with MRI evidence. Which was selected, and why?

(c) The CombiRx trial [reference 177] defined and reported relapses according to three sets of criteria. Which of these data sets was selected, and why?

Company response:

(a) The outcomes of ARR, 3-month CDA, 6-month CDA and treatment discontinuation were selected to inform the economic model and to align with previous appraisals in MS. For all RCTs included in the networks, the definitions of these outcomes were reviewed to ensure alignment with their definitions in the OPTIMUM trial. Outcome data for the primary analyses were selected for the base-case NMAs and subgroup data for the corresponding timepoints were selected for the highly active subgroup NMAs, where available.

(b) In the trial by Boiko et al 2018 [reference 172], number of MRI-confirmed relapses per patient per year were selected on the basis that this was the primary endpoint of the trial. Selection of these data would also ensure that the analysis captured all possible protocol-defined relapses.

(c) In the CombiRx trial [reference 177], only protocol defined exacerbations were selected for the analysis since it is the more stringent definition and only these relapses were included in the primary analysis by the study authors.

A9. The trial by Boiko et al 2018 [reference 172] included two glatiramer acetate 20 mg once daily (QD) arms. Please indicate whether data from Timexon or Copaxone-Teva were included, or whether these data were combined. If the former, please explain why the choice of intervention, if the latter, please explain the approach.

Company response: As per the PICOS for the SLR and NMAs, only treatments and doses licensed in the UK were included in the analyses. Therefore, data from the Copaxone-Teva treatment arm was included in the analysis since this formulation is approved for use in the UK. Data from the Timexon treatment arm was excluded as it is a Russian formulation and not approved for use in the UK.

A10. Please confirm whether any types of early discontinuation were excluded from the NMA (e.g., at specific timepoints, protocol violations)?

Company response: Treatment discontinuations due to any cause were used to inform the NMA; therefore, no types of early discontinuation were excluded from the analysis.

A11. There are several multi-armed trials. Please explain the general approach to selecting the most appropriate comparator arm where this was necessary (for example, in the ASSESS trial [reference 170] the higher dose of fingolimod was selected, whereas in CARE-MS II [reference 176], CLARITY [reference 8] and CONFIRM [reference 178] the lower doses of alemtuzumab, cladribine and dimethyl fumarate, respectively, were selected).

Company response: Selection of the comparator arms from all trials was based on the licensed dose of the respective treatments as per the PICOS. Therefore, the higher dose (fingolimod 0.5 mg) was selected in ASSESS, while the lower doses were selected in CARE-MS II (alemtuzumab 12 mg) Clarity (cladribine 3.5 mg/kg body weight) and CONFIRM (dimethyl fumarate 240 mg two times daily)

A12. A number of publications report data that could be used to derive combined unique active lesions (CUAL). This outcome was a secondary endpoint of OPTIMUM, but this outcome has been identified as one of the most sensitive MRI

measures of active disease. Please explain why these data were not included in an NMA.

Company response: The NMA analyses were primarily conducted to inform the economic model and to align with core analyses presented in previous MS appraisals.

Furthermore, CUAL is a composite outcome generally defined as an active lesion on the T1 Gd or T2 scan, or both, avoiding double counting. However, there is much clinical variation in defining CUAL and in many cases it may or may not be reported. Therefore, the CUAL outcomes are not consistent across studies.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question. We note that at the time of submission, ofatumumab and ozanimod were still undergoing NICE appraisal. However, NICE have asked us to consider both in our appraisal of ponesimod. Please update the model to incorporate evidence for both ofatumumab and ozanimod and provide all updated results.

As requested by the ERG, Janssen have updated the model to incorporate evidence for ongoing appraisals ofatumumab (ID 1677) and ozanimod (ID 1294). The two new DMTs have been included as comparators for active RRMS and highly active RRMS (ITT population and highly active subgroup, respectively in our model).

The updated NMAs described in response to A2 were used to inform the treatment effects in the model. Updated values for treatment effects on ARR are described in Table 14, while those for disease progression based on 3-month and 6-month CDA are presented in Table 15 (ITT population) and Table 16 (highly active subgroup). Updated inputs for annual treatment discontinuation rates are presented in Table 17.

Table 14 Treatment Effects on Annual Relapse Rates

Treatment	Rate Ratio for Relapse Rate (vs. Natural History) for the ITT Population[a]		Rate Ratio for Relapse Rate (vs. Natural History) for the Highly Active Subgroup[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on relapse rates for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

Table 15 Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the ITT Population

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]

Ozanimod	[redacted]		[redacted]		[redacted]		[redacted]	
Pegylated interferon beta-1a								
Teriflunomide								
Alemtuzumab								
Cladribine								
Fingolimod								
Natalizumab[b]								
Best supportive care[b]								

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] 6-month data assumed to be equal to 3-month data due to lack of data availability.

Table 16 Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the Highly active RRMS Subgroup

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]		[redacted]	
Dimethyl fumarate				
Glatiramer acetate				
Interferon beta-1a 22 mcg[c]				
Interferon beta-1a 30 mcg				
Interferon beta-1a 44 mcg				
Interferon beta-1b				
Ocrelizumab				
Ofatumumab				
Ozanimod				
Pegylated interferon beta-1a				
Teriflunomide				
Alemtuzumab				
Cladribine				
Fingolimod				
Natalizumab[b]				
Best supportive care[b]				

RRMS = relapsing-remitting multiple sclerosis; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] Data are assumed to be equal those for interferon beta-1a 44 mcg due to lack of data availability.

Table 17 Annual Treatment discontinuation Rates

Treatment	Odds Ratio: Ponesimod vs. Treatment[a]		Annual Discontinuation Rate[b]
	Value	Range	
Ponesimod	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Natalizumab[e]	[redacted]	[redacted]	[redacted]
Best supportive care[e]	[redacted]	[redacted]	[redacted]

NA = not applicable; NMA = network meta-analysis; OWSA = one-way sensitivity analysis.

[a] Odds ratios for ponesimod versus treatment for annual risk of discontinuation for all treatments except best supportive care and ponesimod were varied in the OWSA and in the probabilistic sensitivity analysis (the latter utilizing a lognormal distribution); ranges were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in NMA.

[b] Annual discontinuation rates for all treatments were calculated from the annual discontinuation rate of ponesimod times a relative risk of discontinuation for each treatment versus ponesimod, where the relative risk was calculated from the odds ratios.

[c] Annual discontinuation rate of ponesimod was varied in the OWSA and in the probabilistic sensitivity analysis (the latter using a beta distribution); the range was set to the bounds of the 95% confidence interval from the sampled distribution; that confidence interval was estimated assuming a sample size of 580, the sum of the clinical trial population sizes used for estimating the discontinuation rate of ponesimod in the NMA.

[d] For alemtuzumab and cladribine, this rate is applied only in years 1 to 5. They are both taken for two years and assumed to have no all-cause discontinuation after year 5.

[e] Considered in the model only as a post-discontinuation treatment.

Annual treatment costs for ozanimod and ofatumumab in the updated model are presented in Table 18. The annual administration and monitoring costs for ponesimod, fingolimod were also updated (see also company response to B5)

Table 18 Annual Treatment Costs

Treatment	Acquisition		Administration		Monitoring	
	Year 1	Years 2+	Year 1	Years 2+	Year 1	Years 2+
Ponesimod	[redacted]	[redacted]	£139.00	£0.00	£290.20	£228.82
Fingolimod	£19,175.63	£19,175.63	£628.00	£0.00	£547.65	£228.82
Ozanimod	£17,910.29	£17,910.29	£139.00	£0.00	£290.20	£231.02
Ofatumumab	£22,387.50	£17,910.00	£165.00	£0.00	£408.62	£229.41

A summary of the analysis results comparing ponesimod with other treatments is shown in Table 19 and Table 20.

Results of the base-case incremental cost-effectiveness analysis for the ITT population

The addition of ozanimod and ofatumumab in the base-case analysis aligned to the original company submission: treatment with ponesimod resulted in [redacted] on ponesimod versus [redacted] and [redacted] years on [redacted], respectively). Treatment related costs for ponesimod were [redacted], however ponesimod had [redacted] than both [redacted]. Ponesimod resulted in [redacted] disease management costs and relapse costs during RRMS and SPMS, comparing to [redacted] Compared to [redacted], ponesimod had [redacted] disease management costs than [redacted].

Base case results indicate that ponesimod [redacted] in the updated analysis. However,

ponesimod was [redacted], in line with the original submission. The ICERs for ponesimod versus [redacted] the cost-effectiveness threshold that is accepted by NICE ([redacted] and [redacted], respectively). Compared [redacted], ponesimod had [redacted] however with [redacted], resulting in ponesimod [redacted]. In addition, these results were similar when ponesimod was compared to [redacted]. Consequently, in a proportion of eligible patients with active RRMS, ponesimod offers a cost-effective use of resources. Moreover, patients receiving ponesimod spent [redacted] in the RRMS state and [redacted] as patients receiving other treatments except for [redacted] (i.e., [redacted] with ponesimod, versus a range of [redacted] years with other comparators; [redacted]).

Table 19 Updated CEM results for the ITT population

	PON	TER	DMF	GA	IFNB -1a 22 mg	IFNB-1a 30 mg	IFNB-1a 44 mg	IFNB-1b	OCR	OFA	OZA	PEG
Economic outcomes												
Total costs												
Treatment-related												
Disease management												
Relapse												
Incremental costs, ponesimod vs. comparator												
Health outcomes												
QALYs												
Patients												
Caregivers[a]												
Incremental QALYs, ponesimod vs. comparator												
Life-years												
Time on treatment												
Number of relapses												

Cost-effectiveness													
ICER, ponesimod vs. comparator (£ per QALY)	[redacted]												

CEM = cost-effectiveness model; DMF = dimethyl fumarate; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; ITT = intent-to-treat; NA = not applicable; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PEG = peginterferon beta 1a; PON=ponesimod; QALY = quality-adjusted life-year; TER = teriflunomide

[a] Number of relapses outcomes are undiscounted.

Results of the base-case incremental cost-effectiveness analysis for the highly active population

In patients with highly active RRMS, ponesimod was [redacted] currently recommended for RRMS in the UK. Compared with [redacted], ponesimod was [redacted]. Ponesimod was [redacted] and associated with [redacted] total direct costs. Compared to [redacted]

Treatment with ponesimod resulted in [redacted] treatment-related costs than [redacted], including the [redacted]. However,

ponesimod was associated with [redacted] disease management costs [redacted] and relapse costs resulted in [redacted] total direct costs than [redacted], but lower than the other comparators.

Ponesimod was associated with incremental QALYs of [redacted] compared to ocrelizumab, alemtuzumab, cladribine and ofatumumab and an incremental gain in QALYs of [redacted] and [redacted] compared to [redacted] respectively. Furthermore, ponesimod led to [redacted] compared to ocrelizumab, alemtuzumab, fingolimod, ofatumumab and ozanimod respectively, and [redacted] compared to cladribine. Similar to the results of the ITT population, ponesimod is in [redacted] of the cost-effectiveness plane compared to [redacted] in a small proportion of eligible patients.

Overall, ponesimod offers an alternative to patients eligible for fingolimod, and would offer an alternative to ozanimod (if approved in this population) with its similar mode of action and comparatively higher efficacy. Ponesimod is also a [redacted] for patients who do not wish to experience the inconvenience of intravenous infusion or injection [redacted], who are eligible for a less

aggressive treatment, and who prefer a DMT with a lower side effect profile and lower burden of monitoring.

Table 20 Updated CEM results for the highly active subgroup

	PON	OCR	OFA	OZA	ALE	CLA	FIN
Economic outcomes							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness							
ICER, ponesimod vs. comparator (£ per QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ALE = alemtuzumab; CEM = cost-effectiveness model; CLA = cladribine; FIN = fingolimod; ICER = incremental cost-effectiveness ratio; NA = not applicable; PON = ponesimod; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

[a] Number of relapses outcomes are undiscounted.

B2. Please justify why the CDA 3 month was used to estimate transition probabilities in the base case analysis (and not the CDA 6 month).

Company response: The evidence network for the 3-month CDA informing the base case of the model was more robust with a larger number of closed loops than the 6-month CDA network. Additionally, a greater proportion of trials in the 3-month CDA network defined the outcome as either a primary or secondary endpoint, whereas 6-month CDA was more frequently defined as a secondary or exploratory endpoint across the identified trials.

Based on these results, we considered transition probabilities to be more reliable when based on 3-month CDA as compared to 6-month CDA data and selected this outcome for the base-case analyses. Overall, the results based on 3-month CDA are largely consistent with those based on 6-month CDA with regards to cost effectiveness of ponesimod vs approved first-line and second-line oral and injectable treatments, with the exception of peginterferon beta 1a and interferon beta 1b.

Janssen would like to note that in our model, treatment effects due to peginterferon are based on the ADVANCE trial, which is the only study that informs the CDA networks. Janssen has included this trial based on its eligibility criteria for the SLR and NMA; however, this trial has been excluded from NMAs in previous appraisals as the ERG and committee agreed it produced clinically implausible results, in particular, for 6-month CDA. The ADVANCE trial overestimates the effectiveness of peginterferon versus other interferons, with the clinical experts noting that the results from ADVANCE were clinically implausible. In previous appraisals for ocrelizumab and ofatumumab, the committee acknowledged these limitations when evaluating the results of the cost effectiveness analysis based on 6-month CDA data.

Interferon beta-1b was excluded from the NMAs for 3-month and 6-month CDA due to the lack of reported hazard ratios for these outcomes. While previous appraisals have attempted to address missing data by estimating or extrapolating from published patient proportions, these methods would have increased the uncertainty of an already weak network due to the number of connections that would be based on calculated rather

than reported evidence. Janssen opted to decrease the uncertainty of our economic analyses by ensuring that the model inputs from the NMAs were robust for as many comparators as possible, without excluding any comparators from the analysis. The comparison versus interferon beta-1b is therefore based on a naïve comparison sourced from published data. Any comparisons with peginterferon and interferon beta 1b should be interpreted with extreme caution.

B3. For key efficacy outcomes including annualised relapse rate (ARR) and CDA 3 month, the economic model uses efficacy data vs natural history for each treatment. Please explain why the relative treatment effect from the NMA i.e., ponesimod vs each comparator was not used in the economic model for these outcomes.

Company response: Progression of patients through the model is based on rates derived from the natural history of the disease. Treatment effects of different DMTs are therefore relative to best supportive care and it is appropriate to compare all treatments anchored on placebo. The relative treatment effect is indeed derived from the NMAs described in the CS Section B.2.9; the model inputs for ARR and CDA are equivalent to the rate ratios (or hazard ratios) for DMT vs placebo, and not ponesimod vs DMT. We do not expect to see different outcomes if the model was designed to use relative treatment effect for ponesimod vs comparator DMT, since these are all derived from the same NMAs.

B4. Siponimod has been recommended by NICE for the treatment of patients with secondary progressive multiple sclerosis (SPMS). Please outline why siponimod was not included in the economic model as a treatment option for these patients.

Company response: As noted, the anticipated population of patients for MS is within the RRMS only, since only 2.6% of patients in the OPTIMUM trial had SPMS. At the time of submission, two treatments (interferon beta 1b and siponimod) were recommended by NICE for the treatment of patients with SPMS. However, the decision problem addressed in the company submission is focused on patients with RRMS, specifically active and highly active.

Similar to RRMS, in SPMS there is no data available on the sequence in which Siponimod and interferon beta 1b can be used. There is also limited or no data available on the effectiveness of the two SPMS treatments after a given RRMS treatment in the first line (model ITT population) or second line (model highly active population).

Janssen believes that inclusion of an SPMS treatment in the economic model would confound the costs and may not allow a fair or accurate comparison of the total costs across different DMTs. Furthermore, in clinical practice it is highly unlikely that patients would move from an S1P treatment (i.e., ponesimod or fingolimod) to an S1P treatment i.e., Siponimod. As a result, the model structure was simplified with all patients progressing to best supportive care upon conversion to SPMS in line with the most recent NHS treatment guidelines (NHS 2019). This is also in line with previous appraisals in RRMS, where patients generally discontinue DMTs upon conversion to SPMS.

B5. Please explain why ponesimod was assumed to require 30% of fingolimod monitoring costs in year 1.

Please justify the assumption of no monitoring from year 2 onwards.

Company response: The monitoring costs for ponesimod were assumed to be 30% of the monitoring costs of fingolimod in year 1 only, based on (a) 30% of patients requiring first-dose observation, which was based on a proportion of OPTIMUM patients assessed as "being at risk for symptomatic bradycardia (i.e., HR [hazard ratio] < 55 bpm, first or second degree AV [atrioventricular] block or cardiac disorders in medical history)" and then inflated, since certain cardiovascular conditions were excluded from the trial; (b) per-patient costs of first-dose monitoring for ponesimod, which were assumed to be equal to the per-patient first-dose monitoring costs of fingolimod

The model has now been updated to apply monitoring costs in year 1 and year 2+ in line with the most recent SmPC for ponesimod. The updated model has been submitted alongside the responses to the clarification questions. Janssen would like to note that

these updates in monitoring costs have a minimal impact on the overall results presented originally.

Section C: Textual clarification and additional points

C1. Reference 24 (from the appendices document) 'Janssen Pharmaceutical Co. OPTIMUM Clinical Study Report 2019' is not provided. Does reference 6 (from the submission document) supersede this document, as the final 2020 clinical study report (CSR)? Could the 2019 CSR be provided in the interest of having a complete set?

Company response: Apologies, this is an error in referencing that was missed at the time of submission. Reference 24 in the appendices was erroneously annotated and is identical to Reference 6 in the main submission. A corrected version of the appendices has been submitted alongside the responses to the clarification questions.

C2. Please can you provide an EndNote library (or a compatible file) for the references in your submission?

Company response: A Research Information System (RIS) library for the company submission has been submitted alongside the responses to the clarification questions.

C3. The Section numbers in Table 58 (p144) appear to be incorrect, please provide an amended table with corrected Section numbers.

Company response: We apologise for these errors. Please see below for an updated Table 58, with the corrected table section numbers.

Table 21 Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Population characteristics			
Age	36.7 years	Scenario analysis	B.3.3.1
Gender (female)	64.02%		B.3.3.1
Baseline EDSS distribution	OPTIMUM trial		B.3.3.1
Model structure			
Time horizon	50 years	Fixed	B.3.2.2.2
Cycle length	1 year	Fixed	B.3.2.2.1

Discount rates for costs and outcomes	3.5% for costs and health outcomes	Scenario analysis	B.3.2.2.3
Half cycle correction	Yes	Fixed	B.3.2.2.1
Transition probabilities			
Baseline Relapse Rates for RRMS and SPMS	Values based on Patzold et al. (Table 37)	Lognormal	B.3.3.2.3
Baseline EDSS transitions for RRMS	Values based on British Columbia dataset (Table 32)	Dirichlet; Scenario analysis	B.3.3.2.1
Baseline conversion to SPMS	Values based Mauskopf et al. (Table 36)	Beta	B.3.3.2.2
Baseline EDSS Transitions for SPMS	Values based on London Ontario dataset (Table 35)	Dirichlet	B.3.3.2.1
Relative mortality risk	Values based on Pokorski et al. 1997; with linear interpolation (Table 46)	Lognormal; Scenario analysis	B.3.3.6
Treatment effect			
Relapse rate (relative risk vs natural history)	Values based on Janssen's NMA (Table 38)	Lognormal	B.3.3.3.1
Disability progression (hazard ratio vs natural history)	Values based on Janssen's NMA (Table 39 for ITT) (Table 40 for highly active)	Lognormal; Scenario analysis	B.3.3.3.1
Annual discontinuation risk for ponesimod	OPTIMUM trial; Ponesimod phase 2 trial	Beta; Scenario analysis	B.3.3.3.3
Annual discontinuation risk for comparators (relative risk vs ponesimod)	Values based on Janssen's NMA (Table 41)	Lognormal; Scenario analysis	B.3.3.3.3
Utilities			
Utility values and relapse utility decrements by EDSS score	Values based on by Orme et al. 2007 (Table 49)	Normal	B.3.4.4
Utility decrements due to AEs	Values based on previous NICE appraisals and publications (Table 50)	Beta	B.3.4.4.1
Caregiver disutility	Caregiver disutility included based on Acaster et al (Table 51)	Normal; Scenario analysis	B.3.4.4.2
Adverse events			
Annual incidence of AEs	Based on a SLR conducted by Janssen (Table 42, 43, 44, 45)	Beta	B.3.3.5
Costs			
Direct treatment costs	Table 54	Fixed	B.3.5.1

Direct management costs by EDSS	Values based on previous NICE appraisals and publications (Table 55)	Gamma	B.3.5.2
Direct relapse cost	Values based on previous NICE appraisals and publications (Table 55)	Gamma	B.3.5.2
AE costs	Values based on previous NICE appraisals and publications (Table 56)	Gamma	B.3.5.3

ARR = annualised relapse rate; CDA = confirmed disability progression; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NHS = National Health Service; IFN = interferon; QALY = quality-adjusted life year; RRMS = relapsing-remitting multiple sclerosis, SLR = systematic literature review; SPMS = secondary progressive multiple sclerosis; UK = United Kingdom; WTP = willingness-to-pay.

C4. To ensure that the appraisal process is as transparent as possible, NICE considers it essential that evidence on which the Appraisal Committee's decisions are based is publicly available. Please reconsider the information labelled as confidential in the CS.

Company response:

Revised drafts of the submission documents with updated confidential markings have been submitted alongside the responses to the clarification questions

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

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

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

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Society is the UK's largest MS charity, with 26,000 members across the UK, 5,500 volunteers, over 260 local groups supporting people with MS, and over 300 employees. Our ultimate goal is to find a cure. Until then, we're working to make sure no one has to face MS alone. We are a registered charity, with the vast majority of our income coming from individual and philanthropic donations and legacies.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have knowledge of the views and needs of people with MS gained from years of working alongside them and their carers, and from collecting evidence about their experiences. For this submission, we drew in particular on our 2019 My MS My Needs survey (1) of the experiences of people with MS in the UK, on our 2019 Friends and Family survey (2) of people supporting those with MS in the UK, and on the results of an MS Society funded project that aimed to understand treatment decisions from the perspective of people with relapsing remitting MS (3). 1. https://www.mssociety.org.uk/sites/default/files/2020-08/MMMN3-UK-report.pdf 2. https://www.mssociety.org.uk/sites/default/files/2020-08/MS-family-and-friends-2019-survey-findings.pdf 3. Understanding treatment decisions from the perspective of people with relapsing remitting multiple Sclerosis: A critical interpretive synthesis - Multiple Sclerosis and Related Disorders (msard-journal.com)
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?	More than 130,000 people in the UK live with MS, and nearly 7,000 people are newly diagnosed each year. This means around 1 in every 500 people in the UK has MS, and that each week over 130 people are diagnosed with MS. MS is the most common disabling neurological condition of young adults, and one of the most common in adults of working age. In the UK people are mostly commonly diagnosed in their thirties, forties and fifties, although the first signs of MS often start years earlier. MS affects two to three times as many women as men. MS can be relentless, painful and exhausting. It can make it harder to do everyday things like walk, talk, eat and think. Symptoms can fluctuate, making life unpredictable. They can include loss of balance, stiffness, spasms, speech problems, fatigue, pain, bladder and bowel, and vision problems.

	Living with a chronic, disabling and degenerative condition such as MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week (4). Around 85% of people with multiple sclerosis are first diagnosed with relapsing remitting MS, enduring attacks of new and old symptoms. A relapse is defined as an episode of neurological symptoms which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. Symptoms may last from weeks to months. Relapses can vary from mild to severe. Some acute relapses may require hospital treatment, whilst many relapses are managed at home with the support of healthcare professionals. People with MS can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. Around half of all relapses can leave a range of residual problems. Evidence has highlighted that disability also progresses regardless of whether a person experiences relapses regularly (5). These are further important reasons to reduce the frequency and severity of relapses through ensuring that those who are eligible find the best treatment for them as soon as possible. Relapses can have a resonating emotional impact on a person. The loss of independence that can often come with a relapse mean that people can often feel a burden on their family. Relapses are often unpredictable and distressing, leaving people feeling frustrated, anxious and causing disruption to everyday life. The majority of people with MS experience a progression of disability over the course of the condition. It is estimated that approximately 65% of people with relapsing MS will eventually go on to develop secondary progressive MS 15 years after being diagnosed. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely normal life. As each person's response to DMTs is different the more effective options available on the NHS will result in more people finding a treatment which best suits them. Impact on Carers The progressive, fluctuating nature of MS presents particular challenges to families and carers. It can make balancing work, education and taking care of one's own health and wellbeing difficult. Our 2019 My MS My Needs survey found 32% of people living with MS hadn't received the care and support they needed to assist with daily living in the prior year (1).

	Of those, 40% relied on unpaid care from family members and friends to some extent. The care and support people required ranged from help to complete essential day to day tasks – such as washing and dressing, preparing meals, and administering medications – often alongside support to leave the house, socialise and 'mop and shop' tasks. Of those with unmet care needs, many had also experienced deteriorating health (58%) or felt lonely/isolated (65%) over the same time period. A significant minority (21%) had been unable to work. The survey found that the complexity of these needs increases with age, as the disease progresses. Treatments that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too. Our 2019 Friends and family survey (2) found 41% of respondents spent the equivalent of a full-time job or more each week supporting someone with MS. An overwhelming 90% of respondents reported negative impacts on their health and wellbeing, which is even more concerning considering that 40% of respondents were living with a long-term condition themselves. The fluctuating and progressive nature of MS adds a degree of complexity to their lives, as they may not know from one week to the next what support that person with MS will need. That can make juggling paid work and caring very difficult, which 60% of working-age respondents are doing. 4. Extra Costs Commission, Driving down the costs disabled people face : Final report, June 2015, pp. 13 5. Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Our 2019 "My MS My Needs" survey showed that people with MS report a variation in the standard of care they receive (1). There is a marked variation around the UK in the proportion of people with MS on a DMT, of those suitable to receive one. Whilst 81% of those eligible to receive a DMT in Northern Ireland are taking one, this is true for just 52% of those in Wales.

	The survey also showed a striking variation in ability to access healthcare professionals. 89% of people with MS had both needed to, and been able to, access an MS nurse withing the last year. However, this varies across the nations of the UK by 18 percentage points, from 75-93%. The survey showed that people with progressive forms of MS were less likely to be able to access MS nurses and neurologists when they needed to than people with relapsing forms of MS (40% of those with progressive MS vs 65% of those with relapsing MS). The survey showed that only 16% of people with MS had a care plan, whilst 23% would like one but do not have one at present. Whilst 55% said the professionals involved in their care worked well together completely or to some extent, 16 % said they didn't work well together at all. The survey showed that, across the UK, 60% of those who could benefit from a DMT are currently taking one. This is an improvement from the previous My MS My Needs survey of 2016, when the figure was 56%. There was a clear link between access to healthcare professionals and DMT use; amongst those who could benefit from a DMT who had not seen a specialist MS nurse or neurologist in the past year, just 17% were taking a DMT, compared to 65% of those who had seen a specialist within the past year.
8. Is there an unmet need for patients with this condition?	Those living with relapsing remitting MS now have access to a variety of treatment options including over a dozen DMTs available on the NHS. However, they can still face difficult choices when they come to consider the risks and benefits of the different interventions for their condition. Some existing treatments for MS may have serious side effects, meaning individual patients may be unable to tolerate them or may choose not to receive them. Considering that many people with relapsing MS may need to switch to an alternative DMT during the course of their disease, there remains a need for novel effective DMTs with a good safety profile for relapsing MS. Ponesimod is a modulator of the sphingosine-1-phosphate receptor-1 (S1PR) pathway, as is fingolimod, an existing DMT in the standard treatment of relapsing MS. Adverse events associated with fingolimod have prompted the search for alternative S1PR modulators. Other S1PR modulators include siponimod and ozanimod. Fingolimod acts on four S1PR receptor subtypes, whereas ozanimod is selective to one (6). Whilst safety data from the Phase III trial of ponesimod vs teriflunomide in relapsing MS is yet to be published, a treatment selective to one subtype of the S1PR receptor could potentially represent a safer oral treatment option for people with relapsing MS.

	Patient decisions on which DMT to take are determined by a variety of factors including eligibility, efficacy, side effects, the method and frequency of administration, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. The more effective treatments that are available, the greater the choice for patients and the greater the likelihood that individuals will find a DMT that works for them. Within the currently available DMT treatment range, oral options are limited, and people with relapsing MS would benefit from any further safe and effective oral alternative. Treatment options which do not require clinic or hospital appointments to administer have an obvious advantage potentially reducing pressure on NHS services. References: 6. Sphingosine 1-Phosphate Receptor Modulators for the Treatment of Multiple Sclerosis (nih.gov)
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When it comes to making decisions on DMTs, outcomes important to people with MS include a reduction in relapse rate, the slowing of disability progression, and a reduction in evidence of active disease. People with MS also have concerns about potential safety of individual DMTs (3). Ponesimod has been shown in Phase II clinical trial to significantly reduce the number of new lesions on MRI, as compared to placebo, in relapsing remitting MS (7). Ponesimod was generally well tolerated. The OPTIMUM Phase III trial, a two-year study comparing the efficacy and safety of ponesimod to teriflunomide in adults with relapsing-remitting MS has yet to publish its outcomes in a peer-reviewed journal. However, early results from this trial were made available online as part of the virtual American Academy of Neurology's Annual Meeting (AAN 2020) (8). It was reported that, for those 985 patients with relapsing MS who completed the trial, ponesimod was 30.5% more effective than teriflunomide at reducing annual relapse rates, and 56% more effective at reducing the number of new active lesions on MRI. The trial used a novel tool to assess fatigue- the Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS). It was reported that ponesimod was superior to teriflunomide at improving fatigue, according to the FSIQ-RMS tool. There were no significant differences between the two treatments in 12-week and 24-week confirmed disability accumulation scores, the report said. During a previous presentation of the trials results at the 35th Congress of the European Committee for

	Treatment and Research in Multiple Sclerosis (ECTRIMS) in September 2019 (9), it was reported that the safety of ponesimod was comparable to that of teriflunomide, with very similar incidences of treatment-emergent adverse events, and serious adverse events. Provided that the same results are reported upon peer reviewed publication, it could be concluded that ponesimod represents a valuable addition to the range of treatment options for people with relapsing remitting MS. People with MS require a range of safe and effective treatments which they can take in a way that suits their clinical needs and lifestyle. If made available, ponesimod would represent a new oral option for patients with RRMS. Whilst oral treatment options may not be suitable for all, many people with MS tell us about the convenience of DMTs that can be taken at home. For people with MS of working age and for those with limited mobility, taking time out of work or the need to travel to attend hospital appointments can sometimes be challenging. The CRIMSON study (3) of the experience of people with relapsing MS in choosing treatments reported that, "..treatment compliance is key and PwRRMS need to be able to manage treatment mode and frequency within their own daily regimen and determine what suits them best - daily tablets, or more infrequent induction therapies, or consider the complexities of PwRRMS who need to travel for work and the complexities of managing injections in those circumstances" References: 7. Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial - PubMed (nih.gov) 8. Efficacy Outcome Measures of Oral Ponesimod Compared to Teriflunomide in Patients with Relapsing Multiple Sclerosis: Results of the Randomized, Active-Controlled, Double-Blind, Parallel-Group Phase 3 OPTIMUM Study (3972) | Neurology 9. Efficacy and safety of ponesimod compared to teriflunomide in.... ECTRIMS Online Library. Kappos L. Sep 11 2019; 279416 (ectrims-congress.eu)
Disadvantages of the technology	

10. What do patients or carers think are the disadvantages of the technology?	
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As noted above, for some people with MS who are of working age, and for some of those with limited mobility, or finances, time away from work or the need to travel to hospital can be challenging. Some of these people may benefit from the availability of another treatment option which can be taken at home.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	MS affects two to three times as many women as men. Any decision that resulted in a reduction in the available treatment options for people with MS would have a disproportionate effect on women.

Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • DMT decision making can be complex. The more effective treatment options for people with relapsing remitting MS that are available, the greater the choice for patients and the greater the likelihood that individuals will find a DMT that works for them. • Within the currently available DMT treatment range, oral options are limited, and people with relapsing MS would benefit from any further safe and effective oral alternative.	

Thank you for your time.

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Patient organisation submission

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

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

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

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[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.]	**Janssen** – £30,000 – conference/study day **Bayer** – no funding **Biogen** – £344.00 – advisory board **Celgene/BristolMyersSquibb** – no funding **Genzyme/Sanofi** – £36,000 – mapping MS services **Merck** – £400 – advisory board **Mylan** – no funding **Novartis** – £10,385 – advisory board; conference/study day **Teva** – no funding

If so, please state the name of manufacturer, amount, and purpose of funding.	**Roche** – £50,000 – funding for specialist nurse programme
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?	Clinical trial data have demonstrated the effectiveness of ponesimod compared to teriflunomide: • More effective at reducing the risk of relapses • More effective at reducing invisible MS activity (MS lesions on MRI scans) • More effective at reducing brain volume loss • Equivalent effectiveness in time to three or six month confirmed disability progression • More effective at stabilising fatigue levels, a significant symptom of MS which can have a major impact on work, family and social life • Low level of side effects Ponesimod is highly selective for S1P1 receptors, the target subtype 1 of sphingosine 1-phosphate receptors which are expressed on lymphocytes and lead to sequestration of lymphocytes in lymph nodes. This would be expected to lead to fewer adverse effects compared to other sphingosine 1-phosphate receptor modulators, such as fingolimod. Ponesimod has not been compared directly with fingolimod in a clinical trial, but a comparison of results from studies would suggest that the two treatments have similar efficacy. In clinical trials, ponesimod showed a numerical improvement in confirmed disability progression compared to teriflunomide, but this was not statistically significant. Similar results have been obtained in other clinical trials comparing disease modifying drugs with active comparators. A recent study found that it can take up to 16 months for a disease modifying drug to have a full clinical effect on disability progression[1]. In the case of fingolimod, the therapeutic lag was 11 months. This would suggest that a two-year clinical trial is not long enough to see a significant difference between active comparators, particularly for six month confirmed disability progression.

[1] Roos I, et al. Delay from treatment start to full effect of immunotherapies for multiple sclerosis. Brain 2020; 143(9): 2742-2756.

	Fatigue is one of the most common and debilitating symptoms of MS and can be one of the most challenging to manage and treat. The potential for improvement, or at least stabilisation, of fatigue levels will be a significant advantage for people with MS. Ponesimod is rapidly eliminated and lymphocyte counts return to normal range within 1 week. This will be beneficial for people needing vaccination or for women who want to start a family. Titration of the first dose of ponesimod minimised first-dose cardiac effects; people with MS will not need to be monitored in a hospital clinic while taking the first dose, as is required for fingolimod. Ponesimod has not yet been granted UK marketing authorisation, but if approved for active relapsing remitting MS, patients and clinicians will welcome an alternative first line, oral treatment which would offer several advantages over the two oral treatments currently used for active relapsing remitting MS - dimethyl fumarate and teriflunomide: • Dimethyl fumarate has similar efficacy compared to ponesimod but requires twice daily oral dosing (associated with lower adherence) and causes several side effects, such as gastrointestinal problems and flushing, which some people find intolerable and leads to treatment discontinuation. • Teriflunomide has a lower efficacy compared to ponesimod and has side effects including hair thinning/loss which is a significant concern for some patients. It also has a very long elimination time and carries a risk of serious birth defects; this is a cause of concern for women of child-bearing age.
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 ponesimod clinical trials, side effects caused by ponesimod were mild to moderate. In the OPTIMUM study, the most frequent side effects included nasopharyngitis, headache, chest infections and

	an increase in liver enzymes measured in the blood. Seizures and macular oedema occurred more frequently in those taking ponesimod.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that we are aware of.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Once daily oral route of administration means that ponesimod can be taken at home, eliminating potential delays in starting treatment which has occurred with other disease modifying drugs that require access to outpatient infusion clinics. Overall, this route of administration minimises demands on NHS services.

Key messages

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

- 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.
- Ponesimod 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).
- 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.

Thank you for your time.

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Professional organisation submission

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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- Your response should not be longer than 13 pages.

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

3. Job title or position	[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 ABN is an independent professional representative body for neurologists within the UK. It is funded through membership fees from its members and charitable donations.**
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.]	**No**

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.)	As a disease modifying therapy (DMT) to reduce clinical relapses and MRI activity associated with active relapsing-remitting (RR) multiple sclerosis (MS) and slow clinical disability progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Ideally a significant reduction in relapse rate, MRI activity and confirmed disability progression compared to appropriate active comparator. Relative reduction in confirmed disability progression compared to active comparator is more difficult to ascertain due to the longer-term nature of data needed to determine this in comparison to relapse rate and MRI activity. If non-inferiority alone is achieved then other factors such as tolerance, safety, ease of administration and/or other patient preference issues should also be considered.

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, there is a need in active RR MS for oral first-line therapies which are well tolerated and show significant improved efficacy in comparison to currently available first line oral therapies. This technology in part meets this unmet need as it demonstrates superiority of Ponesimod vs. a NICE-approved 1st line oral therapy (teriflunomide) in a Phase 3 trial (OPTIMUM) including 1,137 participants a significant reduction in relapse rate (by 30%), active MRI lesions and brain volume. No significant difference is seen measuring confirmed disability accumulation.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Standard of care in a majority of people with active RR MS is using disease modifying therapies (DMT) of which this technology is one.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ABN Guidelines published in 2015 in Practical Neurology ABN Guidance on DMTs for MS and Covid-19 Nov 2020 - https://cdn.ymaws.com/www.theabn.org/resource/collection/6750BAE6-4CBC-4DDB-A684-116E03BFE634/ABN_Guidance_on_DMTs_for_MS_and_COVID19_05_Nov_2020.pdf NHS England Treatment Algorithm for MS DMTs updated in 2019 - https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf
• Is the pathway of care well defined? Does it vary or are there	Pathway is broadly defined by the NHSE Treatment algorithm (https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf) but it is recognised that some variation exists and there is no one set defined pathway and patient preference also plays a significant role. MDT meetings are used in all prescribing units for the use of 'higher efficacy' DMTs.
• What impact would the technology have on the current pathway of care?	It would provide a further medium efficacy first-line therapy option to people with active RR MS who may benefit from the possible greater efficacy this technology may offer in comparison to another first line oral therapy option (teriflunomide) that the trial data suggests. Another oral therapy (dimethyl fumarate) also exists in this space and there is no published trial data comparing Ponesimod to this therapy. It is also possible for a much smaller number of people that this technology may represent a second line escalation option for a smaller number of people. It is unlikely that this technology would be considered efficacious enough to represent a first line DMT option to people with highly active or rapidly evolving severe (RES) RR MS.
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?	If priced similarly to other first line oral DMT options for active RR MS then there should be no significant healthcare resource impact.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribing will be principally through specialist clinics via neuroscience centres but may also be derived from a smaller number of non-specialist secondary care clinics where there is local agreement between the regional neuroscience centre and NHS England.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This technology should not require any additional investment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It will add a further therapy option mainly to people with active RR MS who are choosing a first line DMT. Other therapies exist in this area, but this technology has been shown in the OPTIMUM Phase 3 trial (R Fox et al. Neurology 2020) to have significantly greater efficacy in relapse reduction, fatigue and MRI parameters compared to another already approved first line oral DMT (Teriflunomide) and hence may have a meaningful benefit to current care.
• Do you expect the technology to increase length of life more than current care?	It is more likely to be equivalent to current DMT options.
• Do you expect the technology to increase health-related quality of life more than current care?	At least equivalent to current therapy options for this group of patients. It is possible that by preventing a greater number of relapses and brain atrophy than another comparable therapy option (Teriflunomide) there may an increase in health-related quality of life. The OPTIMUM trial showed a significant reduction in fatigue-related symptoms and its impact on physical activity, cognitive and emotional function and coping mechanisms (as measured by the impact questionnaire-relapsing MS [FSIQ-MRI]).

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Likely to be most suitable for people with active RR MS who prefer an oral first line DMT option. Less suitable because of concerns about prevention of confirmed disability accumulation for people with RES or highly active RR MS where other possibly more efficacious DMTs are already available.
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.)	Unlikely to have a significant impact compared to currently available options.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, as set out by NHS England requirements and its Blueteq request system which will state start and stop criteria based on this appraisal and published clinical trial. No additional testing will be required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The technology is similar in its mechanism of action (sphingosine receptor antagonism) to another currently available DMT (fingolimod) although as a more selective drug (antagonising type 1 receptors only) may have an improved cardiac side effect profile which could allow reduced cardiac monitoring at treatment initiation compared with fingolimod. In addition, the technology has a significantly shorter half-life than fingolimod which allows for quicker wash-out if complications/side effects arise which may be an advantage by shortening time for lymphocyte recovery after treatment discontinuation.

improve the way that current need is met?	
• 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?	It offers further choice to the patient with active RR MS which is more efficacious than one of the other already approved DMTs in this group of first line therapies (Teriflunomide) and a further option to some people with highly active RR MS where fingolimod is currently positioned.
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?	Another drug using a similar mechanism of action (fingolimod) is already approved for highly active RR MS and hence there is good clinical familiarity amongst clinicians with this class of drug. Side or adverse effects therefore are likely to be predictable and monitoring familiar with screening for pre-existing cardiac and ophthalmological issues and then monitoring lymphocyte and liver function counts while on the therapy. This is unlikely to significantly affect the patient's quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	In part yes as the active comparator (Teriflunomide) is an approved oral first line DMT for active RR MS in the UK. However, another oral therapy (dimethyl fumarate) is more commonly prescribed in this patient group and there is no trial data comparing this drug with the current technology.

• If not, how could the results be extrapolated to the UK setting?	Clinical experience and 'real-world' studies suggest that a similar drug (Fingolimod) to this technology would be considered at least as effective if not slightly more efficacious than Dimethyl fumarate although there are no direct Phase 3 comparator clinical trials to confirm this.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trial data from the OPTIMUM study is in line with expectations for the mechanism of action of this technology. It would be predicted that this group of drugs from experience with fingolimod, would show significantly better relapse reduction and MRI outcomes than teriflunomide. Demonstrating significantly better disability outcomes in clinical trials, within the short timescale of these studies, is more challenging and the non-significance of this outcome has been noted in other RR MS trials with other DMTs. In the OPTIMUM study patients using the technology had improved fatigue outcomes compared with the comparator. Fatigue is a hugely significant and common symptom in MS however it should be noted that the actual clinical significance particularly in the longer term of the effect measured in the trial is unclear.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Partially. There is correlation between the outcome measures used and long-term clinical outcomes, but the correlation is not complete and the duration of the trial particularly for confirmed disability measures is short.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA624?	No
21. How do data on real-world experience compare with the trial data?	There are no currently available real-world datasets comparing Ponesimod and Teriflunomide. Data does exist showing Fingolimod (similar mechanism of action to Ponesimod) to be superior to Teriflunomide with a greater reduction in relapses and lower discontinuation rate (Kalincik, et al JNNP 2019; Boz, et al. MSARD 2019).
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	This technology would not be suitable for pregnant women given its mechanism of action and experience with a similar drug (Fingolimod).

22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. What definition (or source) is used in NHS clinical practice for relapsing-remitting MS in terms of: a. Progression on disease modifying therapy (including timeframe for assessment) b. Highly active relapsing-remitting MS c. Rapidly evolving severe relapsing-remitting MS	As defined by: NHS England Treatment Algorithm for MS DMTs updated in 2019 - https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf
Key messages	

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

- Efficacy in active RR MS
- Oral first line DMT and some highly active RR MS patients
- Significantly better relapse reduction and MRI compared with Teriflunomide
- Shorter half-life
- Familiar mechanism of action

Thank you for your time.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UKMSSNA**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Represents MS Specialist Nurses across the UK, funded by the membership.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

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.)	To improve relapse rates and delay progression
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in relapse rates and improved protection from future disability
8. In your view, is there an unmet need for patients and	No

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Various other treatments are available
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is variation but guidance gives clear use of each treatment
• What impact would the technology have on the current pathway of care?	Addition to current options

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will be used
• How does healthcare resource use differ between the technology and current care?	NA
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	An addition to current technologies

• Do you expect the technology to increase length of life more than current care?	NA
• Do you expect the technology to increase health-related quality of life more than current care?	Possibly
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Relapsing remitting MS
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	No

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	NA
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	NA

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?	A further treatment resource to add to the current treatments available
• Is the technology a 'step-change' in the management of the condition?	NA
• Does the use of the technology address any particular unmet need of the patient population?	NA
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?	All treatments offered have side effects, this may assist in offering different options if other treatments fail due to side effects and efficacy

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?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any	No

relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA624?	No
21. How do data on real-world experience compare with the trial data?	
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	NA

with current care and why.	
Topic-specific questions	
23. What definition (or source) is used in NHS clinical practice for relapsing-remitting MS in terms of: a. Progression on disease modifying therapy (including timeframe for assessment) b. Highly active relapsing-remitting MS c. Rapidly evolving severe relapsing-remitting MS	
Key messages	

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

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-
-
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Thank you for your time.

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Ponesimod for Relapsing Multiple Sclerosis [ID1393]:

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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List of key issues

Abbreviations

A and E	Accident and Emergency
AE	adverse event
ALT	alanine aminotransferase
ARR	annualised relapse rate
AST	aspartate aminotransferase
BSC	best supportive care
CDA	confirmed disability accumulation
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CNS	central nervous system
CRD	Centre for Reviews and Dissemination
CSR	clinical study report
CS	company submission
CUAL	combined unique active lesions
CV	Cardiovascular
DIC	deviance information criterion
DIS	dissemination in space
DIT	dissemination in time
DMT	disease modifying treatment
DP	decision problem
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol five dimension
ERG	Evidence Review Group
FSIQ-RMS	Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis
Gd+	gadolinium-enhancing
HA	highly active
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IFNB	interferon beta
IQR	Interquartile range
ITC	indirect treatment comparison

ITT	intention-to-treat
LS	least squared
MD	mean difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite measure
MTR	magnetisation transfer ratio
NA	not applicable
NEDA	no evidence of disease activity
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
OR	odds ratio
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PML	progressive multifocal leukoencephalopathy
PSA	probabilistic sensitivity analysis
QA	quality assessment
QALY	quality adjusted life year
RCT	randomised controlled trial
RES	rapidly evolving severe
RR	relative risk
RRMS	relapsing-remitting multiple sclerosis
RSS	risk-sharing scheme
SD	standard deviation
SF-36	Short Form (36) health survey
SLR	systematic literature review
SoT	suboptimally treated
SPMS	secondary progressive multiple sclerosis
TA	technology appraisal
TEAE	treatment-emergent adverse events
TP	treatment period
UTI	urinary tract infection

Vs	Versus
WTP	willingness to pay

1. EXECUTIVE SUMMARY

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

- Section 1.1 provides an overview of the key issues and the differences in the assumptions of the company and the ERG in economic analysis.
- Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER.
- Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.
- Sections 1.6 and 1.7 provide an overview of the ERG's preferred base case and sensitivity analyses undertaken by the ERG.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1. Overview of the ERG's key issues

A brief overview of the key issues identified by the ERG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, and 1.5.

Broadly speaking, the key issues related to uncertainty surrounding the clinical effectiveness estimates for ponesimod and its comparators. This uncertainty has implications for the cost-effectiveness of ponesimod in both the active RRMS population and for people with highly active disease (HA RRMS), and for understanding the most appropriate positioning of ponesimod in the treatment pathway. Furthermore, the company's economic evaluation of ponesimod did not fully represent the 'clinical reality' treatment pathway in RRMS, which is often characterised by treatment sequencing, and there is uncertainty about subsequent treatment assumptions after progress to secondary progressive multiple sclerosis (SPMS).

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue 1	Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	2.3
Key Issue 2	Uncertainty in the clinical efficacy of ponesimod and its comparators	3.3, 3.4, and 3.5
Key Issue 3	Insufficient comparative evidence for the safety of ponesimod	3.4.1, 3.5.3, and 3.5.4
Key Issue 4	Uncertainty surrounding use of 3 month CDA as the primary measure of disease progression in the economic model	1.5 and 6.1.1.1
Key Issue 5	Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	1.5 and 6.1.1.2

Abbreviations: BSC, best supportive care; CDA, confirmed disability accumulation; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

In the economic analysis, the ERG's preferred assumptions vary from the company's in the following ways:

- In the company's base case analysis, the 3-month confirmed disability accumulation (CDA) was chosen as the primary measure of disease progression, which did not align with the preferences of the NICE committees in previous technology appraisals (TAs) (see section 1.5 and 6.1.1.1). The ERG considered that 6-month CDA should be used to estimate disease progression in the model for both the intention-to-treat (ITT) and the HA RRMS highly active populations
- The company assumed that 100% of people who convert to SPMS receive best supportive care (BSC; i.e. largely symptom management). However, the ERG noted that siponimod (TA656)[1] was recommended by NICE in 2020 for the treatment of people with SPMS, and therefore, the analysis should account for some uptake of siponimod in this population. See section 1.5 and 6.1.1.2.

1.2. Overview of key model outcomes

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

Overall, the technology is modelled to affect QALYs by:

- Delaying disease progression. The key driver of clinical effectiveness and associated QALY gain for ponesimod (versus most comparators in both the ITT and HA RRMS populations) was due to improved efficacy for CDA. In the model, a higher proportion of people receiving ponesimod remained in lower RRMS Expanded Disability Status Scale (EDSS) health states, relative to most comparator disease modifying treatments (DMTs). A higher proportion of people on 'less efficacious' treatments transitioned to higher EDSS states, where they experience lower health-related quality of life (HRQoL).
- Avoiding higher mortality multipliers, in higher EDSS states, associated with the risk of mortality from multiple sclerosis (MS). As such, higher efficacy DMTs (including ponesimod), resulted in incremental life years gained vs. moderately effective treatments.

In order to do this the technology is modelled to affect costs by:

- Keeping more people in lower EDSS states (0-6) where disease management costs are significantly less than higher states (7-9). Due to the modelled treatment efficacy, people receiving ponesimod had lower disease management costs versus most comparators.
- Ponesimod was also considered to have lower drug acquisition costs, monitoring and administration costs compared to some comparators. Please note, the company's base case analysis did not include confidential patient access scheme (PAS) discounts for the comparators.

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

- Using six-month CDA for EDSS progression in the model, rather than 3-month CDA (ITT population)
- Using a positioning-based approach to estimate treatment effect (ITT and HA RRMS populations)
- Using an alternative set of annual conversion probabilities, from RRMS to SPMS (ITT population)
- No waning in treatment effect (HA RRMS population)

1.3. Summary of the key issues regarding the decision problem

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal, and identified a key issue relating to the specific inclusion or relevance of different RRMS phenotypes.

The original submission provided by the company did not include evidence for two potential comparators to ponesimod that were under appraisal at the time of submission, however the company presented evidence for these comparators at clarification. While the standard of the evidence presented for these comparators was limited by the timeframe available to the company between submission and their response to clarification, the ERG was satisfied that the evidence presented was sufficiently comparable to other comparators.

Key Issue 1: Uncertainty over the evidence base for the rapidly evolving severe (RES) RRMS population

Report sections	**2.3**
Description of issue and why the ERG has identified it as important	The NICE scope for this appraisal specifies people with RES RRMS as a separate population group; however, in its response to the DP, the company stated that people with RES RRMS were included within its definition of highly active (HA) RRMS, and that no separate subgroup analysis for this population would be presented. The broader HA+RES data was used in the company's base case NMAs, and in the company's economic evaluation. The ERG was unclear whether evidence from a combined HA population could be used to inform a recommendation for the RES population. The ERG understood that while there may be some similarities in presentation between people with HA and RES RRMS in terms of the speed of disease progression, there are differences in the populations: specifically, HA RRMS is disease that progresses despite treatment ('breakthrough disease'), and RES is a separate, rare phenotype of the disease. It is unclear whether relative treatment effects (though often stable across different populations), are comparable in the HA and RES populations. The ERG noted that relative treatment effects in the company's model varied between the ITT and HA population. In addition, the ERG considered that the absolute outcomes and costs for RES RRMS may differ from HA RRMS, which may affect the cost effectiveness of ponesimod versus other available treatments. There has been some uncertainty in previous appraisals about whether recommendations can be generalised across population groups. At clarification the company presented subgroup data for people with RES RRMS from their pivotal trial, though the sample was small, and the comparator treatment (teriflunomide) is not recommended in the NHS for people with RES RRMS. The company's subgroup NMAs

Report sections	2.3
	considered RES within the definition of HA only. The ERG noted that natalizumab is currently recommended in the NHS for RES RRMS (and not HA RRMS), and that while this treatment was included in the company's NMAs, the results were not reported, and natalizumab was not considered as a comparator in the company's economic model.
What alternative approach has the ERG suggested?	The ERG did not believe that the evidence presented by the company is sufficient to evaluate the effectiveness of ponesimod in the RES RRMS population; however further clinical input and evidence may help to resolve this issue.
What is the expected effect on the cost-effectiveness estimates?	The results of the company's economic evaluation vary between the ITT and HA population, though it is unclear whether differences would be seen between the HA and RES populations. Without seeing the results for natalizumab, it is unclear whether ponesimod would be cost-effective against this comparator.
What additional evidence or analyses might help to resolve this key issue?	Evidence to demonstrate that treatment effects for ponesimod are stable across baseline risk, and/or across the different populations of RRMS would provide confidence in generalising evidence to the RES population. Clinical evidence should also be presented for the comparison between ponesimod and natalizumab, as well as all other treatments available for people with RES RRMS. In addition, altered modelling assumptions for the RES population may be needed, in order to evaluate whether ponesimod is cost effective in this population.

Abbreviations: DP, decision problem; ERG, Evidence Review Group; HA, highly active; ITT, intention-to-treat; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis

1.4. Summary of the key issues in the clinical effectiveness evidence

The ERG reviewed the clinical effectiveness and safety evidence presented in the CS, and identified the following two key issues for consideration by the committee:

Key Issue 2. Uncertainty in the clinical efficacy of ponesimod and its comparators

Report sections	3.3, 3.4, and 3.5
Description of issue and why the ERG has identified it as important	The clinical effectiveness evidence for ponesimod and its comparators was highly heterogeneous, and there was a paucity of evidence for most of the comparisons in the company's NMAs. Clinical experts to the ERG also noted that the outcomes reported in the included trials were frequently short-term, and that these may be unable to capture meaningful change in disease course. These follow-up durations also varied widely across trials. Treatment effects for all outcomes varied widely between groups treated with placebo, highlighting the extent of the heterogeneity and its impact on treatment effects. Relative treatment effects derived from the NMAs have wide confidence intervals, and there is a

Report sections	3.3, 3.4, and 3.5
	high degree of uncertainty about the true magnitude of the effects reported. The evidence was particularly limited for analyses in the highly active population.
What alternative approach has the ERG suggested?	The ERG appraised the company's NMAs, and validated the methodology and results against previous appraisals, and found that these were consistent. The ERG therefore considered that the methods used by the company were appropriate in the context of the available evidence, and that uncertainty surrounding the clinical effectiveness estimates was principally due to the limitations of the evidence base.
What is the expected effect on the cost-effectiveness estimates?	The ICER was highly sensitive to even small variations in treatment efficacy.
What additional evidence or analyses might help to resolve this key issue?	The ERG was satisfied that the evidence presented by the company is representative of the known treatment effects for ponesimod and its comparators. Until further evidence is available (more direct head-to-head trials of ponesimod, trials with longer follow-up, and evidence identifying whether treatment effects vary according to the sources of heterogeneity in the evidence base), uncertainty surrounding the treatment effects of DMTs is a key issue in appraisals of treatments for RRMS. The ERG has conducted some scenario analyses to demonstrate the sensitivity of the ICER to variation in the treatment effect of ponesimod (see Section 6.1).

Abbreviations: DMT, disease-modifying treatment; ERG, evidence review group; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis; RRMS, relapsing remitting multiple sclerosis

Key Issue 3. Insufficient comparative evidence for the safety of ponesimod

Report sections	3.2.4.3, 3.5.3, 3.5.4
Description of issue and why the ERG has identified it as important	Treatment decisions for RRMS frequently involve a trade-off between the efficacy and safety of DMTs, in addition to consideration of individuals' preferences (towards routes of administering treatment and typical adverse events). Understanding the relative safety of ponesimod is therefore necessary for understanding its likely positioning in the treatment pathway, and its most relevant comparators. The company's main trial, OPTIMUM, compared the safety of ponesimod with teriflunomide, a moderate-safety, first-line DMT. However, no NMA evaluating the relative safety of ponesimod was reported. The company reported annualised rates of adverse events, obtained from included trials, for ponesimod and each comparator DMT. This approach relies upon a naïve comparison of rates that does not take account of the heterogeneity between the included trials (including variations in sample eligibility criteria, healthcare setting, and the measurement and follow-up of safety outcomes). Trial data also lacks external validity when measuring AEs, and trials of DMTs are frequently too small and/or short to reliably measure the incidence of rare, serious AEs.

Report sections	3.2.4.3, 3.5.3, 3.5.4
What alternative approach has the ERG suggested?	The ERG compared the rates of AEs for ponesimod and its comparators, and on the basis of this evidence drew tentative conclusions that ponesimod may be acceptably safe, including in respect to elevated liver enzymes and infections when compared to comparators in the first and second line. With regards to rare serious adverse events, it was uncertain whether ponesimod provides an improved safety profile due to the lack of data in a large enough group of participants. From these data, the ERG drew a comparison between the rates reported for ponesimod and fingolimod. This comparison was chosen as the company posited that ponesimod may be considered a safer alternative to fingolimod, and clinical experts advised that a comparison of the safety of these treatments would aid understanding of the appropriate positioning of ponesimod in the treatment pathway. The evidence did not satisfactorily demonstrate that ponesimod was associated with a lower risk of AEs, including AEs related to liver toxicity. The ERG conducted a further naïve comparison of AE rates reported by the company from the OPTIMUM trial with those reported for fingolimod in its appraisal by NICE in 2012. This comparison was intended to identify rates of cardiac events, macular oedema and treatment discontinuations due to adverse events, which were not reported in the CS for comparators to ponesimod. Based on these data, ponesimod appeared to be an acceptable alternative to fingolimod for macular oedema; however, treatment discontinuations were higher among participants treated with ponesimod. No cardiac data was available from the NICE appraisal of fingolimod.
What is the expected effect on the cost-effectiveness estimates?	The data appeared to suggest that ponesimod is a moderate-safety treatment; however, the quality of safety evidence is poor, and further evidence would inform its most appropriate positioning in the treatment pathway, and therefore the identification of its most relevant comparators in cost-effectiveness evaluations. The risk of rare serious adverse events manifesting over the long-term informs assumptions related to monitoring, as well as healthcare resource use. Increased treatment discontinuations may also affect health resource use. However, the ERG identified that the impact of monitoring has little impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	A further NMA evaluating the relative risk of discontinuation due to AEs as compared to other available DMTs would contribute to an understanding of the overall safety of ponesimod. While this NMA would also be limited by heterogeneity in the trials, discontinuation gives an overall picture of tolerability, and may be more consistently measured across trials. Moreover, published NMAs of treatments for RRMS often present a graph plotting the relative safety vs. efficacy of all available treatments, which would be useful to aid decision-makers in identifying the most appropriate positioning for ponesimod. Higher quality evidence for the safety of ponesimod, including long-term real-world evidence in

Report sections	3.2.4.3, 3.5.3, 3.5.4
	larger groups of people, would give a more informed insight into the safety of ponesimod, particularly in terms of rare serious adverse events, such as PML. Clinical experts to the ERG also suggested that clearer positioning within the same class of treatment (e.g. if/when to use ponesimod, fingolimod, and siponimod) would be useful to understanding the appropriate positioning of ponesimod.

Abbreviations: DMT, disease-modifying treatment; ERG, Evidence Review Group; HA, highly active; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis

1.5. Summary of the key issues in the cost effectiveness evidence

The ERG reviewed the company health economic evidence and economic evaluation presented in the CS, and identified the following key issues for consideration by the committee:

Key Issue 4. Six-month confirmed disability accumulation (CDA) is considered a more appropriate measure of disease progression

Report sections	4.2.6 and 6.1.1.1
Description of issue and why the ERG has identified it as important	The key driver of clinical effectiveness in the model was treatment effects for 3-month CDA. However the ERG considered 6-month CDA to be a more robust measure of progression. This was following clinical advice to the ERG that 3-month CDA can overestimate progression due to natural fluctuations in the disease. Previous NICE committees have also expressed a preference for 6-month CDA in appraisals of treatments for RRMS (e.g. the NICE appraisal of alemtuzumab, TA312[2]). The company provided additional justification for using 3-month CDA data in the base case (see Section 4.2.6 or their response). However, despite the comparatively lower availability of evidence for 6-month CDA, the ERG considered that this should have been used in the company's base case as it is a more robust measure of progression. The company included an option in their model to use 6-month CDA as the preferred estimate of treatment efficacy.
What alternative approach has the ERG suggested?	The ERG used 6-month CDA estimates in their base case. Results are discussed and reported in Section 6.1.1.1.
What is the expected effect on the cost-effectiveness estimates?	Results were sensitive to using 6-month CDA estimates in the ITT population.
What additional evidence or analyses might help to resolve this key issue?	In the absence of direct head-to-head data, the ERG considered that the use of 6-month CDA data from the NMAs was reasonable. However, 6-month CDA estimates derived from head-to-head studies would increase the validity of these results.

Abbreviations: CDA, confirmed disability accumulation; ERG, Evidence Review Group; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RRMS, relapsing-remitting multiple sclerosis

Key Issue 5. The assumption that 100% of people who progress to SPMS receive BSC may not be appropriate

Report sections	4.2.6.1 and 6.1.1.2
Description of issue and why the ERG has identified it as important	In the base case analysis, the company assumed that 100% of people who discontinue treatment go on to receive BSC. Although this is reflective of previous NICE TAs, the ERG were aware that siponimod had recently been accepted by NICE for use in people with SPMS[1], and will soon be available. Clinical advice to the ERG was that some people who have been diagnosed with SPMS will also receive dimethyl fumarate, though this is not considered to be highly efficacious. As siponimod has only recently been approved, there was uncertainty about the rate of uptake in the SPMS population. Based on clinical input to the ERG, the proportion of people who are likely to receive siponimod after converting to SPMS could be approximately 25%; this accounts for a proportion of people who choose not to receive treatment or are ineligible.
What alternative approach has the ERG suggested?	The ERG conducted a scenario analysis that assumed 25% of people who converted to SPMS received siponimod, whilst 75% received BSC. This scenario accounted for the additional costs of managing siponimod in people converting to SPMS, but did not account for the clinical efficacy of siponimod, due to the uncertainty surrounding the expected clinical efficacy
What is the expected effect on the cost-effectiveness estimates?	This scenario analysis did not have a significant impact on the base case results (in either the ITT or HA RRMS populations), however the ERG considered that including this assumption within the base case analysis was likely to better reflect clinical practice.
What additional evidence or analyses might help to resolve this key issue?	Treatment uptake data surrounding siponimod use in the UK (in both the active RRMS and highly active RRMS populations) would help to resolve this issue. The company and ERG model were unable to fully account for the impact of subsequent treatments, and so the potential impact of treatment with siponimod and other DMTs on the cost effectiveness of ponesimod was uncertain.

Abbreviations: BSC, best supportive care; DMT, disease modifying treatment; ERG, Evidence Review Group; HA, highly active; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal

1.6. Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions for the ITT and HA RRMS are listed in Table 2 and Table 4 below. Results are presented in Table 3 and Table 5; please note that these do not include confidential PAS discounts for comparator treatments. For further details of the exploratory and sensitivity analyses conducted by the ERG, see Section 6.1.

Table 2. ERG preferred assumptions (ITT population)

Preferred assumption	Report Section
Company base-case	*5.1.1*
6 month CDA used to model disease progression	*4.2.6.1 and 6.1.1.1*
25% of people receive siponimod after converting to SPMS, 75% receive BSC	*4.2.6 and 6.1.1.2*

Abbreviations: BSC, best supportive care; CDA, confirmed disability accumulation; ERG, Evidence Review Group; ITT, intention-to-treat; SPMS, secondary progressive multiple sclerosis

Table 3. ERG's preferred case results (ITT population)

Outcomes	ERG base case			Company base case
Ponesimod vs Comparator	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	ICER (£/QALY)
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30mcg IM	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125mcg SC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality adjusted life year

Table 4. ERG preferred assumptions (HA RRMS population)

Preferred assumption	Report Section
Company base-case	5.1.1
6 month CDA used to model disease progression	4.2.6.1 and 6.1.1.1

Preferred assumption	Report Section
25% of people receive siponimod after converting to SPMS, 75% receive BSC	4.2.6 and 6.1.1.2

Abbreviations: CDA, confirmed disability accumulation, ERG, Evidence Review Group; HA, highly active; SPMS, secondary progressive multiple sclerosis

Table 5. ERG's preferred base case results (HA RRMS population)

Outcomes	ERG base case			Company base case
Ponesimod vs Comparator	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	ICER (£/QALY)
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; HA, highly active; ICER, incremental cost-effectiveness ratio; RRMS, relapsing-remitting multiple sclerosis

1.7. Summary of exploratory and sensitivity analyses undertaken by the ERG

A summary of the ERG's scenario analyses is provided in Table 6 below. For results, please see Section 6.1

Table 6: ERG scenario analyses (ITT population)

Scenario	Report Section
Company base case	*5.1.1*
Scenario 1: 6 month CDA used to model disease progression	*6.1.1.1*
Scenario 2: 25% of SPMS people assumed to receive siponimod and 75% receive BSC	*6.1.1.2*

Scenario	Report Section
Scenario 3: Population characteristics based on UK RSS data	*6.1.1.3*
Scenario 4: Alternative subsequent treatment assumptions	*6.1.1.4*
Scenario 5: No difference in discontinuation rates (assumed 5% for all treatments)	*6.1.1.5*
Scenario 6: No waning in treatment effect (applies to all treatments)	*6.1.1.6*
Scenario 7: Alternative modelled clinical effectiveness parameters	*6.1.1.7*
Scenario 8: Monitoring costs for ponesimod in year 1 assumed to be equal to fingolimod	*6.1.1.8*
Scenario 9: Alternative EDSS health state costs	*6.1.1.9*
Scenario 10: Alternative cost associated with relapse	*6.1.1.10*
Scenario 11: Alternative EDSS health state utilities	*6.1.1.11*
Scenario 12: Alternative annual conversion probabilities (from RRMS to SPMS)	*6.1.1.12*

Abbreviations: BSC, best supportive care; CDA, confirmed disability accumulation; EDSS, Expanded Disability Status Scale; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; ITT, intention-to-treat; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 7: ERG scenario analyses (highly active population)

Scenario	Report Section
Company base case	*5.1.1*
Scenario 1: 6 month CDA used to model disease progression	*6.1.1.1*
Scenario 2: 25% of SPMS people assumed to receive siponimod and 75% receive BSC	*6.1.1.2*
Scenario 3: Population characteristics based on UK RSS data	*6.1.1.3*
Scenario 4: Alternative subsequent treatment assumptions	*6.1.1.4*
Scenario 5: No difference in discontinuation rates (assumed 5% for all treatments)	*6.1.1.5*
Scenario 6: No waning in treatment effect (applies to all treatments)	*6.1.1.6*
Scenario 7: Alternative modelled clinical effectiveness parameters	*6.1.1.7*
Scenario 8: Monitoring costs for ponesimod in year 1 assumed to be equal to fingolimod	*6.1.1.8*
Scenario 9: Alternative EDSS health state costs	*6.1.1.9*
Scenario 10: Alternative cost associated with relapse	*6.1.1.10*
Scenario 11: Alternative EDSS health state utilities	*6.1.1.11*
Scenario 12: Alternative annual conversion probabilities (from RRMS to SPMS)	*6.1.1.12*

Abbreviations: BSC, best supportive care; CDA, confirmed disability accumulation; EDSS, Expanded Disability Status Scale; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Please note that all page references to the company submission (CS) are using version 2, submitted by the company on 29th March 2021.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

Multiple sclerosis (MS) is a chronic disease caused by dysfunction of the immune system, which leads to damage to the myelin within the central nervous system. Myelin is an insulating layer surrounding the axons of nerve cells and supports rapid and efficient transmission of electrical impulses along nerve cells. Degradation of this layer leads to neurodegeneration as the electrical impulses transmitted throughout the brain and spinal cord are impeded. Areas where the myelin is damaged are known as lesions, the accumulation of which causes neurological impairment and multifaceted disability.

The symptoms of MS vary between people but can include the following: fatigue; vision issues; numbness or tingling; muscle spasms; stiffness and weakness; mobility issues; pain; issues with cognitive; depression or anxiety; sexual issues; bladder or bowel control issues as well as speech and swallowing difficulties. Public Health England estimates indicate that there are around 105,800 people[3] suffering from all MS forms in the UK. In the general population, MS is twice as common in women as men, although in those aged between 50-59 years the prevalence is three times higher in women[3].

The most common subtype of MS is relapsing remitting MS (RRMS). RRMS is generally diagnosed in when people are in their twenties or thirties, and it accounts for around 85% of those diagnosed with MS[4]. RRMS is characterised by periods of remission interspersed with relapses. A relapse is identified through the presence of new symptoms, or an exacerbation of existing symptoms, lasting over 48 hours. Following a relapse, there will be a period of recovery which may or may not be complete. The recovery from attacks often becomes less complete over time, and residual disability accumulates. The frequency and nature of relapses varies, with natural fluctuation over the disease course, though relapses typically reduce as people age.

People with RRMS will ultimately be considered to have progressed to secondary progressive (SPMS) disease, where they are considered to suffer from fewer attacks but nevertheless show a gradual increase in disability. This is caused by neurodegeneration from existing lesions. SPMS is difficult to diagnose, with the diagnosis often done retrospectively based on a clinical review of symptoms. It is estimated that people with RRMS will progress to SPMS after an average of approximately eight to ten years; this rate has not been shown to change meaningfully since the introduction of disease-modifying treatments (DMTs).

RRMS diagnosis is complex due to the vast range of symptoms and widely varying clinical presentation. Clinicians use the revised McDonald criteria (Thompson et al. 2018[5]), which takes into account the number of relapses and lesions people have, as well as the location of lesions within the central nervous system (CNS), in order to make a judgment. Lesions are detected with magnetic resonance imaging (MRI), of which there are two types used in MS diagnosis; gadolinium (Gd)-enhanced T1 and T2. RRMS can be further categorised by the level of disease activity, as per the categories below. These categories aim to identify those people whose disease will progress more rapidly, in order to inform the choice of treatment.

- **Inactive RRMS** is defined as no relapses and no evidence of new lesions on MRI.
- **Active RRMS** is defined either by up to two relapses per year and/or new MRI activity.
- **Highly active (HA) RRMS** is less easily defined, as there are a range of definitions used internationally. The National Health Service (NHS) defines HA RRMS as: 'People with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon'[6]. Conversely, the definition used in the US is more focused on the radiological burden of MS and rapid disability progression following onset.
- **Rapidly evolving severe (RES) RRMS** can be defined as either two or more disabling relapses in a year and one or more gadolinium-enhanced (Gd+) lesions, or a significant increase in T2 lesion load when compared with an earlier MRI.

People in the UK are currently treated with DMTs according to the NHS treatment algorithm[6]. An MS consultant and a specialist MS nurse will work in conjunction with multi-disciplinary teams from specialist MS centres across the country to determine the optimal treatment course for an individual. Where people have more complex disease, or where clinicians are considering treatment with a DMT with a higher risk of adverse events, such as cladribine or monoclonal antibodies, a meeting is typically held with a specialist team of MS clinicians.

2.2. Background

2.2.1. Current treatment for RRMS

There are a variety of DMTs currently used to treat RRMS in the UK. The company provided an overview of the NHS England (NHSE) treatment algorithm for DMTs[6], with first-line treatments positioned according to disease features, such as relapse frequency. The ERG considered that the pathway presented by the company accurately represented the NHSE pathway; however

understood that in practice, distinctions between first- and second-line treatments may be an over-simplification as people may receive several lines of therapy within the categories proposed in the NHSE pathway. The choice of a treatment is determined based on a balance of efficacy and safety, while also taking into consideration personal preference with regards to the mode of administration and risk of serious side-effects. Clinicians may choose either an escalation or an induction approach: the former involves administering a first-line, moderate-efficacy, high-safety treatment, with subsequent switching to a second-line treatment more-effective, lower-safety drug after the disease progresses (NHS algorithm [6]; Thompson et al. (2018)[7]); the induction approach involves first administering a highly effective, typically second line drug, to attain rapid remission of highly active MS (two or more severe relapses per year) and prevent rapid disability accumulation (NHS algorithm[6]; Thompson et al. (2018)[7]). Currently, trials to determine which of these approaches are most effective are being conducted (Coyle 2020[8]). People following the escalation approach may receive one or more 'first line' treatments, according to their disease severity, and the individual's and their clinicians' preference. The reasons for switching between first-line DMTs also include inadequate response not fulfilling criteria for second line treatment, adverse reactions or problems with tolerability, or justifiable lateral switches (e.g. low-dose to high-dose interferon beta, or vice versa)[9]. The treatment pathway is therefore highly varied between individuals, and first and second lines are broadly used to offer therapies as a proportion of people show a response to first line therapies and do not need to go to a second line therapy, which are riskier and more costly (NHSE 2019[6], Thompson 2018[7]).

DMTs are intended for use early in the disease course, when CNS inflammation is greatest. This 'window of opportunity' for treatment with DMTs continues until the onset of SPMS, at which point the disease is characterised as a chronic and progressive neurodegenerative process, and DMTs are considered to have little effect in slowing or stopping it (Díaz, Zarco, Rivera 2019[10]). At present, there are only two DMTs available for people with SPMS. Siponimod (TA656)[1] has recently been approved in the UK and is yet to be widely prescribed, while interferon beta (IFNB)-1b (TA527)[11] was approved in the UK in 2018. .

At the time of appraisal, both ozanimod (GID-TA10299)[12] and ofatumumab (TA699)[13] were both under appraisal by NICE as treatments for both first and second line RRMS, and it was not clear where in the treatment pathway these treatments would be positioned if recommended.

2.2.2. The technology

Ponesimod is a sphingosine 1-phosphate type 1 ($S1P_1$) receptor modulator that sequesters lymphocytes in lymph nodes by blocking S1P signalling. It can, therefore, be classified as an immunosuppressant drug in the same class as fingolimod (TA254[14]; second line treatment for RRMS/HA RRMS), ozanimod (GID-TA10299[12]; currently under appraisal for first and second line RRMS) and siponimod (TA656[1]; for the treatment of SPMS). However, these drugs are less specific, with fingolimod binding to S1P Type 1 as well as Types 3 to 5, while ozanimod and siponimod bind to S1P Types 1 and 5[15]. The off-target interactions with other S1P types are thought to cause undesirable effects as these receptor types are found in various cells, including tissues of the heart muscle and smooth arterial muscle. These effects range from cardiomyopathy and high blood pressure generally to bradyarrythmias, macular oedema and varicella-zoster viral infections with fingolimod specifically (Chaudhry 2017[15], Gajofatto 2015[9]). As a result of its increased specificity for $S1P_1$, ponesimod is proposed by the company to have fewer adverse effects than others in its class, however as with other DMTs, infections are still a potential concern due to its immuno-suppressive effects.

The company proposed that ponesimod may be used to treat people with active or highly active RRMS, and therefore could be considered as either a first- or second-line treatment for RRMS. As the line of treatment received by people with RRMS is guided by the balance in efficacy and safety shown by treatments, the appropriate positioning for ponesimod will be informed by clinicians' views towards its performance relative to existing treatments. The company further suggest that ponesimod may be preferred by people who prefer an oral treatment and/or a treatment with a shorter half-life. While covered under the licence, the company have not presented evidence for the use of ponesimod to treat people with SPMS, as few participants with SPMS were included in the trials of ponesimod. The ERG was unclear whether the company intended to position ponesimod towards people with RES RRMS: while people with RES RRMS were included in the company's clinical trials, and covered under the company's chosen definition of HA RRMS, the company excluded evidence for one of the treatments currently used to treat RES RRMS in the NHS (natalizumab).

Generally, the ERG considered that there may be a role for ponesimod to treat people with RRMS; however, there is no fixed position for ponesimod in the treatment pathway, due to variation in the pathway between people with RRMS, and the need to identify the relative balance of efficacy and safety of ponesimod. Clinical experts to the ERG stressed that DMT for HA RRMS need to show high efficacy, as there are efficacious treatments already available and

clinicians typically prefer an early, high efficacy treatment for people with this faster progressing disease course.

The ERG was aware that the treatment pathway for RRMS has changed within the context of the SARS-CoV 2 coronavirus pandemic, following updated guidelines from the Association of British Neurologists (ABN)[16]. As all DMTs interact with the immune system, the guidance aims to identify and prioritise those DMTs that pose a lower risk of infection or where the risk of lymphocyte rebound is greater than the risk of infection. The recommendations state that it is safe to start or continue on all NHSE first line treatments with the exception of ocrelizumab, as these DMTs pose a small risk of infection. Fingolimod poses a moderate risk of infection, but the risk of lymphocyte rebound is considered a larger risk. Alemtuzumab, cladribine and ocrelizumab are not recommended due to significantly heightened risk of viral infection. As ponesimod belongs to the same drug class as fingolimod, and is reported as having lower lymphocyte rebound, it is likely to pose a small to moderate risk of infection and would probably be considered safe in the pandemic context. There is uncertainty about when these guidelines will change, though clinical experts advised the ERG that some of the changes (for example around the frequency of monitoring) may be retained on a long-term basis.

2.3. Critique of company's definition of decision problem

The ERG's critique of the company's definition of the decision problem is provided in Table 8.

Table 8: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with relapsing MS	People with RRMS (limited to people with active RRMS and people with highly active RRMS)	The decision problem is focused on a sub-population of people with MS because there is limited evidence available for ponesimod in SPMS for health technology evaluation. The evidence presented in the submission is based on a RCT (OPTIMUM) that evaluated ponesimod compared to teriflunomide in people with RMS. At study entry, most people in the trial were diagnosed with RRMS (97.4%). The trial included only a small proportion of people with SPMS (2.6%). Phase 3 data for people with RRMS is more robust in people with active RRMS and highly active RRMS (35% of trial population) and so the submission focuses on these two subgroups i.e. not in people with RES RRMS.	The company positioning of ponesimod has been adjusted since the NICE scope to focus on the treatment of people with active and highly active RRMS, and to exclude people with SPMS. This means that the intended use of ponesimod following this appraisal is narrower than the product licence for ponesimod. The ERG agrees that the available evidence for ponesimod is strongest in these populations, and it would not be possible for the ERG to evaluate the clinical efficacy of ponesimod in the SPMS population. There is no internationally standard definition of highly active RRMS, and all definitions rely on the judgement of the treating clinician. This creates heterogeneity in the evidence base, and some uncertainty in generalising evidence to the UK HA population. The company's definition of highly active varies from the definition used by NHS England, and includes people with RES. At clarification, the company presented a post-hoc subgroup analyses of data

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				from their main trial in the RES population.
Intervention	Ponesimod	As per scope	N/A	The intervention in the company's main trial, OPTIMUM, matches the scope and licence for ponesimod. The company's Phase 2 trial compared the licensed dose of ponesimod with a higher and lower dose; the ERG appraisal of this trial is restricted to the licensed dose.
Comparator(s)	For people with active RRMS: • beta-interferon • dimethyl fumarate • glatiramer acetate • teriflunomide • ocrelizumab • peginterferon beta-1a • ozanimod (subject to ongoing NICE appraisal) • ofatumumab (subject to ongoing NICE appraisal) For people with highly active RRMS despite previous treatment: • alemtuzumab • cladribine • fingolimod • ocrelizumab (only if alemtuzumab is	For people with active RRMS (disease activity and treatment naïve): • beta-interferon • dimethyl fumarate • glatiramer acetate • teriflunomide • ocrelizumab • peginterferon beta-1a For people with highly active RRMS (i.e. disease activity whilst on 1st line therapy) • alemtuzumab • cladribine • fingolimod • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	At the time of submission, ozanimod and ofatumumab have not been recommended by NICE as treatment options for MS and cannot be considered as standard of care within the NHS. Therefore, they not been considered in the submission. The OPTIMUM trial included only [redacted] SPMS population, therefore it was deemed that there is insufficient evidence for this population In line with previous clinical trials in MS, the definition of highly active RRMS employed in the OPTIMUM trial was broad, and thus also incorporates people with RES RRMS as defined by NHS England [6,17,18]. As a result, separate subgroup analyses of people with	At the time of writing, the ERG understood that ozanimod and ofatumumab were still under consideration by NICE. Previous appraisals of technologies for RRMS have included evidence for technologies currently under appraisal by NICE, and it was the view of the ERG and NICE that the company should have therefore included these comparators in their evidence base and economic model. At clarification the company provided this evidence, however within the timeframe, the company stated that their updated submission would be less rigorous (e.g. less comprehensive searching, and limitations in the way these treatments were added to the model). The ERG nevertheless

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) • ofatumumab (subject to ongoing NICE appraisal) For people with RES RRMS • alemtuzumab • cladribine • natalizumab • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal) • ofatumumab (subject to ongoing NICE appraisal) For people with active SPMS (evidenced by continuing relapses) • established clinical management, including IFN-beta or other DMTs used outside their marketing authorisations • siponimod (subject to ongoing NICE appraisal)		RES RRMS were not part of the prespecified analysis.	considered the updated submission to be sufficient. The ERG agreed with the exclusion of siponimod as a direct comparator to ponesimod, due to the low numbers of people with SPMS included in the available trials. However, as SPMS health states were included in the company model, the ERG considered that evidence for siponimod should have been included in the company model (no treatment effects or costs for siponimod were included). The ERG was uncertain as to whether the company wish to position ponesimod for the treatment of people with RES RRMS; if so, the ERG considered that the company should have presented data for the relative efficacy of ponesimod to natalizumab.
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse	The outcome measures to be considered include: • relapse rate • ARR	The outcomes captured by the OPTIMUM clinical trial of ponesimod are relevant for people with active RRMS or highly active RRMS and are	The outcomes reported by the company for the trial OPTIMUM are relevant to the NICE scope, and clinically meaningful for evaluating the efficacy of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• disability (for example, EDSS) • disease progression • symptoms of MS (such as fatigue, cognition and visual disturbance) • freedom from disease activity (for example lesions on MRI scans) • mortality • adverse effects of treatment • HRQoL	• Time to first confirmed relapse • disability • change from baseline in EDSS score • disease progression • 12-week CDA • 24-week CDA • symptoms of MS • change from baseline in FSIQ-RMS score • freedom from disease activity • CUAL • NEDA-3 • NEDA-4 • adverse effects of treatment • mortality • HRQoL • Change from baseline in SF-36 score • Change from baseline in MSFC Z-score	representative of current clinical practice in England. Outcomes such as severity of relapse and mortality could not be included in the pharmacoeconomic analyses due to the absence of comparative trial data. The OPTIMUM trial did not formally measure severity of relapse, which is difficult to measure in trials for MS. The OPTIMUM trial captures new Gd+ T1 lesions plus new or enlarging T2 lesions, which can indirectly denote disease severity. OPTIMUM trial outcomes are in line with outcome measures in previous MS trials appraised by NICE.	treatments for RRMS. The ERG agreed that measuring relapse severity is challenging, though was aware that the importance of distinguishing the severity of relapse has been noted previously by NICE. In addition to the outcomes noted by the company, the ERG noted that the company also measured additional markers of severity, including duration of relapse and relapses requiring hospitalisation (the latter was retrieved from the trial CSR)[19]. The ERG noted that most outcomes were only comprehensively measured and/or reported for OPTIMUM, and only a subset of the outcomes were reported for the extension phase of OPTIMUM and the company's placebo-controlled Phase 2 trial.
Economic analysis	Cost utility analysis	As per the scope, a cost utility analysis has been presented, whereby QALYs were used to capture the health benefits of ponesimod and comparator treatments. Costs were considered from an NHS and Personal Social Services perspective. Carer disutility has been included in the company's base case.	N/A	The ERG considered that the cost utility analysis was appropriate and matched the analysis outlined by the company in the scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Subgroups	Highly active RRMS	As per scope	N/A	No comment
Special considerations including issues related to equity or equality	None	The company did not identify any equity or equality concerns in the scope	N/A	The ERG agreed that there are no equity or equality concerns to be considered in this appraisal.

Abbreviations ARR, annualised relapse rate; CDA, confirmed disability accumulation; CSR, clinical study report; CUAL, combined unique active lesions; DMT, disease modifying therapy; EDSS, expanded disability status scale; ERG, Evidence Review Group; FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire-relapsing multiple sclerosis; Gd+, gadolinium-enhancing; HA, highly active; HRQoL, health-related quality of life; IFN, interferon; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite measure; NA, not applicable; NEDA, no evidence of disease activity; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life years; RCT, randomised controlled trial; RES, rapidly evolving severe; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SF-36, 36-item short form survey; SPMS, secondary progressive multiple sclerosis

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The Company undertook a single systematic literature review (SLR) to identify evidence for ponesimod (summarised in Section 3.2) and to identify evidence for comparators to ponesimod to inform their indirect treatment comparison (Section 3.3 and 3.4). An overview of the methods used in the SLR is provided in Table 9 below.

Table 9: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D	The searches are thorough and well constructed. Searches have been run in three Ovid databases at once, and the results for each database have been extracted from the total results. The searches are therefore difficult to interpret or replicate but appear to be correctly executed. Suitable RCT filters have been used[20,21]. Search strategies for supplementary searches (e.g. in clinical trials registries) are not given, so it is not possible to determine how comprehensive these are. The ERG carried out some additional searches for multiple sclerosis NMAs in Medline and Embase from 2016 onwards (Appendix A) and found 1,044 papers. The company did not carry out any additional searches for adverse effects. Because the clinical effectiveness searches were limited to RCTs, any additional safety data not in RCTs may not have been found by the searches. The ERG carried out some additional searches for adverse effects for ponesimod in Medline and Embase (Appendix A) and found 148 papers, 30 of these were considered eligible following full-text screening.
Inclusion criteria	Appendix D	The ERG considered that that inclusion criteria used by the company in their review were broadly appropriate. However, the ERG disagreed with the

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		company's decision to exclude phase 4 trials from the NMA. The company rationale for this exclusion was due to variability in the methods used in phase 4 trials, however the ERG considered that problematic methods could have been accounted for in specific exclusion criteria. The ERG noted that these criteria led to the exclusion of several RCTs that have been included in previous NMAs of DMTs for RRMS, and could have expanded the available body of evidence for the company's analyses. However, the effect estimates for these comparators were not expected to alter greatly if the trials were included, and therefore the ERG did not investigate this further.
Screening	Appendix D	Conducted appropriately
Data extraction	Appendix D	Not described
Tool for quality assessment of included study or studies	TBA	Risk of bias assessment of OPTIMUM in the main body of the CS was reported according to the CRD tool, while the Cochrane risk of bias tool (version 1) was used to evaluate all RCTs included in the company's ITC. The Phase 2 trial and all trials included in the company's NMA were evaluated using the Cochrane risk of bias tool v.1. Both methods are appropriate for evaluating the quality of RCTs though the updated Cochrane v2 tool is generally preferred. No risk of bias assessment was reported for either of the long-term trial extensions to OPTIMUM or the Phase 2 trial.
Evidence synthesis	TBA	No synthesis of the ponesimod trials was conducted, as there is only one trial per comparison available. The company conducted several (number uncertain) NMAs to evaluate the comparative efficacy of ponesimod with other available treatments. Separate NMAs were conducted for trial-specified RRMS (ITT population, including both active and HA participants) and HA RRMS participants analysed in separate subgroup analyses. The ERG considered that further outcomes could have been evaluated in the NMAs, although as the company did not report their feasibility assessment in full, it is

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		not possible to determine if these outcomes were considered but found not feasible for analysis. The methods used in the NMAs were appropriate, though the ERG highlighted concerns about heterogeneity in the networks and the paucity of evidence, which both contributed to uncertainty in the results. The ERG also noted that several key outputs of the NMAs were not reported in the CS.

Abbreviations: CRD, Centre for Reviews and Dissemination; CS, Company submission; DMT, disease modifying therapy; ERG, Evidence Review Group; HA, highly active; ITT, intention-to-treat; NMA, network meta-analysis; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis

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

The company presented evidence for ponesimod from one head-to-head Phase 3 randomised controlled trial (RCT; OPTIMUM) and one Phase 2 placebo-controlled dose-finding trial in participants with RRMS (B202). Each of these studies were followed by an extension phase evaluating ponesimod only. An overview of the methods used in these studies is presented across the following sections (Sections 3.2.1 to 3.2.4).

3.2.1. Study design

The company's primary evidence for ponesimod is derived from OPTIMUM, a randomised, double-blind, parallel-group, multicentre Phase 3 trial of ponesimod 20 mg vs. teriflunomide 14 mg in participants with RRMS. The trial measured a broad range of clinical efficacy and safety outcomes up to 108 weeks. OPTIMUM is a well-designed RCT, and the ERG agreed with the company approach to place the evidence from this trial in greater prominence than the earlier Phase 2 trial. However, clinical advisors to the ERG cautioned that the trial follow-up may be too short to evaluate meaningful disease progression. This may lead to some uncertainty surrounding disability estimates, including impact on conversion to SPMS (where levels of disability are most pronounced. It was also noted that the sample size of OPTIMUM may be too small to identify the risk of rare, but serious adverse events.

The double-blind phase of OPTIMUM was followed by AC-058B303, a single-arm extension phase for those participants who completed the double-blind phase, and wished to continue on ponesimod or switch to ponesimod from teriflunomide. Follow-up of the extension was up to 132

weeks following the double-blind phase. The CS contains a subset of the clinical efficacy and safety outcomes measured for OPTIMUM for the extension phase, and a full clinical study report (CSR) for the extension phase was not provided by the company. However, despite reporting data at a longer follow-up than the core trial, treatment was open-label and uncontrolled, and is therefore of a lower evidence quality.

The Phase 2 trial, AC-058B202, was a randomised dose-finding trial of ponesimod, which compared three doses of ponesimod with each other and with placebo. The trial lasted 24 weeks, after which point all people receiving placebo were offered ponesimod. The extension phase lasted 552 weeks and consisted of three phases, over which groups were randomised to different doses of ponesimod until in the final phase all people received a 20 mg dose of ponesimod only (the current licensed dose). As differences in efficacy and safety were noted across the doses, for the purposes of this appraisal the ERG focused on the subset of people who received the 20 mg dose continually across all phases of the trial (n=147)

An overview of the trial designs is provided in Table 10.

Table 10: Overview of ponesimod trial designs

Study name and acronym	Study design	Phase	Intervention / Comparator	Study Objectives	Population
OPTIMUM; AC-058B301 [NCT02425644]	Randomised, double-blind, active-controlled parallel trial Follow-up: 108 weeks	3	Ponesimod 20 mg once daily / Teriflunomide 14 mg once daily	Efficacy and safety	N = 1,133 Participants with active RRMS who were treatment naïve or have received previous treatment with interferons, glatiramer acetate, natalizumab, or dimethyl fumarate. Participants were ambulatory, with EDSS score 0-5.5 at screening and baseline. Subgroup analyses were conducted in highly active RRMS.
OPTIMUM-LT; AC-058B303 [NCT03232073]	Single-group, open-label, non-comparative long-term	3	Ponesimod, gradually up-titrated over day 1 to 14 until a maintenance	Long-term safety and control of RMS	N = 877. Extension in participants who completed up to week 108 of the OPTIMUM trial.

Study name and acronym	Study design	Phase	Intervention / Comparator	Study Objectives	Population
	extension of OPTIMUM Follow-up: up to 132 weeks		dose of 20 mg is reached on day 15 / No comparator		
AC-058B201[a] [NCT01006265] (Olsson et al. 2014[22])	Randomised, double-blind, placebo-controlled dose-finding study Follow-up: 24 weeks	2b	Ponesimod 10, 20, or 40 mg once daily / Matching unspecified placebo once daily	Efficacy, safety and tolerability of ponesimod at various doses	N = 237. Participants with RRMS (per revised 2005 McDonald criteria[23]) with ≥ 1 documented relapse(s) within 12-months before screening, ≥ 2 relapses within 24 months before screening, or at least one T1-weighted Gd+ lesion on brain MRI at screening. EDSS score 0-5.5.
AC-058B202[a] [NCT01093326]	Randomised, double-blind, multiple-dose, uncontrolled long-term extension of AC-058B202 Follow-up: 528 weeks	2b	Ponesimod 10, 20, or 40 mg once daily / No comparator	Long-term efficacy, safety and tolerability of ponesimod at various doses	N = 147. Extension in participants who completed the dose-finding study AC-058B201.

Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; N, number; RRMS, relapsing-remitting multiple sclerosis

Notes: [a] Number of people reported are the total of those randomised to ponesimod 20 mg and placebo only

3.2.2. Trial populations

Population eligibility and characteristics are outlined in this section, including comparability of the trials and trial arms, and generalisability of the trial samples to the target population.

3.2.2.1. Eligibility criteria

Key inclusion and exclusion criteria used in the two included trials are summarised in Table 11 below. The trials identified participants according to the McDonald 2010[24] (OPTIMUM) and McDonald 2005[23] (Phase 2) criteria; while these criteria were most recently updated in 2017, the earlier versions are appropriate for this appraisal, as the update mainly affects those earlier in the disease course who would not normally be considered for DMT. The trials sought to exclude

people with progressive MS, including both primary and secondary progressive MS; however, OPTIMUM did include a small minority of people with SPMS in their final results. The most likely explanation for this is that the diagnosis of SPMS is often done retrospectively, and so participants may have received a diagnosis following inclusion in the trial. The age and EDSS inclusion criteria for participants in the trials were appropriate for the target population.

Both treatment-naïve and previously treated people were included in the trials, which aligns with the proposed positioning of ponesimod as either a first or second line treatment. Where appropriate, the previous DMT was required to have washed out prior to the start of the trial, and no previous treatment with cladribine or ocrelizumab was permitted.

The trials excluded people with certain cardiovascular (CV) comorbidities and abnormal liver diagnostics; this may have been a precaution as both are known risks with fingolimod treatment. These exclusion criteria were broadly comparable with the contraindications outlined in the licence for ponesimod, though the ERG noted that people who had experienced macular oedema in the past were still eligible for inclusion (macular oedema is also a known risk of treatment with S1P modulators. The exclusion of people at risk of these outcomes may also be an obstacle in identifying similarities in the safety profile of ponesimod and other S1P modulators.

For the long-term extensions, all participants who completed the core phases of each trial and were willing to continue were eligible for inclusion. However, those participants who discontinued ponesimod for any reason, including for adverse events (AEs) or lack of efficacy, would not have been included in the long-term trial extensions. This is generally reflective of likely use in UK practice since people who do not tolerate ponesimod for any reason will not continue on treatment for any extended period.

Table 11: Eligibility for the included trials

Study	Inclusion criteria	Exclusion criteria
OPTIMUM	Aged 18-55 MS with relapsing course from onset (2010 revised McDonald[24] criteria): • 1+ attacks with onset within 12-1 months prior to baseline EDSS or; • 2+ attacks with onset within 24-1 months prior to baseline EDSS or; • 1+ (Gd+) lesions on an MRI within 6 months prior to baseline EDSS Treatment-naïve or previously treated with IFN beta-1a, IFN beta-1b, glatiramer acetate, natalizumab, or dimethyl fumarate Ambulatory with EDSS of 0-5.5 Agreed to use an accelerated elimination for teriflunomide after study	Lactating/pregnant women Progressive MS Significant medical conditions or receiving therapies for such conditions Unlikely to comply
B201	Aged 18-55 Presented with RRMS as defined by revised McDonald criteria (2005) At least one of the following characteristics of RRMS: • 1+ relapse within 12 months prior to screening • 2+ relapses within 24 months prior to screening • 1+ Gd+ lesion Ambulatory with EDSS 0-5.5 No exacerbation last 30 days	Progressive MS Treatment with the following medications within 30 days prior to randomisation: Systemic corticosteroids or adrenocorticotropic hormone Beta-blockers, diltiazem, verapamil or digoxin or QT-prolonging drugs Pregnancy; or women breast-feeding Treatment with certain DMTs and immunosuppressive agent within 3-6 months of trial start Treatment with the following medications at any time prior to randomization: Cyclophosphamide, mitoxantrone or cladribine

Study	Inclusion criteria	Exclusion criteria
		Lymphocyte-depleting biologic agents
		Autoimmune disorder other than MS
		Ongoing bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), positive hepatitis B surface antigen or hepatitis C antibody tests
		Certain current infections
		History or presence of malignancy
		Poorly controlled type I or type II diabetes and associated complications
		History of clinically significant drug or alcohol abuse
		People with certain CV or pulmonary conditions
		Abnormal LFTs
		Abnormal blood test results
		Known allergy to any of the study drug excipients
		Any other condition which would put the person at risk by participating in the study
		Unlikely to comply

Abbreviations: CV, cardiovascular; DMT, disease modifying therapy; EDSS, expanded disability status scale; Gd+ gadolinium-enhancing; IFN, interferon; LFT, liver function test; MRI, magnetic resonance imaging; MS, multiple sclerosis; QT, start of the Q wave to end of the T wave on electrocardiogram; RRMS, relapsing-remitting multiple sclerosis

3.2.2.2. Baseline characteristics

The baseline characteristics of the participants in the included trials are summarised in Table 12 alongside comparative characteristics of the UK risk-sharing scheme (RSS) population. No separate population characteristics were reported for the HA populations included in the included trials. In the following sections, the ERG summarised the comparability of the trial arms in the included trials, as well as the relevance of the trial populations to the NHS target population.

Table 12: Baseline characteristics of the intention-to-treat populations of the included trials, and their comparability with UK risk-sharing scheme populations

Characteristic	OPTIMUM		Phase 2 trial (B202)		UK RSS[25]
	Ponesimod	Teriflunomide	Ponesimod 20mg	Placebo	
Age (SD)	36.7 (8.74)	36.8 (8.74)	35.5 (8.5)	36.6 (8.6)	39.4(9.05)
Female	64%	65.7%	67.5%	70.2%	74.2%
Received 1+ prior DMT	[redacted]	[redacted]	35.1%	39.7%	
DMT received in 2 years prior to randomisation	37.6%	37.3%			
EDSS (Median (Q1-Q3))	[redacted] Range: [redacted]	[redacted] Range: [redacted]	2.0 (1.5-3.0) Range: 0.0-5.5	2.0 (1.5-3.0) Range: 0.0-5.5	3.5 (2.0-5.0)
Years since first symptoms at randomisation (SD)	7.63 (6.781)	7.65 (6.782)	7.3(6.25)	6.9(5.7)	8.8(7.47)
Mean relapses within year prior to study	1.2 (0.61)	1.3 (0.65)			

Characteristic	OPTIMUM		Phase 2 trial (B202)		UK RSS[25]
entry (SD)					
Mean months since last relapse (SD)	[redacted]	[redacted]	5.1(5.51)	5.6(4.53)	
Disease subtype	97% RRMS 3% SPMS	98% RRMS 2% SPMS			86.2% RRMS 13.8% SPMS
Presence of Gd+ T1 lesions	39.9%	45.4%	40%	47.4%	
Number of T2 lesions	[redacted]	[redacted]			
Mean volume of T2 lesions (mm^3 (SD))	8301.4 (10346.28)	9489.2 (11265.42)	7747(10,005)	6125(8988)	
Mean BMI kg/m^2 (SD)	[redacted]	[redacted]			
Geographic region	[redacted]	[redacted]			
Mean FSIQ-RMS weekly symptom	31.9 (20.4)	32.8 (19.1)			

Characteristic	OPTIMUM		Phase 2 trial (B202)		UK RSS[25]
s score (SD)					
% of people 'highly active'	35.6%	35.3%			
% of people with RES	[redacted]	[redacted]			
White race	97.2%	97.7%	98.2%	94.2%	
Number of relapses in last 24 months	NR	NR	0 – 1.8% 1 – 43% 2+ - 55.3%	0 – 0.8% 1 – 40.5% 2+ - 58.7%	3 (2-3) Median (quartiles)
Mean relapses in last year (SD)	1.2 (0.61)	1.3 (0.65)	1.2 (0.62)	1.3 (0.68)	
Mean number of Gd+ T1 lesions (SD)	NR	NR	2.5 (6.61)	1.7 (3.31)	

Abbreviations: BMI, body mass index; DMT, disease modifying therapy; EDSS, expanded disability status scale; EU, European Union; FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire-relapsing multiple sclerosis; Gd+ gadolinium-enhancing; Q1, quartile 1; Q3, quartile 3; RES, rapidly evolving severe; RoW, rest of the world; RRMS, relapsing-remitting multiple sclerosis; RSS, risk-sharing scheme; SD, standard deviation; SPMS, secondary progressive multiple sclerosis

Comparability of trial arms

The baseline characteristics of participants in the ITT population of the included studies were balanced across arms. Randomisation had been stratified by EDSS score at baseline and prior DMT in the previous two years. Baseline characteristics were not reported separately for the HA population, and so it was not possible to determine if characteristics were also balanced for the company's subgroup analyses.

Relevance of trial populations to the target population

Based on the data reported, the ITT population characteristics in both included trials investigating ponesimod appear broadly similar to people in the UK population who are eligible for first or second line DMTs; this was a view shared by clinical advisors to the ERG. The EDSS scores in both ponesimod trials appear marginally lower than in the RSS population[25], suggesting that people in the trials had lower disability than the target population; however this is likely due to a higher proportion of people with SPMS in the RSS population, and because people in the RSS population generally had a longer disease course without early access to DMT.

However, the definition of HA RRMS used in OPTIMUM included people with RES RRMS, which varies from the definition used in the NHS. Overall, [redacted] of the people in OPTIMUM had RES, equating to [redacted] of the highly active population. People diagnosed with RES are at a higher risk of disease progression, and therefore absolute clinical outcomes may vary from the active and highly active RRMS populations. It is unclear whether treatment efficacy may also vary in people with RES, though they may be treated with different, more efficacious treatments earlier in the disease course (and typically not with teriflunomide). The variation in the definition of HA reflects the international nature of the OPTIMUM trial, given that there is no universally accepted definition of 'highly active' RRMS (see Section 2.1 and Table 13 below for a comparison of these definitions). The generalisability of evidence to different RRMS populations is an area of uncertainty within this appraisal.

The ERG noted that participants in OPTIMUM had on average been symptomatic for over seven years, and that [redacted] were treatment naïve, with the remaining [redacted] having had at least one DMT previously. Clinical advice to the ERG was that use of DMT within the first two years of the disease is associated with better outcomes, though the ERG was aware that many people with RRMS choose not to receive DMT. Amongst participants who had previously

received DMT, previous treatments were generally consistent with those prescribed in the NHS, though as to be expected with an international trial, some minor differences were noted. Notably, the inclusion of participants with HA RRMS in OPTIMUM is an alteration from the NHS treatment pathway, as teriflunomide is not used to treat HA RRMS in the UK.

The ERG was unclear to what extent evidence from this population would generalise across populations at different lines of treatment; the company did not report any subgroup analyses according to line of treatment, and little is known about how treatment effects vary according to the previous treatments people with RRMS have received. Clinical advice to the ERG was that evidence from people who have stopped treatment due to a lack of efficacy may represent people with more active disease, and therefore subgroup analyses in the HA population may identify if treatment effects vary as compared to the main ITT population. The ERG recognised the broad inclusion criteria of OPTIMUM as an attempt to evaluate ponesimod across a broad RRMS population; however, the trial was potentially not large enough for comprehensive subgroup analyses to explore variation in treatment effects across variability in the trial population. As little is known about effect modifiers in the broader RRMS literature, there is some uncertainty about the generalisability of evidence from the included trials to the target NHS populations.

Table 13: Currently used definitions of highly active disease

Source	Definition of highly active population	Includes RES
OPTIMUM	Any DMT for MS received within 12 months prior to randomisation and one or both of the following: - ≥1 relapse within 1 year prior to study entry and the baseline MRI read centrally showed either ≥1 Gd+ T1 lesion and/or ≥9 T2 lesions. - Number of relapses within 1 year prior to study entry ≥ number of relapses between 2 and 1 year prior to study entry, for people with at least one relapse within 2 years prior to study entry. ≥2 relapses within the 1 year prior to study entry and baseline EDSS score >2 and baseline MRI read centrally showed ≥1 Gd+ T1 lesion.	Yes
NHS	People with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon.	No
TA254[14] (25/04/2012)	People with high disease activity despite treatment with a beta-interferon. A treatment failure is defined as a lack of response to a full and adequate course of beta interferon (normally at least one year of treatment). People should have had at least one relapse in the previous year while on therapy and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. They may also be defined as people with an unchanged or increased relapse rate or ongoing severe relapses compared to the previous year	No
TA312[2] (28/05/2014)	Adults with high disease activity despite treatment with a beta interferon (normally at least one year of treatment). People have at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion; OR unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.	Yes
TA533[26] (25/07/2018)	Treated with interferon or glatiramer acetate for ≥1 year and had: (1) ≥1 relapse in the previous year; (2) ≥1 gadolinium-enhancing T1 lesion at baseline; (3) ≥9 hyperintense T2 lesions at baseline.	No
TA616[27] (19/12/2019)	The NICE committee considered that the sub optimally treated (SoT) group in the company submission best reflected the UK HA population. SoT was defined as at least 1 relapse in the previous year while the person was on disease-modifying therapy, and at least 1 T1 gadolinium-enhancing lesion or 9 T2 lesions	Yes

Abbreviations: DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HA, highly active; MRI, magnetic resonance imaging; MS, multiple sclerosis; RES rapidly evolving severe; SoT, suboptimally treated

3.2.3. Intervention characteristics

The intervention characteristics delivered during the included trials are summarised in Table 14 below. Ponesimod is delivered as an oral treatment taken as one 20 mg tablet each day. This dose was selected following the company's Phase 2 dose-finding trial, which also evaluated a lower (10 mg) and higher (40 mg) dose of ponesimod. This trial showed that the higher dose of ponesimod resulted in an increased risk of adverse events without a commensurate benefit for efficacy. Interestingly, a recent analysis reported that a 40 mg of ponesimod resulted in the worst rate of discontinuations due to adverse events as compared to other DMTs in the active population (Tong 2021 et al.[28]). No reductions or increases in dose were permitted during OPTIMUM, and none are specified in the licence for ponesimod.

The company recommends a period of up-titration for ponesimod, which they stated in section B.2.50 of the CS is to avoid cardiac adverse events such as those associated with fingolimod. Different up-titration protocols were used in the two trials, with a longer (two weeks) period used in OPTIMUM compared to the Phase 2 trial (one week).

Many concomitant therapies were used by participants in OPTIMUM to manage the symptoms of RRMS and adverse events experienced during the trial. Their use was broadly comparable between the ponesimod and teriflunomide arms; however, the ERG noted lower use of corticosteroids in the ponesimod arm (31.4% of the ponesimod group used corticosteroids, compared to 43.1% of those in the teriflunomide arm). Corticosteroids have an established safety profile, though side effects were considered unlikely to alter the efficacy of treatments in the trial.

Table 14: Intervention characteristics of the included trials

Trial		Treatment
OPTIMUM	Ponesimod	Up titration at initiation from 2 mg to 10 mg over first 14 days 20 mg daily from Day 15 onwards 108 weeks
	Teriflunomide	Mock up-titration of 14 mg for first 14 days 14 mg taken daily 108 weeks
OPTIMUM Extension		As above, up to 240 weeks
Phase 2 trial (B201)[a]		10 mg on days 1-7 Up-titrated to 20 mg on Day 8

Trial		Treatment
		24 weeks
B201 Extension	10mg Group	10 mg up to 96 weeks (core study and TP1) 10 mg during TP2 Increased to 20 mg for TP3
	20 mg Group	20 mg up to 432 weeks (TP1, 2 and 3)
	40 mg Group	40 mg up to 96 weeks (core study and TP1) Randomised 1:1 to 10 mg and 20 mg for TP2 All received 20 mg in TP3
	Placebo	Once daily placebo for 24 weeks Placebo populations switched to one of the above treatment regimens for long term extension

Abbreviation: TP, treatment period

Notes: [a] As a dose-finding study, Olsson et al.[22] also treated groups with 10 mg and 40 mg, the ERG has excluded these groups here as they are outside the licensed dose.

3.2.4. Clinical effectiveness results

3.2.4.1. Outcome measurement

As noted previously, the choice of DMT for RRMS frequently involves a trade-off between efficacy and safety (see Section 2.2). Clinical advice to the ERG was that the clinical efficacy of DMTs is firstly demonstrated by a reduced risk of relapse, including neurological evidence that disease progression is delayed (e.g. reduced number and size of lesions). Reduced disability and impact on HRQoL are also important outcomes, and clinical advice was that reducing the relapses may lead to benefits in these outcomes. DMTs are not expected to reverse disease progression or disability, and therefore efficacy is demonstrated by stability or slower disease progression at follow-up.

Specific safety concerns associated with DMTs for RRMS include infection, due to the immune-suppressive mechanisms of the treatments, hypertension and cardiac events, liver disorders, malignancy, and macular oedema. The ERG noted that fingolimod, also a sphingosine 1-phosphate (S1P) receptor modulator, has been associated with an increased risk of liver and cardiac events[29], which means that some people are ineligible for treatment, and increased monitoring for adverse effects is required during treatment.

The company reported a range of absolute and relative effect estimates to evaluate the efficacy of ponesimod. The clinical efficacy outcomes reported by the company can be grouped into measures of the *risk of relapse*, *neurological/radiological outcomes*, and measures of *disability and HRQoL*. In addition, the company reported *safety* based on the risks of treatment-emergent adverse events and discontinuation due to adverse events. The company also reported *additional outcomes*, including rates of NEDA, which is the rate of people demonstrating an absence of disease activity as a composite of several clinical outcomes, and the rate of all-cause discontinuation, which represents discontinuations due to either efficacy or tolerability (or trial attrition). The bulk of these outcomes were only measured and reported for OPTIMUM, with a subset only report for the long-term phase of OPTIMUM and for the Phase 2 trial. An overview of outcome definitions and their measurement is provided below. These descriptions also capture limitations with measurements in the included trials.

Relapse

Clinical advice to the ERG was that the company's definition of relapse was broadly appropriate: the company defined relapse as new, worsening, or recurrent neurological symptoms occurring ≥30 days following the onset of a prior relapse and sustained ≥24 hours without fever or infection (CS Document B, p. 45). However, clinical advice to the ERG was that this definition may include an exacerbation of symptoms caused by anxiety or stress that is not a relapse. This difficulty highlights the subjective nature of measuring relapse, which requires the judgement of the person with RRMS and their clinicians.

The primary outcome of OPTIMUM was annualised relapse rate (ARR), which represents the number of reported relapses per patient-year. The average relapse rate for people receiving ponesimod at baseline was

[redacted]

The company reported a variety of further measures to characterise the efficacy of ponesimod on relapse rates, including: time to first confirmed relapse; proportion of participants with ≥1 relapse; duration of relapse; and rates of relapse requiring corticosteroids. The ERG also identified rates of relapse resulting in hospitalisations and A&E admission from the trial CSR[30]. As discussed in Section 2.3, previous NICE appraisal committees have highlighted the importance of distinguishing variation in the severity of relapses experienced by people. The

severity of relapse is challenging to define, though relapse resulting in hospitalisation is sometimes used.

Neurological/radiological outcomes

The company reported a range of neurological and radiological outcomes, including the proportion of new or enlarging lesions across various definitions, and magnetisation transfer ratio (MTR) values. These outcomes are typically challenging to interpret, due to reliability issues in MRI measures and uncertainty about the relationship of the measures with disease progression. However, clinical advice to the ERG was that the rate of combined unique active lesions (CUALs) and loss in brain volume are both considered to be useful markers of disease progression. At clarification, the company noted that measurement of CUAL may vary across trials, thus making any evaluation challenging.

Disability

The principal measure of disability used in evaluations of DMT for RRMS is the time to confirmed disability accumulation (CDA), which is a measure of sustained, meaningful change in disability. The company definition is consistent with previous appraisals; i.e. an increase of ≥1.5 in expanded disability status scale (EDSS) score for people with a baseline EDSS score of 0.0, an increase of ≥1.0 for people with a baseline score of 1.0 to 5.0, or an increase of ≥0.5 for people with a baseline score of ≥5.5. To account for natural fluctuation in RRMS, a change in disability is considered to have occurred if the change in EDSS score is maintained for a prolonged period. The company evaluated CDA confirmed at 12 weeks (CDA at 3 months, or CDA-3) or at 24 weeks (CDA at 6 months, or CDA-6). While these time periods are consistent with those evaluated in previous appraisals of RRMS treatments, committees have commented that these time periods may be too short to evaluate a meaningful change in disability. These concerns were echoed by clinical advice to the ERG. The company also separately reported change in participants' EDSS scores.

Health-related quality of life and participant-reported outcomes

Health-related quality of life (HRQoL) was measured by the SF-36 (domain and composite scores); however, these data were not reported in the CS, apart from some categorised data of the proportion of people who considered their health to be 'much better' during the trial. The ERG considered the latter data to be highly limited, and the absence of HRQoL data in the CS

was considered to be a major omission. These data were therefore retrieved from the trial CSR[30].

Additional participant-reported outcome data was available from the Multiple Sclerosis Functional Composite (MSFC) scale. The MSFC combines three separate measures to assess lower extremity, upper extremity, and cognitive function. People are asked to complete a series of tasks, which are then rated by a trained observer. For each measure, participants' scores are standardised into a z-score using a reference population (e.g. representing the standard deviation from baseline scores for the trial population), which are then combined to give an overall measure of function across the three measures. Higher positive scores were associated with improvement, while negative scores were associated with deterioration. It has been suggested that a change of 15-20% can be considered clinically meaningful; a threshold chosen in part because lower thresholds may reflect natural fluctuations in functioning[31]. The company did not report a threshold to interpret the results of the MSFC, and data were not reported as a percentage change.

The Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis (FSIQ-RMS) is a new scale developed by the company[32] to measure fatigue, which can significantly affect the lives of people with RRMS. The company proposed that this scale better represents the symptoms of fatigue in RRMS than other available measures as it evaluates both cognitive and physical symptoms. The FSIQ-RMS consists of two scales, one measuring symptoms and one measuring the impact of symptoms. On both scales, higher scores represent more fatigue or impact. As the FSIQ-RMS is a new tool, it has not been evaluated in previous appraisals or research, and the associated publication did not report a threshold for what change or difference in scores would be considered clinically meaningful.

No HRQoL or PRO outcomes were considered in the company's ITC.

Safety

The ERG noted that ascertainment of AEs was conducted through voluntary reporting or non-directed interviewing of participants, and considered this approach to be reasonable. Safety assessments for post-treatment follow-up, both for those entering the extension of OPTIMUM and those who did not, as well as post-treatment observation, for those people who discontinued the study prematurely, as reported in the CSR for OPTIMUM[19] appear reasonable.

From the Phase 2b core study publication (Olsson 2014[22]), the details of these assessments appear similar to those for OPTIMUM.

S1P modulators such as fingolimod and ozanimod have known safety concerns, i.e. cardiovascular, immune, ophthalmologic, pulmonary and hepatic effects (Novartis 2019[29], Gajofatto & Benedetti 2015[9], Swallow 2020[33]). The coverage of safety assessments for people treated with ponesimod, as reported by the company in the CSR for OPTIMUM[19] and for the Phase 2b core study (Olsson 2014[22]), seemed reasonable.

With regards to the handling of data, the company reported receiving scientific advice approving of the pooling strategy of safety data across the Phase 2b and OPTIMUM trials, as well as their extensions, with consideration given to differences in characteristics of the trials.

Clinical advice to the ERG indicated that the length of follow-up of the included trials for ponesimod may not be sufficient to detect rare, serious AEs; as has been the case in the NICE appraisal of fingolimod (TA254) in 2012. Following approval, cases of progressive multifocal leukoencephalopathy (PML) have occurred in the post-marketing context. The duration of both trials assessing direct comparisons of fingolimod in this appraisal were 12 and 24 months, [redacted]). The company reported [redacted] in the Phase 2b study and its extension, indicating that some rare serious AEs, were they to have occurred, may have manifested by the time of submission, though the sample size of this study is very limited (n=[redacted]).

Other outcomes

The company also reported NEDA, representing the absence of disease activity according to several levels of criteria. The company cited references proposing that NEDA-3 (the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions and 12-week CDA) is considered to be a valuable treatment goal of DMT, as it may have a stronger association with long-term outcomes as compared to single measures. However, the ERG understood that there is uncertainty about whether the criteria appropriately measure disease progression, and to what extent this outcome is able to predict further progression. The company reported data from OPTIMUM for NEDA-3 as well as NEDA-4 (NEDA-3 criteria plus absence of brain atrophy). Neither outcome was considered in the company's NMA.

The company also reported data for the rate of all-cause discontinuation. This outcome could be considered to represent a composite of discontinuation due to either efficacy or safety, though it

could also include discontinuation due to trial attrition. As DMTs for RRMS often involve a compromise of efficacy and safety, comparisons of all-cause discontinuation will derive very different results from analyses restricted to discontinuation due to either efficacy or safety.

3.2.4.2. Results

Clinical efficacy

Key clinical efficacy results for the ITT populations in the OPTIMUM trial and its extension, and the Phase 2 trial and its extension, are summarised in Table 15. The company did not report clinical effectiveness data specifically from the Phase 2 placebo-controlled trial of ponesimod (B201), opting instead to report limited clinical efficacy data from across the core and long-term phases of the trial; however the ERG identified select data points from the trial CSR[19]. Limited data only were provided by the company for the long-term extension of OPTIMUM in the CS, and no full CSR was provided to the ERG.

Overall, the results showed [redacted]. Measures of brain volume loss, CUALs, and NEDA also suggested that participants receiving ponesimod [redacted]. The ERG noted that [redacted]. Both OPTIMUM and the Phase 2 trial showed [redacted] in the ponesimod arm, [redacted]

However, [redacted]

[redacted]

No data for these outcomes were reported for the Phase 2 trial.

The company reported that ponesimod was associated with [redacted]

Data from OPTIMUM suggested that approximately [redacted]. A similar breakdown was not available in the Phase 2 trial, though overall rates of discontinuation were [redacted].

Table 15: Clinical effectiveness results for ponesimod (ITT population; OPTIMUM and Phase 2 trial)

Outcome	Outcome measurement	OPTIMUM Follow-up 108 weeks		OPTIMUM Extension. Follow-up 132 weeks	B201 Follow-up 24 weeks		B201 Extension Follow-up 432 weeks
Treatment		Ponesimod	Teriflunomide	Ponesimod	Ponesimod[#]	Placebo	Ponesimod[#]
ITT sample		567	566	877	116	121	145
Relapse	Total relapses (n)	242	344	NR	[redacted]	[redacted]	[redacted]
	ARR (mean)	0.202 (95%cl 0.173, 0.235)	0.290 (95%cl 0.254, 0.331)	[redacted]	[redacted]	[redacted]	[redacted]
	ARR (relative rate)	0.695 (95%cl 0.570, 0.848)[¥]		-	[redacted]		-
	Population with ≥1 relapse (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Time to first relapse (HR)	[redacted]		-	[redacted]		-
	Median (IQR) duration of relapse (days)	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
	Relapses requiring corticosteroid treatment	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
	Relapses requiring hospitalisation	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
	Relapses requiring A&E admission	[redacted]	[redacted]	NR	NR	NR	NR
3-month CDA	Rate (%)	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]

Outcome	Outcome measurement	OPTIMUM Follow-up 108 weeks		OPTIMUM Extension. Follow-up 132 weeks	B201 Follow-up 24 weeks		B201 Extension Follow-up 432 weeks
	HR	0.83 (95%cl 0.58, 1.18)		-	NR		-
6-month CDA	Rate	8.1%	9.9%	[redacted]	NR	NR	[redacted]
	Risk reduction	0.84 (95%cl 0.57, 1.24)		-	NR		-
Trial discontinuation	All-cause	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
	Rate due to safety or tolerability	[redacted]	[redacted]	NR	NR	NR	[redacted]
	Rate due to efficacy	[redacted]	[redacted]	NR	NR	NR	[redacted]
CUALs	Mean (annualised)	1.405	3.164	NR	NR	NR	[redacted]
	RR (95%CI)	0.44 (0.364, 0.542)		-	NR		-
Brain volume loss	LS mean Δ	-0.91%	-1.25%	NR	NR	NR	NR
	LS mean difference (95%CI)	0.34% (0.17, 0.50)		-	NR		-
	Rate of populations with annual brain volume decrease ≥0.4% from baseline	33%	42%	NR	NR	NR	NR
Fatigue	FSIQ-RMS LS mean Δ from baseline	-0.01	3.56	NR	NR	NR	NR
	LS MD	-3.57 (95%cl -5.83, -1.32)		-	NR		-

Outcome	Outcome measurement	OPTIMUM Follow-up 108 weeks		OPTIMUM Extension. Follow-up 132 weeks	B201 Follow-up 24 weeks		B201 Extension Follow-up 432 weeks
	OR for improvement or stable response (Δ≤6.3 from baseline)^	[redacted]		-	NR		-
mFIS	Mean Δ from baseline	[redacted]	NR	NR	[redacted]	[redacted]	NR
EDSS	Mean Δ from baseline	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
	LS Mean diff	[redacted]		-	NR		-
NEDA	NEDA-3 (rate)	[redacted]	[redacted]	NR	NR	NR	NR
	NEDA-3 (OR)	1.70 (95%cl 1.27, 2.28)		-	NR		-
	NEDA-4 (rate)	[redacted]	[redacted]	NR	NR	NR	
	NEDA-4 (OR)	1.85 (95%cl 1.24, 2.76)		-	NR		-
MSFC	LS mean change in z-score	[redacted]	[redacted]	NR	NR	NR	NR
	LS mean difference	[redacted]		-	NR		-
SF-36	Physical component mean (SD)	[redacted]	[redacted]	NR	NR	NR	NR
	Mental component mean (SD)	[redacted]	[redacted]	NR	NR	NR	NR

Abbreviations: A & E, Accident and Emergency; ARR, annualised relapse rate; CDA, confirmed disability accumulation; CI, confidence interval; CUAL, combined unique active lesions; EDSS, Expanded Disability Status Scale (scale 0-10; higher is poorer outcome); FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis; HR, hazard ratio; IQR, interquartile range; ITT, intention-to-treat; LS, least squared; MD, mean difference; mFIS, Modified fatigue impact scale (scale 0 – 84, higher is poorer outcome); MSFC, multiple sclerosis functional composite measure; NR, not reported, NEDA, no evidence of disease activity; OR, odds ratio; RR, relative risk; SD, standard deviation; SF-36, short-form-36 health survey; TEAE, treatment-emergent adverse event

Source: CS, Document B and the trial CSR[19]; All-cause discontinuation data is from the company's clarification response

[#] Figures reported are for populations who received 20mg throughout the trial. $from baseline of OPTIMUM through to end of follow-up period ¥Adjusted for EDSS strata (≤3.5 vs >3.5), DMT in 2 years prior to trial, and number of relapses in year prior to trial (≤1 vs ≥2). [≠]Effects for ARR are reported in the per protocol population.

Subgroup analyses

The company reported subgroup analyses of the OPTIMUM trial data for HA participants (pre-planned definition that included participants with RES; [redacted]), HA participants according to the NICE definition (post-hoc analysis excluding RES participants; [redacted]), for the RES population (post-hoc analysis; n=[redacted]), and for the ITT population excluding participants with SPMS (pre-planned analysis; [redacted]). Few outcomes were reported for each of the subgroup analyses, and as 95% confidence intervals were proportionally wider for each analysis, it was difficult to draw conclusions about whether population was an effect modifier. As to be expected, the absolute rates of relapse and disability were [redacted] in both arms of OPTIMUM as compared to the ITT population, at follow-up, [redacted].

[redacted]

In general, relative treatment effects are stable across baseline risk, and clinical advisors to the ERG were unaware of any reason why treatment efficacy would vary across the difference RRMS subgroups. A comparison with the results for the ITT population showed [redacted] for both CDA-3 and CDA-6 as compared to teriflunomide in the HA and RES groups; [redacted] The ERG identified evidence from the CSR of OPTIMUM(OPTIMUM trial CSR[19]) [redacted]

- CDA-3: [redacted]
- ARR: [redacted]

Unsurprisingly, [redacted]. Population subgroup analyses were not reported for the Phase 2 trial, due to there being a lack of statistical power.

Table 16: Population subgroup analyses from OPTIMUM (HA, HA excluding RES, RES, and ITT excluding SPMS)

Outcome	Measurement	OPTIMUM HA		OPTIMUM HA (NICE definition)		OPTIMUM RES		OPTIMUM ITT excluding SPMS	
Treatment		Ponesimod	Teriflunomide	Ponesimod	Teriflunomide	Ponesimod	Teriflunomide	Ponesimod	Teriflunomide
ITT sample		202	200	177	172	34	40	552	552
Relapse	ARR (mean, 95%cl)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ARR (rate ratio, 95%cl)	[redacted]		[redacted]		[redacted]		[redacted]	
3-month CDA	Rate (%)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
	HR	[redacted]		[redacted]		[redacted]		[redacted]	
6-month CDA	Rate (%)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
	Risk reduction (95%cl)	[redacted]		NR		[redacted]		[redacted]	
CUALs	Mean	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]	[redacted]
	RR	[redacted]		NR	NR	NR	NR	NR	
Fatigue	FSIQ-RMS LS mean Δ from baseline	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]	[redacted]
	LS MD (95%cl)	[redacted]		NR	NR	NR	NR	[redacted]	

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; CI, confidence interval; CUAL. combined unique active lesions; FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis; HA, highly active; HR, hazard ratio; ITT, intention-to-treat; LS, least squared; MD, mean difference; NICE, National Institute for Health and Care Excellence; RES, rapidly evolving severe; RR, relative risk; SPMS, secondary progressive multiple sclerosis

Adverse effects

The company reported direct safety evidence for ponesimod from OPTIMUM and the Phase 2 core study, as well as a long-term safety set pooling evidence from all participants receiving ponesimod during OPTIMUM, its extension (OPTIMUM-LT), the Phase 2 trial, or its extension. Safety evidence from a sample of all randomised participants in the OPTIMUM trial who received a dose of either ponesimod 20 mg or teriflunomide 14 mg resulted in a comparative safety set of 1,131 participants. Only two participants who should have, but did not, receive ponesimod 20 mg were excluded from this analysis. No separate comparison of AEs was reported for different population subgroups.

Results provided by the company for overall treatment-emergent adverse events (TEAEs) in OPTIMUM are presented in Table 17, and showed that the vast majority of participants experienced one or more TEAE.

Table 17: Participants with at least one treatment-emergent adverse event in the OPTIMUM trial

Person with at least one:	Ponesimod 20 mg n=565 (%)	Teriflunomide 14 mg n=566 (%)
AE	502 (88.8)	499 (88.2)
Severe AE	[redacted]	[redacted]
AE leading to study discontinuation	49 (8.7)	34 (6.0)
Serious AE	49 (8.7)	46 (8.1)

Abbreviations: AE, adverse events

The company reported similar overall TEAEs in the ponesimod 20 mg (88.8%) and teriflunomide 14 mg (88.2%) groups, though higher rates of treatment discontinuations due to adverse events (AEs) were observed in the ponesimod group (8.7%) when compared to the teriflunomide group (6.0%). The proportion of participants with serious TEAEs are similar across treatment groups: 8.7% of participants in the ponesimod group and 8.1% of participants in the teriflunomide group experienced a serious TEAE; though no TEAEs in either group were fatal. Two fatalities occurred in the teriflunomide group but were considered unrelated to teriflunomide by the study investigator; no fatalities occurred in people treated with ponesimod in the OPTIMUM trial. Clinical advice to the ERG suggested that this rate of TEAE is broadly consistent with other DMTs, though noted that the sample size and length of follow-up in the trials may not yet have identified rare serious side effects.

The company reported the rates of AEs experienced by ≥5% of people in the CS (CS appendices, page 185); the ERG has summarised TEAEs of particular interest in Table 18.

Table 18: Incidence of key treatment-emergent adverse events in the OPTIMUM trial

Safety set	Ponesimod 20 mg n=565 (%)	Teriflunomide 14 mg n=566 (%)
People with ≥1 TEAE, n (%)	502 (88.8)	499 (88.2)
Infections[a]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
AST increased	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
UTI	[redacted]	[redacted]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; UTI, urinary tract infection

Note:
a Composite number of people with infections comprising nasopharyngitis, upper respiratory tract infection, urinary tract infection; total number of all infections may therefore be greater

From these data, the ERG noted that hepatobiliary disorders and liver test abnormalities occurred more frequently in the ponesimod arm, but a lower proportion were serious as compared to the teriflunomide arm. It was unclear from the data presented by the company whether ponesimod posed a higher risk for cardiac disorders when compared to teriflunomide over the course of treatment, but the evidence indicated that ponesimod may lead to an increased risk of cardiovascular effects initially than teriflunomide.

[redacted] of TEAEs related to [redacted] ([redacted] versus [redacted] in the ponesimod and teriflunomide groups, respectively), before becoming more comparable over the full course of the study ([redacted] in the ponesimod and [redacted] in the teriflunomide group). However conversely,

[redacted]

Ponesimod was also associated with

[redacted]

[redacted]).

[redacted]

The paper by Olsson et al. (2014)[22] reported the safety results of the Phase 2 core study. The results were similar to those reported for OPTIMUM, though marginally smaller proportions of participants experienced TEAEs and liver abnormalities when compared to participants who received ponesimod 20 mg in the OPTIMUM trial. Lower occurrences would be expected due to the shorter follow-up of 24 weeks (compared to 108 in OPTIMUM); though the similarity in the proportions suggested the possibility that most TEAEs with ponesimod have an early onset. All AEs related to heart rate and rhythm were also reported as occurring on Day 1 of treatment. No fatalities were reported in the ponesimod 20 mg group, or any other trial arms. The ERG summarised key TEAEs from the Phase 2 core study in Table 19.

Table 19: Key treatment-emergent adverse events in the Phase 2b core trial

Event	Ponesimod 20 mg n=114 (%)	Placebo n=121 (%)
People with ≥ 1 TEAE, n (%)	88 (77.2)	90 (74.4)
Infections[a]	36 (31.6)	47 (38.8)
Bronchitis	4 (3.5)	2 (1.7)
Gastroenteritis	3 (2.6)	4 (3.3)
Influenza	3 (2.6)	2 (1.7)
Nasopharyngitis	11 (9.6)	17 (14.0)
Sinusitis	5 (4.4)	5 (4.1)
Upper respiratory tract infection	9 (7.9)	11 (9.1)
UTI	1 (0.9)	6 (5.0)
ALT increased	7 (6.1)	1 (0.8)
AST increased	-	-

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; UTI, urinary tract infection

Notes: [a] Composite number of people with infections comprising bronchitis, gastroenteritis, influenza, nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection; total number of all infections may therefore be different

The company also reported safety evidence from a long-term pooled safety analysis, which included all [redacted] participants who received ponesimod 20 mg in either the OPTIMUM or Phase 2 trial (representing [redacted] patient-years of exposure from the Phase 2 and [redacted] patient-years of exposure from OPTIMUM, with data cut-off for both extensions at [redacted]).

These long-term data showed similar proportions of people with at least one TEAE, treatment discontinuation due to TEAE and at least one serious TEAE when compared to the ponesimod group in OPTIMUM. The proportion of participants with elevated ALT and AST levels were [redacted], respectively) than in OPTIMUM; [redacted] (Table 25, pp.93-94 of the CS) in the pooled set. The company did not report proportions of participants experiencing effects on heart rate and rhythm, or macular oedema, but Table 25, pp.93-94 in the CS showed that [redacted] and [redacted], in participants on ponesimod. [redacted] were reported as part of the long-term safety analysis.

3.2.5. [redacted] Quality assessment of the included trials

The company used two different quality appraisal tools to appraise the quality of the OPTIMUM trial (CRD tool, CS Document B p.53-54 and Cochrane Risk of Bias Tool v.1, CS appendices p.160-161), whereas the Phase 2 trial was evaluated by the Cochrane Risk of Bias Tool v.1 tool only. While both tools are acceptable for evaluating risk of bias in RCTs, in 2019 the Cochrane tool was updated and would have been a preferable tool. For the Cochrane tool, the company evaluated an additional domain under the 'other' category of the tool, which they titled 'balance of dropouts and baseline traits'. No explanation of this domain was provided, and the ERG was unclear whether this double counted for differential attrition already covered within the attrition domain of the Cochrane tool, or assessed something different.

The company appraised the core phases of both trials to be at low risk of bias; this assessment was made at the trial level, with no differential ratings given across outcomes. The ERG agreed with the assessments made by the company according to the domains of the tools used, though noted that outcome measurement in both trials was subject to some limitations. The clinical outcomes of the trials may be subject to some measurement error, and the short-term evaluation of outcomes may not provide a reliable measure of changes in disability. In particular, clinical advice to the ERG was that CDA-3 may be likely to over-estimate disability due to natural fluctuations in the condition, and therefore CDA-6 is a more reliable measure (see Key Issue 4). Clinical advice to the ERG was also that the samples of both trials are likely too

small to identify rare serious adverse events associated with treatment. These issues were expected to apply equally to both arms.

No quality assessment or commentary about risk of bias was provided for the long-term extensions of either trial. The ERG considered both to be at a high risk of bias. The extension to OPTIMUM was uncontrolled, meaning that it is not possible to determine to what extent clinical outcomes were determined by treatment or by natural changes in the disease course or chance adverse events. It was also open-label, meaning that all outcomes that required a degree of subjectivity in measurement (particularly relapse rate, CDA, and PROs, but to some extent also neurological/radiological outcomes) are at a high risk of bias. All arms of the Phase 2 extension received ponesimod, and therefore comparisons can be made between doses of ponesimod only. While the different doses were blinded to participants, all were nevertheless aware that they were receiving an active treatment.

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

3.3.1. Search strategy

A single search strategy was used to identify RCTs evaluating the efficacy and safety of ponesimod and comparators for RRMS for the company submission; the methods are described in Section 3.1.

3.3.2. Feasibility assessment

The company did not clearly state whether they conducted a feasibility assessment to inform the analyses for this appraisal. It is therefore not possible for the ERG to evaluate the scope of any assessment, and appraise the rigour and rationale of decision-making for the company's NMAs. The company did report that several outcomes they considered were not "feasible". At clarification, the company reported that the choice of outcomes was based on the outcomes needed to populate the economic model, however it's unclear to the ERG why the company did not conduct NMAs for relative safety (discontinuation due to adverse events) or HRQoL, which could have informed both the clinical and economic evaluations of ponesimod. The ERG further noted that some analyses were stated to have been conducted but the results not reported in the CS, and so overall there was a lack of certainty about the analyses planned, conducted, and found not to be feasible.

The company stated that analyses restricted to the active RRMS population were not possible, due to the lack of available comparator data. Therefore, the company base case analyses are conducted with the ITT populations of the included trials. Evidence in the HA population is still more sparse, and the company reported that data from the ITT population were needed to complete the networks for the HA population, and that an NMA evaluating all-cause discontinuation was not feasible in this population. Without a comprehensive report of any feasibility assessment, it is unclear when company decisions to 'flex' inclusion criteria were deemed appropriate to complete networks, and when not. All networks were unadjusted for effect modifiers, and it is unclear whether the company explored this as an option but found that it was not feasible.

Tables presenting limited details about the included studies were provided, though the ERG considered that these did not fully reflect key factors that may create heterogeneity in the network. The ERG was aware that the evidence base for treatments of RRMS is highly heterogeneous, in study design, population characteristics/definitions, intervention delivery, and outcome follow-up and measurement. While to some extent these issues are unavoidable for these appraisals, a rigorous and transparent feasibility assessment would nevertheless have added trust to the analyses.

3.3.3. Study selection criteria

The selection criteria used by the company are described in the CS appendices, with a summary presented in Table 2 of Section D.3 (p.14-16). The ERG considered the selection criteria used by the company to be broadly appropriate.

As stated in Section 3.3.2, the company stated that it was not feasible to conduct analyses only in the active RRMS population, which would have been most pertinent to the decision problem. Instead, the company base case analyses were conducted in the ITT populations of the included trials, provided that at least 80% of trial samples should be people with RRMS (an arbitrary threshold based on IQWiG guidance). The ERG considered this to be a reasonable, pragmatic approach. The company further conducted subgroup NMAs using the OPTIMUM-definition of HA, which includes a small proportion of RES participants. In general, relative treatment effects are stable across baseline disease severity, though the ERG was unclear if this had been established in the RRMS population. Furthermore, the ERG was aware that different treatment recommendations are used in the NHS for people with differing RRMS

disease severity. Accordingly, the ERG considered that the generalisability of evidence across people with different disease severity was unclear.

Other selection criteria were judged to be appropriate, or to likely have minimal impact on the effect estimates. Notably, interventions included in the analysis were restricted to those recommended for each population (active and HA), and at licensed doses used in the NHS, which the ERG accepted.

The company chose to exclude phase 4 trials, which the ERG did not consider appropriate, since any problematic variation in methods between trials (the company's given rationale) could be more appropriately managed through more specific exclusion criteria. These criteria led to the exclusion of several trials that the ERG considered should have been included in the company's analyses; however, a comparison of treatment effects between the company's NMAs and those previously published that contained the excluded studies did not demonstrate major differences in reported effects, and therefore the ERG did not consider this to be a major concern for the analyses.

The company implemented several exclusion criteria following the completion of screening, which is generally considered to be a risk of bias. However, the ERG considered all the criteria implemented (e.g. excluding trials with fewer than 10 people in any treatment arm, and trials with zero events) were reasonable.

3.3.4. Included studies

The ERG found the flow of studies identified for the NMAs to be unclearly reported in the CS, and the descriptions contained some discrepancies in numbers; however, this lack of clarity was aided by information provided by the company at clarification. Following the inclusion of evidence for ofatumumab, the company reported that 41 RCTs were identified for inclusion in the ITT analyses, and 12 RCTs were included in the HA analyses. 42 trials reported discontinuation in the ITT population. However less than half of the trials reported CDA (three month CDA n=22; six-month CDA n=20 [note that all trials reporting six-month CDA also reported three-month CDA]).

The majority of trials were placebo-controlled (n=26), though 15 trials included a head-to-head comparison (not including trials that compared different doses of the same treatment). Included RCTs for each of the comparator treatments were as follows: beta-interferons n=18; glatiramer acetate n=9; fingolimod n=5; teriflunomide n=5; ozanimod n=3; dimethyl fumarate n=4;

alemtuzumab n=3; ocrelizumab n=3; natalizumab n=2; ponesimod n=2; peginterferon beta-1a n=1; cladribine n=1, and placebo n=26). The trials included 4 extensions to other included trials[36-39].

Enrollment periods for the included trials ranged from 1993 to 2020 (as reported in table 6 of the company's clarification response; question A4). The trials were conducted across a range of different geographic areas and healthcare settings. Most trials were conducted across multiple countries (n=33), with other trials conducted in the US (n=3), Japan (n=2), Iran (n=1), and Russia (n=1) and Italy (n=1). The median follow-up, based on the company's clarification response, was 96 weeks (range of 24-144 weeks).

Table 7 of the CS appendices (p. 128) reported the population eligibility criteria for the included studies (for ofatumumab these were reported in the company's clarification response). The table showed further variation in the diagnostic criteria and definition of active and highly active RRMS used within the trials. While this variation introduces some uncertainty into the analysis, clinical advice to the ERG was that these differences are unlikely to have a major impact on the comparability of the trials. Since the earliest trials, there have been various changes to the diagnostic criteria of RRMS, however clinical experts also considered that this is unlikely to undermine the analysis; the changes to diagnosis may have led to earlier diagnosis of RRMS, though the most impact will be for people not eligible for DMTs.

3.3.5. Quality assessment of studies included in indirect treatment comparison

The company reported using the Cochrane risk of bias tool (version 1) to assess the quality of trials included in the ITC. The ERG noted that the domains used in the assessments were appropriate for Cochrane risk of bias. The judgements are summarised in a colour-coded table in the appendices to the CS (Appendix D.7). Overall, the company reported that studies included in the NMA were generally at low risk of selection, attrition and reporting bias, with greater variability reported with regards to performance bias and other bias. The company did not, however, provide justifications for their quality judgments. This made it difficult to assess whether these judgments were reasonable, in particular for the composite 'other bias' domain, described as both a balance of baseline characteristics and drop-outs. It was also not stated whether these were done independently in duplicate, making it difficult for the ERG to assess whether these judgments were unbiased.

Within the timeframe of this appraisal it was not feasible for the ERG to independently assess the risk of bias for all trials included in the ITC. However, the ERG compared the judgments in the company submission with those reported in other NICE RRMS appraisals, finding that there was a good level of agreement.

In general, several trials included in the NMA had some uncertainty around selection bias, but few of these had issues around the balance of baseline characteristics; indicating few trials with serious problems regarding randomisation or allocation concealment. A considerable number of included trials were at high risk of performance bias, and less posed a risk of detection bias. Given the nature of the outcomes, which requires the individual's involvement in identifying relapses and disability, it is difficult to assess the impact of these biases on trial results. The ERG noted that very few trials had issues related to attrition or reporting bias, but nearly half of the included trials had high risk related to imbalances in baseline characteristics and/or attrition.

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

The following sections contain the ERG's appraisal of the company's NMA methods and results. Overall, the ERG considered that the choice of analyses could have been more comprehensive towards the decision problem; for example, analyses comparing treatment discontinuation due to adverse events and HRQoL would have been informative, as well as further analyses in populations specific to the NHS treatment pathway. However, it is possible that further analyses were not feasible, due to a paucity of evidence across other comparisons. The ERG identified a number of limitations with the NMAs, particularly for the analyses conducted in the HA population, which significantly undermine the validity of the results. These limitations were generally due to the paucity and quality of evidence for ponesimod and comparator treatments, and not because of the company's methods for selecting and analysing evidence.

3.4.1. Summary of analyses undertaken

The ERG was unclear how many NMAs the company conducted in total, though this included eight NMAs in the ≥80% RRMS population (random- and fixed-effects models of ARR, CDA-3, CDA-6, and all-cause discontinuation); six in the HA population (random- and fixed-effects models of ARR, CDA-3, CDA-6) and three in the RRMS only population (ARR, CDA-3, CDA-6). The company also stated that additional NMAs were conducted to explore the impact of informed priors (CS Document B p.70) and to replace HA subgroup data for two teriflunomide trials with the ITT data (CS appendix p.148); however, it was not clear which outcomes were

subjected to these sensitivity analyses, and while model fit statistics were reported for one of the analyses using informed priors, the priors used and the remaining results were not reported. The CS appendix also reported the results of an NMA of effect estimates for trials with long-term follow-up of ARR, which at clarification the company stated included trials with comparative follow-up data beyond the core trial period

The NMAs were conducted using a Bayesian framework, based on a Markov Chain Monte Carlo simulation. Consistent with NICE Decision Support Unit (DSU) guidance, vague prior distributions assuming no pre-existing information on the values of treatment effects, trial baselines, and common regression terms were used in the base case analyses. Model fit was assessed using the residual deviance (ResDev), deviance information criterion (DIC), and estimated between-study SD. The posterior mean deviance (of individual data points for ARR and treatment discontinuation and individual studies for three- and six-month CDA) was used to investigate consistency. The company did not report estimates separately for direct and indirect evidence, and did not comment on consistency of the networks. The company also did not state how heterogeneity would be evaluated: between-study SD was stated to inform model selection, though it was not stated if this would be used to investigate heterogeneity, and no further measures (e.g. I^2, Cochran's Q, chi-square) were reported.

For ARR, the company used a Poisson model with log link to generate relative rates, while HRs were derived for three- and six-month CDA using log HRs and a Normal model with identity link. A binomial model with logit link was used to calculate ORs for all-cause treatment discontinuations. The analyses were conducted in R and JAGS, and the full code used was provided in the CS appendix for the main (fixed- and random-effects) analyses (Section D5). The code was consistent with the analyses described, and appeared to contain no errors. The company stated that they calculated the probability of being best, the probability that ponesimod is better than other interventions in the network, and the Surface Under the Cumulative Ranking curve (SUCRA); however, only the 'rank' of ponesimod against other treatments based on SUCRA was reported, and this data was not accompanied by confidence intervals: this is a limitation of the analysis, given that ranking data such as SUCRA are very sensitive to uncertainty in the relative treatment effects, which is a concern for the analyses in this submission.

All analyses were unadjusted for covariates, and at clarification the company confirmed that only unadjusted rates were used from the included trials. Previous NMAs in this field have also

selected unadjusted rates, due to variation in the covariates used to adjust treatment effects across trials

The company conducted both random- and fixed-effects models, and reported the findings of both in the CS. The company selected fixed-effects models for ARR and three- and six-month CDA for the ≥80% RRMS population on the basis that the DIC criterion suggested a better fit to the data. The ERG considered that DIC is an estimate of model fit rather than of heterogeneity in the network, and therefore did not agree with the rationale for selecting fixed effects models on this basis. Rather, in recognition of the high degree of heterogeneity in the studies included in the network, the ERG considered that a random-effects approach should have been taken for all analyses. The principal difference between random- and fixed- effects models were the certainty of the effect estimates, and some of the differences reported between treatments were no longer statistically significant when using the random effects analyses.

3.4.2. Critique of assumptions used in the indirect treatment comparison

The company's analyses proceeded despite known heterogeneity in the evidence base. At clarification, the company outlined their approach to selecting the effect estimates from the included trials; all of these decisions appeared reasonable, though they demonstrated the complexity of an evidence base characterised by varying population definitions, trials conducted in different international healthcare settings across a span of decades, and where disease outcome measures are not standard and involve some measurement subjectivity/error. The impact of this heterogeneity was evident in the wide variation of placebo effects: the input data used for the company's NMAs, provided at clarification, showed that ARR ranged from 0.18 to 1.73 (n=26; for context, the ERG noted that the differences in ARR between ponesimod and comparator treatments were all <0.1), and the rate of treatment discontinuation ranged from 0% to 62.8% (n=25), without this variation being explained from length of follow-up only. Due to the paucity of evidence for each comparison in the networks, it was not possible to fully evaluate the range in effects in the CDA networks and for other treatments.

The company used unadjusted effects from each of the included trials, which they stated was due to variation in the adjustments made within each trial, and the company did not calculate effects using meta-regression: in effect, therefore, the company have assumed homogeneity in the trial evidence, despite evidence that this is not the case. The ERG was aware that previous appraisals of treatments for RRMS have required the acceptance of heterogeneity in networks to generate indirect treatment effects, due to the lack of direct head-to-head evidence. In all

cases, concerns about the impact of this heterogeneity have been noted as significantly undermining the validity of the treatment effects due to the differential effects of known or unknown effect modifiers (Klawiter 2009[40]; Jansen 2011[41]).

Finally, the ERG considered it a limitation of the company's analyses that the analyses do not represent the line and sequencing of treatments that would be expected in practice: all treatments available within each population are compared, no matter the line they would be received in practice. As in practice people would not be 'at risk' of every treatment, this undermines the transivity assumption of the analyses (Rouse 2017[42]). Moreover, as participants in the included trials were treated at varying lines of treatment, it's unclear to what extent effects are generalisability to the target population.

3.4.3. Relevance to the target population

As described above, the company's analyses are pragmatic and do not fully represent the populations and treatment pathways present within the NHS. While analyses were restricted to treatments available within the NHS, the analyses involve a comparison of treatment effects across participants with varying disease severity and on various lines of treatment. There is a lack of evidence for treatment effect modifiers in RRMS, though it is known that treatment efficacy varies widely between individuals, and discontinuing treatment is dependent on previous treatment history, and several demographic, radiological and clinical characteristics[43]. It is therefore unclear to what extent the mixed evidence base in the company's NMAs is generalisable to the target UK population.

3.4.4. Results of the indirect treatment comparison

3.4.4.1. RRMS participants (trial ITT populations)

A summary of the results from the company's updated base case NMAs is provided in Table 20 and Table 21 below (updated from the CS to include ofatumumab).

In the company's base case analyses, 95% credible intervals around the effects comparing ponesimod and the other comparators were extremely wide for all outcomes, indicating a high degree of uncertainty in the true effects. This was particularly the case for the CDA outcomes and for all-cause treatment discontinuation. This was likely due in part to the distance between ponesimod and the other comparators in the network, as well as the paucity and heterogeneity of the evidence for all treatments. To aid interpretation, the ERG have used colouring in the table to highlight both statistically significant differences and large numerical differences (i.e.

outside thresholds of 0.80 – 1.25) that were not statistically significant. However, the ERG acknowledged that there is greater uncertainty in determining the latter of these, and that smaller differences may nevertheless be clinically meaningful. In addition, effects estimated for all comparators as compared to placebo are summarised in Table 21, where the effects are more precise due to the weight and proximity of evidence for placebo relative to all treatments.

The results suggested that ponesimod was [redacted] the risk of relapse in people with active RRMS than interferon beta 1-a (all doses), interferon beta 1-b, glatiramer acetate (all doses), and teriflunomide.

[redacted] Clinical advice to the ERG was also that these treatments are used less in clinical practice, due to a lack of clinical efficacy.

[redacted] Rank data suggested that ponesimod was [redacted] for ARR, three-month CDA, six-month CDA, and all-cause treatment discontinuations, respectively; as noted earlier, no confidence intervals around the ranks were reported.

Table 20: NMA outcomes for ponesimod vs. comparator in ≥80% RRMS population (company base case)

Comparator	Dose	ARR, Rate ratio (95% CrI)[a]	3-month CDA[a]	6-month CDA[a]	All-cause discontinuation[b]
interferon beta-1a	22SC TIW	[redacted]	[redacted]	[redacted]	[redacted]
	44SC TIW	[redacted]	[redacted]	[redacted]	[redacted]
	30 IM QW	[redacted]	[redacted]	[redacted]	[redacted]
glatiramer acetate	20QD	[redacted]	[redacted]	[redacted]	[redacted]
	40 TIW	[redacted]	[redacted]	[redacted]	[redacted]
peginterferon beta-1a		[redacted]	[redacted]	[redacted]	[redacted]

Comparator	Dose	ARR, Rate ratio (95% CrI)[a]	3-month CDA[a]	6-month CDA[a]	All-cause discontinuation[b]
ocrelizumab		[redacted]	[redacted]	[redacted]	[redacted]
interferon beta 1b		[redacted]	[redacted]	[redacted]	[redacted]
dimethyl fumarate		[redacted]	[redacted]	[redacted]	[redacted]
teriflunomide		[redacted]	[redacted]	[redacted]	[redacted]
alemtuzumab		[redacted]	[redacted]	[redacted]	[redacted]
Cladribine		[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod		[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod		[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab		[redacted]	[redacted]	[redacted]	[redacted]
Placebo		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; CrI, credible interval; IM, intramuscular; NMA, network meta-analysis; QD, once a day; QW, weekly; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; TIW, three times weekly

Notes: [a] fixed effects NMA; [b] random effects NMA. Darker coloured cells represent statistically significant differences: green cells are in favour of ponesimod, red cells are in favour of the comparator. Lighter shading is used to represent large numerical differences in outcome (≥0.80 – 1.25) that were not statistically significant.

Table 21: NMA outcomes for all treatments vs. placebo in ≥80% RRMS population (company base case)

	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 µg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; HR, hazard ratio; NMA, network meta-analysis; OR, odds ratio; RRMS, relapsing-remitting multiple sclerosis

Notes: Darker coloured cells represent statistically significant differences: green cells are in favour of ponesimod, red cells are in favour of the comparator. Lighter shading is used to represent large numerical differences in outcome (≥0.80 – 1.25) that were not statistically significant

3.4.4.2. Highly active subgroup

An overview of the company results from the highly active networks is provided in Table 22 and Table 23 below. Networks evaluated ARR and 3- and 6-month CDA only; no analysis was conducted to evaluate relative effects for treatment discontinuation due to a lack of evidence for this outcome in the HA population.

Across the clinical outcomes, the data suggested that ponesimod performed better than interferon beta 1a and teriflunomide, although neither of these treatments are currently recommended for treating people with HA RRMS. There [redacted].

The results were comparable with those in the company's ≥80% RRMS base case analysis, although there was [redacted].

Table 22: NMA outcomes for ponesimod vs. comparator in the highly active population

Comparator	Dose	ARR, Rate ratio (95% CrI)[a]	3-month CDA[a]	6-month CDA[a]
interferon beta-1a	44SC TIW	[redacted]	[redacted]	[redacted]
	30 IM QW	[redacted]	[redacted]	[redacted]
Ocrelizumab		[redacted]	[redacted]	[redacted]
Teriflunomide		[redacted]	[redacted]	[redacted]
Alemtuzumab		[redacted]	[redacted]	[redacted]
Cladribine		[redacted]	[redacted]	[redacted]
Fingolimod		[redacted]	[redacted]	[redacted]
Ofatumumab		[redacted]	[redacted]	[redacted]
Ozanimod		[redacted]	[redacted]	[redacted]
Placebo		[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; CrI, credible interval; NMA, network meta-analysis; QW, weekly; TIW, three times weekly

Notes: Darker coloured cells represent statistically significant differences: green cells are in favour of ponesimod, red cells are in favour of the comparator. Lighter shading is used to represent large numerical differences in outcome (≥0.80 – 1.25) that were not statistically significant

Table 23: NMA outcomes for all treatments vs. placebo in the highly active population

	ARR	CDA-3	CDA-6
Ponesimod	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	0.62 (0.43 - 0.90)	0.62 (0.43 - 0.90)
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; NMA, network meta-analysis

Notes: Darker coloured cells represent statistically significant differences: green cells are in favour of ponesimod, red cells are in favour of the comparator. Lighter shading is used to represent large numerical differences in outcome (≥0.80 – 1.25) that were not statistically significant

3.4.4.3. Additional sensitivity analyses

Additional sensitivity analyses reported by the company were random- (ARR, CDA-3, and CDA-6) and fixed- (all-cause treatment discontinuation) effects analyses, restricted inclusion to long-term follow-up data (definition not provided; ARR only), and inclusion of ITT data for the teriflunomide trials in the highly active population (CDA-3 and CDA-6). The analyses revealed little that was pertinent to the appraisal: partly because the analyses do not address the key uncertainties with the company's analyses, and partly because wide confidence intervals in all analyses meant that it was not possible to detect whether differences across analyses conveyed meaningful effect modifiers.

3.4.5. Conclusions on the indirect treatment comparison

The ERG appraised the company's methods for the NMAs as pragmatic and appropriate in context of the available evidence. The ERG considered that a broader range of outcomes, to include the relative safety and impact on HRQoL of ponesimod, would have been informative to the appraisal; though as the company did not report their feasibility assessment, it was unclear whether these outcomes were not considered or were not feasible. There was a paucity of evidence across treatments for RRMS that could be used to inform these analyses; many

parameters in the networks relied on one or two studies only, which is particularly problematic in RRMS where both the condition and the available trials are heterogeneous in nature. However, the ERG considered that the company should have presented further outcome data from their NMAs, in addition to further exploration of heterogeneity and inconsistency in the networks.

Overall, the ERG considered the company's base case analyses to suggest that ponesimod could be considered as a moderate efficacy treatment for active RRMS amongst the treatments available, in terms of relapse rate and CDA of 3- and 6-months. However, clinical advice to the ERG was that the treatments that ponesimod out-performed were [redacted] Overall, the company's NMAs were associated with a high degree of uncertainty: the ERG considered that the true magnitude of any treatment effects in the analyses were uncertain, due to major limitations in the available evidence base. Finally, the ERG did not consider the company to have presented evidence of the relative efficacy of ponesimod in the RES population.

3.5. Additional work on clinical effectiveness undertaken by the ERG

The ERG conducted additional work to validate the company's NMAs and address uncertainty in treatment effects, and to address gaps in the evidence base for the safety of ponesimod. Specifically, the ERG:

- Conducted additional literature searches to identify (a) previous NMAs conducted in RRMS, with a particular focus on people with HA RRMS and (b) additional evidence of the safety of ponesimod (Section 3.5.1).
- Compared the methods used in previous TA appraisals for defining HA RRMS and for comparing treatments for HA (Section 3.5.2.1).
- Validated the treatment effects in the company's NMAs by comparing these with previous TAs/published NMAs (Section 3.5.2.2).

- Appraised the adverse event rates for all comparators, as identified by the company's SLR of RCT data, to evaluate the comparative safety of ponesimod (Section 3.5.3).
- Conducted a naïve comparison of the safety of ponesimod with fingolimod using evidence from the NICE appraisal (TA254[14])(Section 3.5.4).

An overview of this work is provided in the following sections, with supplementary information in the appendices.

3.5.1. Additional searches

The ERG carried out some additional searches for multiple sclerosis NMAs in Medline and Embase from 2016 onwards (Appendix A) and found 1,044 papers. This was a partial (modified) update of the searches used in Melendez-Torres (2018)[44], limited to papers published in 2016 onwards. These searches informed additional work conducted by the ERG to validate the methods and results of the company's NMAs.

In addition the ERG carried out some additional searches for adverse effects for ponesimod in Medline and Embase (Appendix A) and found 148 papers. This search used the broad adverse effects expert search filter from Ovid (Adverse Effects - Medline – Broad[45]) without any study type filter, in order to find any additional (non RCT) papers reporting safety data. Safety evidence measured within clinical trials can lack external validity (e.g. due to restrictive population eligibility criteria, and treatment use that may not reflect real world use). The search was also translated into Embase using the equivalent Ovid search filter (Adverse Effects – Embase – Broad[45]). This search was used to inform additional work conducted by the ERG to evaluate the relative safety of ponesimod.

Within the timeframe of this appraisal, it was not possible for the ERG to fully appraise the results of this search; though a single reviewer screened the results: 30 papers were found eligible, of which 20 papers were related to the included Phase 2 and OPTIMUM trials and their extensions. The remaining records were safety studies in healthy volunteers, and therefore were outside the scope of this appraisal. Within the timeframe of this appraisal, the ERG were unable to consider these papers in detail, to identify whether the evidence could meaningfully impact on this appraisal. However, based on the results of the search, the ERG concluded that the company included all available safety evidence for ponesimod.

3.5.2. Validation of the company's NMAs

Within the timeframe of this appraisal, it was not feasible for the ERG to conduct a comprehensive review and comparison of methods and effect estimates across previous NMAs. However, in order to validate the findings of the company's NMA, particularly for the HA subgroup where there is a high degree of uncertainty in the estimates, the ERG sought to compare the company's NMAs with those previously conducted. To this end, the ERG screened and selected published NMAs from targeted searches (described in 3.5.1) to identify previous NMAs evaluating treatments for RRMS.

3.5.2.1. Comparison of methods

The previous NMAs conducted in the HA RRMS population identified by the ERG, and a brief overview of the included trials and methodology used, are provided in Table 58 in the appendix. As with the company's NMAs, all required a broad definition of HA, to account for the various definitions used in the available trials. These analyses also always required the inclusion of indirect evidence to complete the network; either from indirect populations and/or treatments. The analyses were all associated with more uncertainty than analyses in the RRMS population. Based on the evidence accessible to the ERG, the impact of the assumptions used in the analyses were not investigated, with the exception of a meta-regression conducted by the company for TA616 (NICE evaluation of cladribine), which adjusted treatment effects for baseline disease severity. Unfortunately, the results from this analysis were considered by the ERG to show that effects were also affected by additional effect modifiers, which undermined the validity of the results.

Previous NICE committees have accepted the variability in HA population definitions in NMAs presented by companies, and have further accepted the inclusion of indirect evidence to complete networks as pragmatic. However, it is clear that all NMAs in the HA population include highly heterogeneous data, with unknown impacts on effect estimates, which cannot easily be resolved through statistical techniques.

A review of previous appraisals highlighted ongoing uncertainty in whether effect estimates could be generalised between the active HA and RES populations. Notably, for TA699[13] the committee heard from clinical experts who proposed that definitions of HA and RES may not be used in practice, in favour of classifications based on relapse severity and line of treatment, and in this case the committee concluded that recommendations could be made for the HA and RES populations based on evidence from a broad RRMS population. Conversely, within TA10299[12]

the committee considered that they could not make a recommendation for ozanimod in the 2nd line population as the company had not presented evidence specific to these people in its submission. The ERG considered that these discrepancies in opinion may be inevitable in a disease where population definitions are not standardised, and where there is a lack of evidence for treatment effect modifiers.

Overall, the ERG concluded that the methods used by the company to evaluate the relative efficacy of treatments in the HA RRMS population were broadly consistent with previous appraisals, and pragmatic according to the available evidence. The uncertainties in this analysis were considered to be related to the quality of the available evidence, and the ERG considered it unlikely that these uncertainties could have been adequately resolved by the company in their submission.

3.5.2.2. Comparison of relative effects in the intention-to-treat versus the highly active populations

The NMA in the HA subgroup had very sparse data for all clinical effectiveness outcomes. To determine whether data from the base case in the ITT population could be used to form a more complete network in the HA population, the ERG compared the relative effects for clinical outcomes between these populations using the effects reported in the company NMA. Relative effects were extracted from the league tables presented in the appendices to the company submission for ARR (Figures 2 and 5), CDA at 3 months (Figures 6 and 9) and CDA at 6 months (Figures 10 and 13) and tabulated to enable a comparison. The data used in this comparison are summarised in Tables C1-3 of Appendix C.

The ERG found differences in effects between the HA and ITT populations across ARR, CDA at 3 months and CDA at 6 months. Thresholds of 0.1 and 0.2 were used to identify differences in relative effects, both of which are within the bounds found to have a meaningful impact on the ICER; higher ARRs and hazard ratios for CDA, both at 3 and 6 months, were more frequently observed in the ITT population. Differences in nominal significance between results were low for ARR and CDA at 3 months, and larger for CDA at 6 months. Results from the ITT population were more frequently significant in these cases. While these comparisons are not conclusive, due to the wide confidence intervals reported around the effects, the ERG considered there to be some uncertainty in the use of ITT data to complete networks in the HA subgroup, given the frequency of significant and less favourable findings in the ITT population.

The ERG conducted further comparative analyses to establish whether there is a differential treatment effect for DMTs in the ITT versus the HA populations. To do this, the ERG calculated the ratio of the relative effect in the HA group to the relative effect in the ITT group for all DMTs compared to placebo. These ratios are available in the far right columns of Tables C1-3 in Appendix C. Using the approach from Cochrane guidance[46] for interpreting the importance of relative measures, these ratios were classified as 'inappreciably' or 'appreciably' lower or higher in the HA group using the cut-offs of 0.75 and 1.25. Inappreciably higher or lower ratios were considered as a comparable effect of treatments in the two populations on the outcome of interest. A summary of these conclusions for ARR, CDA at 3 months and CDA at 6 months is presented in Table 22.

Table 24: ERG conclusions on the estimated relative efficacy of disease modifying treatments in the highly active population compared to the intention-to-treat population

DMT	ARR	CDA at 3 months	CDA at 6 months
Alemtuzumab	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; DMT, disease modifying treatment; ERG, Evidence Review Group; HA, highly active; IFNB, interferon beta

[redacted]

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3.5.3. Trial adverse event rates for ponesimod and its comparators

The company reported the rates of specific AEs for comparator treatments to ponesimod using annualised safety data obtained from trials identified by their SLR. These rates were reported in

Tables 42 to 45 of the CS (Document B, p 122 - 125). Please note that safety data was not reported in this table for ofatumumab or ozanimod, as AE data for these comparators were not submitted by the company during clarification. As the company's NMAs did not include an indirect comparison of safety between ponesimod and comparator treatments, the ERG reviewed the reported rates to inform a judgement on the relative safety of ponesimod to other available treatments. Reported rates of key AEs, with potentially large implications for healthcare resource use and/or safety, are reported in Table 24, and rates of these AEs that were serious are reported in Table 25.

The ERG noted that these rates are subject to a high degree of uncertainty, as all are based on trial data, which lacks external validity for estimating the risk of AEs. In addition, the trials were highly heterogeneous, with variations in health setting and country, population eligibility criteria, definition and measurement of safety outcomes, and length of follow-up. The ERG therefore considered that the rates reported may be indicative of the comparative safety of ponesimod, but that they should be interpreted with caution. Using these data, a naïve comparison of adverse event rates between ponesimod and fingolimod is summarised in Section 3.5.3.1, and between ponesimod and all other comparators in Section 3.5.3.2.

Table 25: Incidence of key adverse events reported in trials of ponesimod and its comparators

Treatment	Elevated ALT	Elevated AST	Infections [a]	Non-fatal PML	Fatal PML
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Elevated ALT	Elevated AST	Infections [a]	Non-fatal PML	Fatal PML
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PML, progressive multifocal leukoencephalopathy

Note:

[a] Composite percentage of participants with infections comprising nasopharyngitis, upper respiratory tract infection, urinary tract infection; total number of all infections may therefore be greater

Source: CS Document B, p.122-123

Table 26: Proportions of key adverse events that were serious for ponesimod and its comparators

Treatment	Elevated ALT	Elevated AST	Infections [a]	Non-fatal PML [b]	Fatal PML [b]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pegylated interferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N/A, not applicable; PML, progressive multifocal leukoencephalopathy

Note:

[a] Composite percentage of participants with infections comprising nasopharyngitis, upper respiratory tract infection, urinary tract infection; total number of all infections may therefore be greater

[b] Due to its serious nature, all PML events are considered serious adverse events. Cells with N/A reflect DMTs with no reported incidence of PML and, therefore, no calculable proportions of serious PML

Source: CS Document B, p. 124-125

3.5.3.1. Naïve comparison of AE rates for ponesimod vs. fingolimod

The company posited that ponesimod may be a safer alternative to fingolimod, due to its increased specificity on the $S1P_1$ receptor. A comparison between the rates of AEs reported for ponesimod and fingolimod suggested [redacted]. The ERG noted that [redacted]. In the absence of larger participant samples in trials of ponesimod and considering the rarity of these events, however, it is uncertain whether [redacted].

The rates of cardiac events and macular oedema (both known AEs of S1P modulators) from the trials of comparator treatments were not reported, and therefore the ERG was unable to evaluate whether the risk of these events was lower for ponesimod as compared to fingolimod. To address this, the ERG conducted a naïve comparison between the ponesimod trials and the evidence base for fingolimod considered in its appraisal by NICE (see Section 3.5.4)

Overall, as the relative safety evidence for ponesimod and fingolimod relies on a naïve comparison between heterogeneous trials, the ERG considered that it was not possible to draw firm conclusions about whether ponesimod does present a reduced risk of AEs due to its increased specificity on the $S1P_1$ receptor. Clinical advisors to the ERG considered that, pending further safety evidence, the monitoring of people receiving ponesimod should be comparable to that used for fingolimod.

3.5.3.2. Naïve comparison of AE rates for ponesimod vs. other comparators

Ponesimod showed [redacted] compared to other comparators: [redacted]

[redacted]

[redacted] (discussed in Section 3.5.3.1).

Overall, as noted above, the ERG considered the relative safety data to be highly limited, and that conclusions about the relative safety of ponesimod should be interpreted with caution, due to the heterogeneity in the trial methods.

[redacted] however, the ERG maintained that a NMA comparing discontinuation due to AEs would further inform the relative safety of ponesimod. There were outstanding uncertainties [redacted] (such as PML), and further safety data exploring these outcomes would inform the appropriate positioning of ponesimod in the treatment pathway, as well as the frequency of monitoring.

3.5.4. Naïve comparison of macular oedema rates and treatment discontinuation due to adverse events between ponesimod and fingolimod

The ERG noted that the company did not provide any data on the risk of cardiac events, macular oedema or treatment discontinuation due to AEs for comparators to ponesimod. As cardiac events and macular oedema are considered important AEs related to S1P modulators, and treatment discontinuations are a useful marker of overall tolerability, the ERG conducted a naïve comparison of these outcomes for ponesimod versus fingolimod, using safety data from the OPTIMUM trial for ponesimod and from the NICE technology appraisal for fingolimod (TA254[14]). Fingolimod was prioritised for this comparison as it is in the same drug class as ponesimod (S1P modulators) but is thought to have a less specific action on S1P receptors than ponesimod. Ponesimod is, therefore, posited by the company to have an improved safety profile. A limitation of this comparison was that additional safety evidence for fingolimod has been published since its appraisal by NICE[47] in 2012, including evidence that has highlighted

concerns about liver toxicity[48]. It is therefore feasible that the data appraised by NICE does not present a full picture of other serious AEs. However, in the timeframe of this appraisal, the ERG was unable to review the full evidence base for fingolimod, and this comparison should therefore be considered indicative, but interpreted with caution.

The results showed that the rate of treatment discontinuations due to AEs [redacted] than in either of the trials of fingolimod included in the NICE appraisal: 2.2% to 3.1% of people discontinued due to AEs in the FREEDOMS and TRANSFORMS trials, respectively, [redacted] of people treated with ponesimod in the OPTIMUM trial.

No cardiac event data were reported in the NICE appraisal of fingolimod, and therefore the ERG was unable to comment on whether ponesimod is safer for these events. The risk of macular oedema was [redacted] the NICE appraisal of fingolimod (0.4%, as reported from the SmPC), though, the Phase 2 trial of ponesimod reported a higher rate (2/114, 1.8%)[22].

Based on the evidence reviewed by the ERG, [redacted]. This comparison is limited, and has the same limitations due to trial heterogeneity as the comparison of AE rates in Section 3.5.3 (and in the company's NMAs). However overall, the ERG did not consider that [redacted].

3.6. Conclusions of the clinical effectiveness section

The clinical evidence presented by the company suggested that there may be a place for ponesimod in the current treatment pathway for people with active RRMS: based on the evidence available, ponesimod demonstrated [redacted] The ERG also considered the shorter half-life of ponesimod and its use as an oral treatment as potential benefits to people with RRMS. However, the ERG considered that weaknesses in the collective evidence base meant that the magnitude of clinical benefits relative to other comparators were uncertain, and combined with the paucity of reliable comparative safety evidence, this created some uncertainty as to the most appropriate positioning of ponesimod in the current treatment

pathway. The uncertainty was most evident in the HA RRMS population, where uncertainty in clinical effects was greatest, and there was no relevant direct head-to-head comparison (as teriflunomide is not recommended for the treatment of HA RRMS).

[redacted]. It may be reasonable to consider ponesimod as an alternative to fingolimod, particularly if the increased specificity of ponesimod to the $S1P_1$ receptor results in an improved safety profile, as posited by the company. However, the ERG did not consider that the company had demonstrated this in the evidence provided. Finally, the ERG did not consider that sufficient evidence had been presented to consider ponesimod for the treatment of RES RRMS.

4. COST-EFFECTIVENESS

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

The company carried out a SLR, using a single search strategy, to identify existing cost-effectiveness evidence, HRQoL evidence, and cost and resource use evidence for ponesimod in multiple sclerosis. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 27.

Table 27. Summary of ERG's critique of the methods implemented by the company to identify health economic evidence

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost-effectiveness evidence	HRQoL evidence	Cost and resource use evidence	
Searches	Appendix G	Appendix G	Appendix G	The same search strategy was used for all three searches and was an update of the searches for TA624. It only covered Nov 2018 to July 2020. The cost-effectiveness/HRQoL/Costs searches were carried out as one search. The strategy did not use a recognised search filter to identify relevant publications such as those by SIGN[21] or CADTH[49]. The search strategy did not include any search terms for siponimod, ozanimod, ofatumumab or ponesimod. Therefore few or no papers will have been identified for these interventions. In clarification the company agreed to carry out some additional searches for ofatumumab and the results were shared with the ERG. The ERG carried out additional searches for the additional technologies in Medline and Embase (Appendix A) and found 105 papers.

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost-effectiveness evidence	HRQoL evidence	Cost and resource use evidence	
Inclusion criteria	Appendix G.1.3	Appendix G.1.3	Appendix G.1.3	The inclusion criteria were appropriate.
Data extraction	Appendix G.1.4 and 1.5	Appendix G.1.4 and 1.5	Appendix G.1.4 and 1.5	Methods for screening and data extraction were clearly described, and were considered appropriate.
Quality appraisal	NA	NA	Appendix G.1.6, and I	Quality appraisal of economic evaluations was conducted using the Drummond[50] checklist, which was appropriate. The evidence submitted by the company was consistent with the NICE reference case.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality-of-life; NA, not applicable; SIGN, Scottish Intercollegiate Guideline Network

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

4.2.1. NICE reference case checklist

Table 28: NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for participants or, when relevant, carers	QALYs were estimated for participants and carer disutilities were included in the company's base case.
Perspective on costs	NHS and PSS	NHS and PSS as appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A 50 years time horizon was used in the base case analysis. The ERG considered the base case time horizon to be appropriate.
Synthesis of evidence on health effects	Based on systematic review	For the active and HA RRMS populations, clinical effectiveness data pertaining to ARR, CDA and treatment discontinuation were based on

Attribute	Reference case	ERG comment on company's submission
		NMAs conducted by the company. Treatment efficacy in the economic model is based on the relative risk vs. natural history
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate.
Source of data for measurement of health-related quality of life	Reported directly by participants and/or carers	Utility values were derived from published literature.(Orme 2007[51]) The ERG considered this to be an appropriate source, however for completeness an alternative source has been tested in a scenario analysis.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Dolan et al.[52] as appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There were no equity concerns.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	NHS reference costs and PSSRU were used as appropriate. Resource use estimates were based on previous NICE MS appraisals including ocrelizumab (TA533[53]) and peginterferon beta 1a (TA624[54]).
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and outcomes were discounted at 3.5% as appropriate.

Key: EQ-5D, EuroQol 5 dimension; HA, highly active; HRQoL: health-related quality of life; NHS, National Health Service; NMA, network meta-analysis; PSS, Pseronal Social Services; QALY: quality-adjusted life year; RRMS, relapsing-remitting multiple sclerosis; TA: technology appraisal

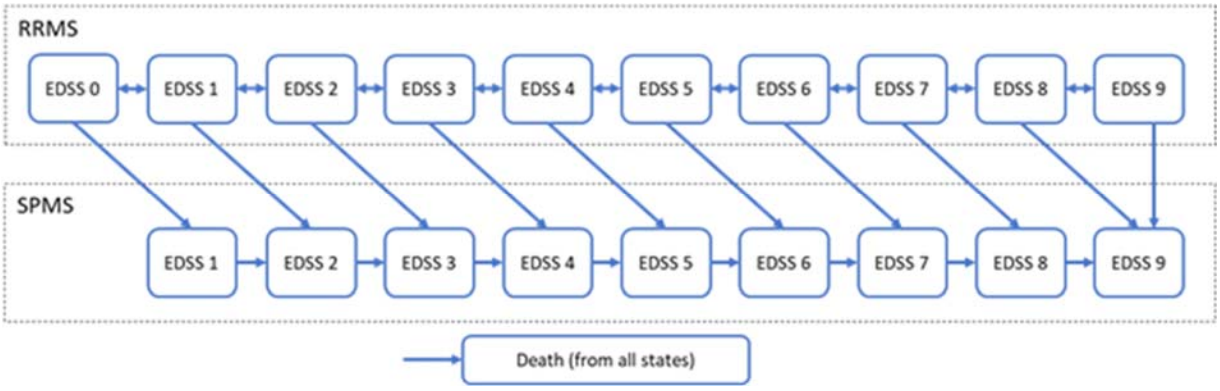
4.2.2. Model structure

The company submitted a Markov model consisting of 20 health states, based on EDSS scores (EDSS 0-9 for RRMS, EDSS 1-9 for SPMS and death, which was assumed to be equivalent to EDSS 10 for both RRMS and SPMS). People moved through EDSS health states based on treatment transition probabilities, which were derived from natural history data and adjusted to

account for treatment effect. See Section 4.2.6 for further detail surrounding the estimation of transition probabilities.

Whilst in the RRMS part of the model, people were capable of improving (moving to lower EDSS states) or getting worse (moving to higher EDSS states), upon progression into the SPMS part of the model, people were only able to move to higher EDSS states (see p.98 for further detail surrounding the probability of converting to SPMS and treatment discontinuation assumptions).The ERG acknowledged that the model structure was broadly in line with models used in previous NICE MS appraisals including fingolimod (TA254)[14], teriflunomide (TA303)[55], alemtuzumab (TA312)[2], dimethyl fumarate (TA320)[56], beta interferons and glatiramer acetate (TA527)[11] and peginterferon beta-1a (TA624)[54], which were based on 21 EDSS health states (previous models had included a EDSS 0 health state for SPMS). The company justified removing this on the basis that the conversion assumption (which assumes people who convert to SPMS move into an EDSS score of +1), had been used previously in a study by Mauskopf et al.[57] and previous NICE TAs including ocrelizumab (TA533)[53].

Figure 1: Model structure



4.2.3. Population

The company presented cost effectiveness results for two RRMS populations: the ITT population, which reflected the ITT population from OPTIMUM, used to represent people with active RRMS; and the HA RRMS population, which reflected the subgroup population of OPTIMUM, including people with highly active or RES RRMS (see Document B, p.110).

For the ITT population, people entered the model based on their baseline EDSS distribution in the OPTIMUM study. As outlined in Table 29, approximately [redacted] of participants had an EDSS

score of three or less, with [redacted] in EDSS 4 and 5. For the HA subgroup ([redacted]), comparatively fewer participants had a baseline EDSS score of three or less ([redacted]), whilst a higher proportion of participants had an EDSS score of 4 and 5 ([redacted]).

Table 29: Baseline EDSS distribution of participants within the economic model

	Baseline EDSS distribution (ITT population)	Baseline EDSS distribution (HA RRMS)
EDSS 0	[redacted]	[redacted]
EDSS 1	[redacted]	[redacted]
EDSS 2	[redacted]	[redacted]
EDSS 3	[redacted]	[redacted]
EDSS 4	[redacted]	[redacted]
EDSS 5	[redacted]	[redacted]

Abbreviations: EDSS, expanded disability status scale; HA, highly active; ITT, intention-to-treat; MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis

The ERG noted that OPTIMUM was a global multi-centre study that included relatively few participants from the UK. However, based on clinical input to the ERG, participant characteristics from OPTIMUM for both the active and HA populations were considered to be broadly generalisable to the UK. Therefore the ERG considered these characteristics to be appropriate for use in the model. For completeness the ERG conducted a scenario analysis that used population characteristic data from the UK RSS dataset for the ITT population; however, while this population is based in the UK, it also included people with SPMS, and people who had a longer disease duration without access to DMTs, and may therefore not be highly generaliseable to the target population. It is worth noting that using UK RSS population data in the model did not have a material impact on the base case results (see Section 6.1.1.3).

Finally, in Document B, p107, the ERG noted that a relatively small proportion of participants in OPTIMUM had SPMS; i.e. [redacted]. Due to the small proportion of participants with SPMS, the ERG considered that the inclusion of this group was unlikely to be a key concern. In support of this, subgroup analyses from OPTIMUM removing these participants showed comparable findings to the ITT population.

4.2.4. Interventions and comparators

In the ITT population, the company initially compared ponesimod to teriflunomide, dimethyl fumarate, pegylated interferon beta-1a, glatiramer acetate, interferon beta-1a (22 mcg, 44 mcg),

interferon beta-1a (30mcg), interferon beta-1b and ocrelizumab. The company stated that the comparators were selected based on approved first line treatments for RRMS, as per the NHSE treatment algorithm. Based on clinical expert opinion to the ERG, the comparators appeared appropriate; however, two treatments (ofatumumab and ozanimod), which are currently under NICE review, were not included as part of the clinical or economic analyses. During the clarification stage, the ERG asked the company to update the NMA's and economic model to incorporate evidence for both treatments and provide updated results. This was subsequently provided, though the ERG acknowledged that it was unclear if these treatments would be recommended for the treatment of active RRMS.

For the HA RRMS subgroup, the company compared ponesimod to alemtuzumab, cladribine, fingolimod and ocrelizumab. Clinical input to the ERG confirmed that these treatments are widely used to treat people with HA RRMS in the UK (see Section 5.1.1.2 for results). At clarification the company also provided clinical and cost effectiveness analyses comparing ponesimod to ozanimod and ofatumumab in the HA RRMS population. Again, the ERG acknowledged that at the time of writing, it was unclear whether ozanimod and ofatumumab would be recommended by NICE for the treatment of HA RRMS.

4.2.5. Time horizon, perspective and discounting

A 50-year (lifetime) horizon was used in the company's base case. As MS is considered to be a progressive, lifelong condition the ERG considered that 50 years was sufficiently long enough to capture the differences in costs and effects between treatments. Furthermore, a 50-year time horizon has been used and accepted in previous MS submissions to NICE including fingolimod (TA254)[14], teriflunomide (TA303)[55], alemtuzumab (TA312)[2], dimethyl fumarate (TA320)[56], beta interferons and glatiramer acetate (TA527)[11], ocrelizumab (TA533)[53] and peginterferon beta-1a (TA624)[54]. Overall, the ERG considered the modelled time horizon to be reasonable.

The cycle length used in the model was one year. In the CS (Document B, p.108) the company stated that this was selected in order to be consistent with MS natural history data, as reported by Palace (2014)[25] and Mauskopf (2016)[57]. The ERG considered this justification to be reasonable and acknowledged the appropriateness of a 1 year cycle length in the model, but noted that the model did not allow for the cycle length to be varied.

There were no concerns surrounding discounting. Costs and benefits were discounted at 3.5% which reflects NICE guidance. All costs and outcomes were estimated from an NHS and PSS perspective, as appropriate.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Modelled treatment efficacy based on 3-month CDA

As noted in Section 4.2.3, people entered the model according to their OPTIMUM baseline EDSS score and moved through the EDSS health states via treatment-specific transition probabilities. Transition probabilities were estimated using clinical data from the company's NMA outlined in Tables Table 30 and Table 31 below; i.e. 3-month CDA hazard ratios vs. placebo were applied to natural history data from the British Columbia MS dataset[25] (see Document B, p112 for the transition matrix). Based on the results from the company's 3-month CDA NMA for the ITT population, ponesimod was associated with a lower risk of 3-month CDA than many of the other DMTs, with the exception of alemtuzumab, ofatumumab and ocrelizumab. For the HA subgroup, ponesimod was less effective for reducing the risk of 3-month CDA than cladribine, ofatumumab and ocrelizumab.

The ERG were uncertain why the company used three-month CDA as the primary outcome measure for disease progression, when six-month CDA estimates from the NMAs were also available for all but one comparator (interferon beta 1a SC22). The ERG opined that the six-month CDA was a more appropriate measure of disease progression on the basis of clinical advice, which noted that three-month CDA may potentially overestimate progression due to natural fluctuations in the disease. Furthermore, six-month CDA was considered as NICE's preferred measure of disease progression in previous MS TAs, including alemtuzumab (TA312)[2].

During the clarification stage the company was asked to comment on why six-month CDA was not used in the base case analysis to derive treatment effect estimates. The company commented that there were a larger number of closed loops in the three-month CDA and that it was considered more robust, stating that the six-month CDA was defined more frequently as a secondary outcome in the networks. Furthermore, the company noted that in the NICE appraisal of ocrelizumab (TA533)[53] and ofatumumab (TA699)[13], committee members had identified concerns surrounding the inclusion of the ADVANCE study for peginterferon beta-1a, as it produced clinically implausible six-month CDA results. The ERG acknowledged the potential limitations surrounding the six-month CDA highlighted by the company, noting that

heterogeneity and a lack of robust evidence is a significant cause of uncertainty across all of the company's NMAs. However on balance, the ERG still considered six-month CDA to be a more valid measure of disease progression, and preferred this outcome measure in the its preferred base case.

Clinical efficacy data used in the economic model

With respect to the key clinical efficacy data used in the company's economic model, the ERG considered the robustness of the NMAs to be a key area of concern (see Section 3.4.5). Clinical effectiveness estimates (based on 3-month CDA) used to derive transition probabilities, relapse rates and treatment discontinuation rates, were all associated with a high degree of uncertainty, and were surrounded by relatively wide confidence intervals. As a means of testing uncertainty surrounding modelled treatment effect estimates, the ERG conducted a further scenario analysis which derived DMT clinical effectiveness estimates by grouping treatments according to their positioning and using the median effect estimate to parameterise the model (see section 6.1.1.7 for further detail).

Natural history progression

In terms of the natural progression data used within the model, the ERG considered the British Columbia dataset used by the company to be an appropriate source for the active RRMS population (see CS Document B, p112 for the transition matrix). This Canadian observational study, which followed 898 people with RRMS and SPMS over 15 years, has also been accepted in previous NICE RRMS appraisals, including the appraisal of cladribine (TA493)[27], beta interferon and glatiramer acetate (TA527)[11], ocrelizumab (TA533)[53] and peg interferon beta 1a (TA624)[54]. The ERG was aware of an alternative natural history dataset (London Ontario), which could have been used to estimate base case transition probabilities for the active RRMS population; however previous NICE TAs, including teriflunomide (TA303)[55] and alemtuzumab (TA312)[2], have noted limitations in the use of this dataset, given that the study did not collect data on people whose disease had improved.

As a means of exploring the impact of using an alternative set of natural history transition probabilities in the model, the company conducted a scenario analysis using a combination of data from the placebo arm of DEFINE[58], a dimethyl fumarate trial, and the London Ontario dataset. Transition probabilities for EDSS states 0-7 were therefore derived from DEFINE whilst transitions between EDSS states 8-9 were taken from the London Ontario dataset. The

company stated that this analysis represented RRMS progression in a controlled environment, though the ERG were unclear on the company's rationale for selecting DEFINE for this analysis. As outlined in Document B, p171, results were not overly sensitive to this analysis. The ERG acknowledged that the scenario of using alternative natural history transition probabilities was useful, however considered the British Columbia dataset to be a better representation of real world disease progression.

For the HA RRMS subgroup, the natural history transition matrix was based on a previous NICE appraisal for ocrelizumab (TA533)[53], which reflected progression of participants in the placebo arm of the AFFIRM trial for natalizumab (for EDSS 0-6). For EDSS 7-9 the company used values from the British Columbia database (Document B, p119). Given that NICE had previously critiqued the use of the London Ontario data to model natural disease progression for the HA population in its appraisal of alemtuzumab (TA312)[2], the ERG considered the company's approach to be reasonable.

For people who progressed to SPMS, people were assumed to transition through health states based on the London Ontario dataset.

Table 30: Modelled CDA (ITT population)

Treatment	**3 month CDA (hazard ratio vs. placebo)**	**6 month CDA (hazard ratio vs. placebo)**
Ponesimod	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Interferon beta-1a 22mcg	[redacted]	[redacted]
Interferon beta-1a 30mcg	[redacted]	[redacted]
Interferon beta-1a 44mcg	[redacted]	[redacted]
Interferon beta-1b 250mcg	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Peginterferon beta-1a 125mcg	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]

Abbreviations: CDA, confirmed disability accumulation; ITT, intention-to-treat

Table 31: Modelled CDA (HA RRMS group)

Treatment	3 month CDA (hazard ratio vs. placebo)	6 month CDA (hazard ratio vs. placebo)
Ponesimod	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]

Abbreviations: CDA, confirmed disability accumulation; HA, highly active; RRMS, relapsing-remitting multiple sclerosis

Annualised relapse rates

The company's model captured the impact of relapse associated with RRMS via the inclusion of annualised relapse rates for each treatment. When a person experienced a relapse, they incurred a utility decrement associated with relapse and incurred a specific relapse cost. See Section 4.2.7.1 and 4.2.8.2 for further detail on modelled disutility and cost per relapse).

For people with active RRMS, default annual relapse rates (or natural history rates) associated with each EDSS health state were derived from published literature (Mauskopf et al.[57]). Annualised relapse rates were then derived by applying treatment-specific rate ratios from the NMA to these natural history data (see Table 32 below). For the HA subgroup, the company derived average annual relapse rates from the placebo arm of the AFFIRM trial from natalizumab (TA127)[59]. The company stated that ARRs in the HA RRMS population are approximately 1.98 times higher compared with the ITT population. The ERG noted that the company did not provide rationale for selecting to use AFFIRM as a means of estimating annualised relapse rates for people with HA RRMS. As such there may be some uncertainty surrounding modelled ARR estimates for people with HA RRMS.

Overall, the ERG identified a number of limitations with the results of the company's NMAs, which increased uncertainty surrounding modelled relapse rates (see Section 3.4.5). The company conducted one-way sensitivity analyses that varied the rate ratio in relapse for DMTs, however this did not have a material impact on the results. Whilst the ERG acknowledged that relapse rates are not the key efficacy driver within the company's model, differences in relapse rates between treatments are expected to impact on the incremental costs and QALYs when varied.

Table 32: Relapse rates used in the company's model for ITT and HA RRMS

Treatment	Rate ratio for relapse vs. placebo (ITT population)	Rate ratio for relapse vs. placebo (HA RRMS)
Ponesimod	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Interferon beta-1a 22mcg	[redacted]	[redacted]
Interferon beta-1a 30mcg	[redacted]	[redacted]
Interferon beta-1a 44mcg	[redacted]	[redacted]
Interferon beta-1b 250mcg	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Peginterferon beta-1a 125mcg	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]

Abbreviations: RRMS, relapsing remitting multiple sclerosis

Progression from RRMS to SPMS

The modelled annual EDSS baseline probability of progressing from RRMS to SPMS was derived from a US study by Mauskopf (2016)[57], which estimated the cost effectiveness of delayed release dimethyl fumarate for the treatment of RRMS. Annual SPMS conversion probabilities were based on the London Ontario natural history study, which was considered to be an appropriate data source. Upon progressing to SPMS the company assumed that EDSS would increase by 1. Although the base case conversion rates used by the company were considered reasonable, the ERG noted that these were higher than those used in the submission for peginterferon (TA624)[54]. These values appear to have been derived from hazards presented in the appraisal of daclizumab (TA441)[60], which has recently had its marketing authorisation withdrawn. A comparison of these probabilities is provided in below.

Table 33 Annual probability of converting from RRMS to SPMS

EDSS state	Mauskopf et al.[57]	Peginterferon (TA624)[54]
EDSS 0	0.000	0.004
EDSS 1	0.003	0.002
EDSS 2	0.032	0.029

EDSS state	Mauskopf et al.[57]	Peginterferon (TA624)[54]
EDSS 3	0.117	0.097
EDSS 4	0.210	0.181
EDSS 5	0.299	0.225
EDSS 6	0.237	0.168
EDSS 7	0.254	0.211
EDSS 8	0.153	0.064
EDSS 9	1.000	0.154

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

The company explored uncertainty surrounding this parameter via probabilistic sensitivity analysis and did not conduct one way sensitivity or scenario analyses. As an exploratory analysis, the ERG conducted a scenario analysis using the SPMS annual conversion probabilities reported in pegylated interferon (TA624)[54]. The ERG noted that this scenario analysis had a material impact on the ITT analysis results, though not those in the HA RRMS subgroup. See Section 6.1.1.12 for results and further discussion.

Modelled treatment discontinuation rates

Within the model, people are capable of discontinuing treatment for the following three reasons

1. When a person's EDSS score equals or exceeds 7
2. When a person progresses from RRMS to SPMS
3. When a person discontinues prematurely for any reason (e.g. lack of efficacy, due to adverse events).

As outlined in CS Document B, p.118, discontinuation assumptions 1 and 2 above have been used in previous NICE TAs, including natalizumab (TA127)[59], fingolimod (TA254)[14], alemtuzumab (TA312)[2], cladribine (TA493)[27], ocrelizumab (TA533)[53] and peginterferon beta 1a (TA624)[54], and were considered appropriate. However, there was some uncertainty surrounding assumption 3, which involved estimating annual treatment discontinuation rates using odds ratios for all-cause discontinuation from the ITT population NMA (for ponesimod versus each comparator). To derive annual discontinuation rates, the relative risk of discontinuation for each treatment was then multiplied by the annual discontinuation rate for ponesimod (see annual discontinuation rates in Table 34 below). The annual discontinuation rate for ponesimod was calculated from pooled data from the OPTIMUM and the Phase 2 trial of ponesimod. As noted

previously in Sections 3.4.2 and 3.6, there is a high degree of uncertainty surrounding estimates derived from the company's NMAs. Furthermore, due to the lack of all-cause discontinuation data reported by trials for the HA RRMS population, no NMA was conducted for this outcome and the company assumed that discontinuation rates from the ITT population would be generalisable to the HA population and its relevant comparators. The ERG considered the lack of robust treatment discontinuation data for the HA population to be an area of uncertainty. More broadly, while the company's decision to use all-cause discontinuation in the model may have been pragmatic, the ERG noted that the definition included discontinuation due to trial attrition. Notably, in the OPTIMUM trial, less than half of trial discontinuations were due to efficacy or safety issues (see Table 15). It was therefore unclear to what extent this outcome could be generalised to clinical practice, and how variation in trial methodology and outcome measurement created heterogeneity in the evidence base.

Table 34. Modelled treatment discontinuation rates

Treatment	Annual discontinuation rates (%)
Ponesimod	[redacted]
Teriflunomide	[redacted]
Dimethyl fumarate	[redacted]
Glatiramer acetate	[redacted]
Interferon beta-1a 22mcg	[redacted]
Interferon beta-1a 30mcg	[redacted]
Interferon beta-1a 44mcg	[redacted]
Interferon beta-1b 250mcg	[redacted]
Ocrelizumab	[redacted]
Peginterferon beta-1a 125mcg	[redacted]
Alemtuzumab	[redacted]
Cladribine	[redacted]
Fingolimod	[redacted]
Ofatumumab	[redacted]
Ozanimod	[redacted]

To explore uncertainty in discontinuation rates, the company included an option in the model to apply a common discontinuation rate to all treatments (5%), for both the active RRMS and HA RRMS populations. Whilst this scenario was considered useful for determining the impact of discontinuation rates on the base case results, the ERG noted that in peginterferon beta 1a (TA624)[54], NICE preferred the use of treatment specific discontinuation rates. The ERG acknowledged that assuming a flat discontinuation rate of 5% for all treatments was simplistic

and may not reflect clinical practice, given that each treatment is associated with a specific adverse event and efficacy profile.

The ERG noted that the company's scenario analysis that applied a 5% discontinuation rate to all treatments resulted in increased total costs and QALYs for all treatments; however it did not have a material impact on the base case ICERs. For completeness, the ERG conducted a further scenario analysis that applied a 5% discontinuation rate to all treatments and incorporated the model changes made by the company during the clarification stage. See Section 6.1.1.5 for description and results.

Treatment waning assumptions

The ERG noted that there was a lack of long term clinical effectiveness data for ponesimod and comparator DMTs (input data for the NMAs were generally derived from endpoints under 3 years; range 24-144 weeks, median = 96 weeks). Therefore, there is uncertainty surrounding the maintenance of treatment effects for disease progression and relapse rates over time. In the base case analysis (for both the active RRMS and HA RRMS populations) the company applied the same treatment waning assumption to all DMTs; i.e. a 25% decrease in treatment efficacy was applied from years 2 to 5, followed by a 50% decrease in efficacy applied from year 6 onwards. The ERG noted that this assumption had previously been used in NICE appraisals of dimethyl fumarate (TA320)[56] and peginterferon beta 1a (TA624)[54]. In the appraisal of peginterferon beta 1a (TA624), the committee acknowledged that DMTs are likely to have different waning assumptions in practice, however in the absence of evidence, the same waning assumptions should be applied to all treatments.

The company explored uncertainty surrounding treatment efficacy waning by conducting two scenario analyses using alternative assumptions; i.e. no treatment waning and a further analysis which applied a 50% decrease in treatment effectiveness to all DMTs at 10 years. As outlined in (Document B, p171-174), results in both the ITT and HA populations were not considered sensitive to these scenarios. For completeness, the ERG conducted a scenario analysis which assumed 100% treatment efficacy for all DMTs; i.e. no waning over time. This analysis was based on the company's updated NMAs, which included ozanimod and ofatumumab, as well as alternative monitoring assumptions for ponesimod. See Section 6.1.1.6 for description and results.

Subsequent treatment assumptions

RRMS population

In the base case analysis, the company assumed that all people with active and HA RRMS people who stop treatment will go on to receive BSC. The company justified this approach on the basis that it allows the analysis to highlight differences in treatment effects for the initial phase of treatment and is consistent with previous appraisals including alemtuzumab (TA312)[2], ocrelizumab (TA533)[53], dimethyl fumarate (TA320)[56], beta interferons and glatiramer acetate (TA527)[11]. Although the ERG largely accepted the company's justification and acknowledged that there is precedent for using BSC as the primary treatment option post discontinuation, clinical advice to the ERG outlined that people are highly likely to receive a further DMT in practice (with the choice of subsequent DMT dependent on the rationale for discontinuation; e.g. lack of response or tolerability, or treatment break for pregnancy). The ERG considered conducting scenario analyses using assumptions for subsequent treatments suggested by clinical experts, however given that the choice and probability of subsequent treatment use will differ due to the reasons for discontinuing, the scenario was considered to introduce additional complexity and uncertainty. Furthermore, the ERG was unable to identify any prescribing data, which could inform subsequent treatment use in the model. As a result, the ERG accepted the company's base case assumption; however, acknowledged that it is unlikely to reflect clinical practice.

The company explored the impact of subsequent treatment use on the base case results via scenario analyses: the company assumed that 100% of the ITT population who discontinued went on to receive cladribine, whilst 100% of the HA population who discontinued went on to receive natalizumab (see Document B, p125-126 outlining the company's justification for selecting these as subsequent treatments). This is a simplifying approach, given that, as noted above, the choice of subsequent treatment will depend on the rationale for stopping treatment. It should be noted that, for these scenarios, the company included the clinical effectiveness of subsequent treatments (based on the NMA results). Due to the limitations surrounding the clinical effectiveness estimates, the ERG considered that modelling subsequent treatment effects introduced additional uncertainty.

As an exploratory analysis the ERG conducted a scenario using alternative subsequent treatments for both the ITT and HA RRMS populations. Both of these scenario analyses applied additional costs of subsequent treatments, but did not account for the clinical efficacy of these

treatments. These analyses were therefore considered to evaluate the impact of altered costs of subsequent treatment on the ICER, but would over-estimate rates of disease progression in those who switch treatment. See section 6.1.1.4 for further description and results.

SPMS group

The ERG noted that siponimod (TA656)[1] has been recommended by NICE for the treatments of people with SPMS, however in the model the company has not included siponimod as a treatment option for people who progress to SPMS; i.e. it is assumed that 100% of people who progress to SPMS will go on to receive BSC as the primary subsequent treatment option. Clinical experts to the ERG also noted that in practice a proportion of people with SPMS will receive treatment with interferon beta (IFNB)-1b. During the clarification stage, the company was asked to comment on why siponimod was excluded from the analysis and responded noting that their approach was consistent with NHS treatment guidelines and previous NICE appraisals (clarification question B4). The ERG confirmed that previous appraisals had not included siponimod or IFNB-1b as treatment for SPMS; however following its recent approval by NICE, clinical advisors to the ERG advised that a proportion of people with SPMS will start to routinely receive this. As siponimod is a new treatment, true rates of treatment uptake in the NHS are yet unknown, however clinical experts to the ERG advised between 12% - 50% of people may receive siponimod. As an exploratory analysis, the ERG conducted a scenario analysis that assumed a proportion of people who progress to SPMS receive siponimod. See Section 6.1.1.2 for description and results.

Mortality

All-cause mortality rates for people with RRMS were included for each EDSS health state, based on age and gender mortality risks for the UK, which were taken from UK life tables[61]. These underlying rates were then adjusted by applying a RRMS specific mortality relative risk to each health state using a linear interpolation approach as reported by Pokorski (1997)[62]l. In (Document B, p126), the company stated that there was a lack of data to inform differentiated mortality risk for each EDSS health state in people with SPMS (as compared to RRMS). Therefore, a simplifying assumption was made whereby people with RRMS and SPMS, in the same EDSS health state, were assumed to have the same relative risk of mortality (see Document B, p126 for EDSS mortality used in the model). Given the paucity of data surrounding SPMS mortality risk according to EDSS state, and the acceptance of this assumption previously

in peginterferon beta 1a (TA624)[54], the ERG considered the company's assumption to be reasonable.

The ERG noted that linear interpolation relative risks of mortality from Pokorski et al. were considered appropriate for use by the committee in the NICE appraisal of peginterferon beta 1a (TA624), as these values better reflected the mortality risk versus the general population as EDSS levels increase when compared to non interpolated values. The ERG noted that the company provided a scenario analysis that used raw mortality rates (without interpolation), however this did not have a material impact on the base case results.

4.2.7. Health-related quality of life

4.2.7.1. Baseline EDSS utility

For both the ITT and highly active populations, baseline EDSS utility values were derived from published literature Orme (2007)[51] (see Table 35 below). Orme et al. is a UK study that estimated the effect of disease, functional status and relapses on the utility of people with RRMS in the UK. Within the study, 12,968 people registered on the MS trust database were sent a postal survey, and utility was assessed using the EQ-5D (note only 15% of responses were used in the analysis due to low response rates). Utilities were estimated via an appropriate UK value set using the time trade off method from Dolan et al.[52]. The ERG acknowledged the strengths of Orme et al. as the primary source of EDSS utility; i.e. values were elicited directly from people with RRMS in the UK (or carers), however several key limitations were identified. The primary concern related to the generalisability of these participants to those within the OPTIMUM study. For instance, participants included in the Orme et al. study were older and had more severe disease at baseline compared to those in OPTIMUM. Mean age in Orme et al.[51] was 51.4 years and 59.6% were distributed across EDSS states 4 – 6 (compared to a mean age of [redacted] and [redacted] distribution of ITT participants across EDSS states 4 – 6). As such, it's feasible that utility values within the model could be underestimated.

Based on the appraisal of peginterferon beta 1a (TA624)[54], the ERG were aware of a more recent study by Thompson (2017)[63], which reported quality of life burden and costs associated with RRMS in a UK population. As an exploratory analysis, the ERG conducted a scenario analysis that used baseline EDSS utility values reported in Thompson et al. (2017)[63]. See Section 6.1.1.11 for further description and results.

Based on a review of previous NICE RRMS appraisals, including fingolimod (TA254)[14], alemtuzumab (TA312)[2], teriflunomide (TA303)[55], and ocrelizumab (TA533)[53], the ERG confirmed that Orme et al.[51] had been accepted as an appropriate source of patient utility. As such, the ERG considered Orme et al. to be a reasonable source for use in the base case analysis. However, the ERG noted that the lack of HRQol data from OPTIMUM in the company's model was a source of uncertainty: while HRQoL was measured in OPTIMUM (SF-36), these data were not mapped to EQ-5D values or used in the model. The company did not provide justification for this.

A final limitation surrounding the modelled utility values is the assumption that people with active RRMS and HA RRMS have the same EDSS utilities, which the ERG considered was unlikely due the impact of more severe disease on the lives of people with HA RRMS.

In the model, a person's baseline EDSS utility was assumed to decrease upon progression, relapse and as a result of adverse events. Disutility associated with a relapse was estimated to be -0.071 (based on Orme et al.[51]). The company conducted a one-way sensitivity analysis that varied disutility associated with relapse using upper and lower bound percentiles, however this did not have a material impact on the base case results. Finally, upon progression to SPMS within the model, a further utility decrement of -0.045 was applied to each baseline EDSS utility value (based on Orme et al.[51]).

Table 35: Modelled EDSS utility values (based on Orme et al.[51])

Health state	RRMS	SPMS
EDSS 0	0.870	N/A
EDSS 1	0.799	0.754
EDSS 2	0.705	0.660
EDSS 3	0.574	0.529
EDSS 4	0.610	0.565
EDSS 5	0.518	0.473
EDSS 6	0.460	0.415
EDSS 7	0.297	0.252
EDSS 8	-0.049	-0.094
EDSS 9	-0.195	-0.240

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

4.2.7.2. Carer disutility

For both the ITT and HA populations, the model captured the HRQoL impact for caregivers based on a published study by Acaster et al. (2013)[64] (see disutilities in Table 36 below).

The ERG acknowledged that the inclusion of caregiver disutility was appropriate in the base case and is preferred by NICE, based on its appraisal of fingolimod (TA254)[14] and natalizumab (TA127)[59]. Acaster et al.[64] was a UK observational study that assessed the HRQoL impact on carers of people with RRMS: an online survey of 200 RRMS carers was conducted and compared to a matched control cohort. Impact on HRQoL was assessed using a number of instruments including the EQ-5D, and utilities were estimated using the UK value set from Dolan et al.[52], as appropriate. Carer disutility was estimated for patient-determined disease steps (PDSS) states, which is a self-assessment scale that assesses functional disability in people with MS.

The ERG noted that although similar, the PDSS and EDSS are not identical assessment measures; i.e. the EDSS is clinician led and offers a more granular assessment of disease. As such, there may be some uncertainty surrounding the assumption that PDSS states translate directly to EDSS states. Additionally, from Acaster et al.[64], it was unclear what proportion (if any) of respondents were carers of people with HA RRMS.

The ERG confirmed that Acaster et al. has been used in previous NICE TAs, including beta interferon 1a and 1b and glatiramer acetate (TA527)[11] and peginterferon beta 1a (TA624)[54]; however noted that Gani[65] was the primary source of carer disutility in NICE appraisals of alemtuzumab (TA312)[2], fingolimod (TA254)[14], and terilunomide (TA303)[55]. The UK study by Gani et al.[65] assessed the cost effectiveness of natalizumab compared to other DMTs for people with HA RRMS (see CS Document B, p131 for further description surrounding the estimation of these values). The company provided a scenario analysis that used carer disutility values reported by Gani et al.[65] for the active RRMS population, however the ERG noted that this did not have a material impact on results (see Document B, p166). For completeness, the ERG assessed the impact of using Gani et al.[65] values for the HA RRMS population. Results were not found to be sensitive to these values.

The ERG noted that carer disutility for SPMS was assumed to be the same as RRMS. This is considered to be a limiting assumption, however, given the paucity of data surrounding carer disutility in SPMS, and the fact that this assumption had been previously used in peginteferon beta 1a (TA624)[54], the ERG considered this to be reasonable.

Table 36: Modelled EDSS carer disutilities

	Base case carer disutilities (Acaster et al.)[64]	Scenario carer disutilities (Gani et al.)[65]
EDSS 0	0.002	0.000
EDSS 1	0.002	0.000
EDSS 2	0.045	0.000
EDSS 3	0.045	0.010
EDSS 4	0.142	0.010
EDSS 5	0.160	0.020
EDSS 6	0.173	0.030
EDSS 7	0.030	0.050
EDSS 8	0.095	0.110
EDSS 9	0.095	0.140

Abbreviations: EDSS, expanded disability status scale

4.2.7.3. Adverse event disutility

Disutility associated with serious and non-serious adverse events were captured in the model. Given that each treatment has a specific adverse event profile, the ERG considered adverse event disutility to be appropriate for inclusion (see CS Document B, p130 for the full list of adverse events and disutilities included in the model). For all treatments, the incidence rates for severe and non-severe events were derived from a SLR conducted by the company. The ERG noted that the incidence of adverse events for ponesimod as based on the company's SLR were lower than the incidence rates based from the long-term pooled analysis set for ponesimod reported in the CS (Document B, p.92; see Table 37 below).

Table 37: Adverse event incidence

Adverse event	Ponesimod (AE incidence long term pooled analysis set)	Ponesimod (modelled AE incidence)
Nasopharyngitis	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Backpain	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Upper urinary tract infection	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]

The company conducted one-way sensitivity analysis and probabilistic sensitivity analysis which varied incidence rates and disutilities associated with adverse events for ponesimod and comparator DMT's. However this did not have a material impact on results. The ERG considered that adverse event disutilities in the model were not a key driver of cost effectiveness.

4.2.8. Resources and costs

Medicine acquisition costs were included for all treatments and are outlined in the CS (Document B, p.135). Within the CS, the company presented the annual acquisition cost for each treatment, with the model providing further detail on the calculation of each. Unit costs (price per pack) and dose frequency were primarily derived from the British National Formulary (BNF)[66], which is considered to be an appropriate source. The ERG noted that annual drug acquisition costs in years 1 and 2 were largely in line with previous RRMS apraisals including pegiterferon (TA624) and therefore seemed reasonable.

It should be noted that for alemtuzumab and cladribine treatment acquisition costs, the company assumed that a proportion of people receiving these treatments would require re-treatment, if relapses continued to occur. For alemtuzumab, 28%, 11% and 1% of people were assumed to reinitiate treatment in Years 3, 4 and 5 respectively, and for cladribine this was 9.3%, 4.2% and 3.2% respectively. These rates were derived from the NICE appraisal of cladribine (ID64)[67]. The ERG acknowledged that re-treatment rates for both alemtuzumab and cladribine had been included in previous appraisals of cladribine by NICE (TA493)[27] and the SMC (SMC 1300/18)[68]. In both appraisals, uncertainty surrounding the appropriateness of these rates was outlined (due to the lack of effectiveness evidence on re-exposure). In cladribine (TA493)[27], the ERG conducted an analysis which removed retreatment rates for both treatments, however this did not have a material impact on the base case results. The ERG considered that removing cladribine and alemtuzumab re-treatment rates would result in a decrease in total costs for these treatments, however it was unlikely to have a meaningful impact on results, given the high acquisition costs of both.

4.2.8.1. Administration and monitoring costs

The model included differentiated costs for year one and subsequent years in order to account for differences in monitoring and administration assumptions between treatments. The ERG considered this approach to be consistent with previous NICE TAs for RRMS, and therefore appropriate. Administration costs were included for IV and SC treatments in year 1 and years 2+ (for both treatments in both the ITT and HA RRMS populations). As ponesimod is taken orally (20mg once daily), no administration costs were included in the model in years 1 and 2+. Similarly, administration costs were not included for other oral treatments, including dimethyl fumarate, teriflunomide, ozanimod, and cladribine. The ERG considered that the exclusion of administration costs for oral treatments was reasonable.

For peginterferon beta 1a 125mcg, glatiramer acetate, interferon beta-1a, interferon beta-1b, alemtuzumab and fingolimod, administration costs were estimated based on resource use estimates within NICE (TA624)[54] and ocrelizumab (TA533)[53]. For ofatumumab and ozanimod, resource use estimates were taken from (TA ID1677)[13] and ID1294[12]. Costs were valued using the Personal Social Services Research Unit (PSSRU) and NHS reference costs 2018/19, as appropriate. Overall, the ERG considered the administration costs included in the analysis to be appropriate.

In relation to monitoring costs, annual resource use estimates for each treatment, apart from ponesimod and cladribine, were based on estimates used in the NICE appraisal of ocrelizumab (TA533)[53]. In the company's base case analysis it was assumed that ponesimod would be associated with 30% of the monitoring costs for fingolimod in year 1, and no monitoring required in subsequent years thereafter. With respect to monitoring costs in year 1, the company justified this assumption in the CS (Document B, p134), noting that 30% of participants in OPTIUMUM required monitoring after the first dose, which was based on an estimated 18.5% of participants being at risk of symptomatic bradycardia, then inflated to account for the exclusion of people with certain cardiovascular disorders. The company claimed that the methods for up-titrating ponesimod, and the increased specificity of ponesimod to the $S1P_1$ receptor will result in fewer AEs than fingolimod. Based on clinical input to the ERG and the safety profile of ponesimod reported in Section 3.5.3 and 3.5.4 (which indicated cardio and ophthalmic concerns with ponesimod when compared to teriflunomide), these assumptions were not considered to be have been fully justified. As the data did highlight some concerns of liver toxicity in participants treated with ponesimod, clinical advisors to the ERG suggested that monitoring should match that of fingolimod until further evidence for its safety is available. As an exploratory analysis, the ERG conducted a scenario analysis which assumed fingolimod had identical monitoring costs to fingolimod in year 1. See section 6.1.1.8 for further description and results

During the clarification stage, the company subsequently provided a revised model that updated ponesimod monitoring costs in year 2+, as clinical expert advice to the ERG considered £0 monitoring costs in subsequent years to be inappropriate. The ERG acknowledged that the updated monitoring cost provided by the company (£228.82) was broadly in line with other oral DMTs. Overall, monitoring and administration costs were not a key driver of cost effectiveness results (in either the ITT or HA RRMS populations), given the magnitude of drug acquisition costs and disease management costs for all treatments.

4.2.8.2. **Health state costs**

The model included EDSS health state costs for people with RRMS and SPMS, which represented costs associated with disease management. Costs were derived from a study by Tyas et al. (2007)[69], and included direct health care costs as well as costs for community services i.e. nurse visits, home helper and other major investments (see Document B, p143). Values were inflated to 2019 as appropriate. The ERG noted that indirect costs (e.g. informal care, productivity losses) were excluded. Given that the analysis was conducted from an NHS and PSS perspective, this was considered to be reasonable.

Tyas et al.[69] was a UK study that examined the cost of RRMS according to disease severity. The ERG noted that Tyas et al.[69] had been used previously in NICE appraisals for RRMS including teriflunomide (TA303)[55], alemtuzumab (TA312)[2] and ocrelizumab (TA533)[53]. The ERG noted that the company did not provide results for a scenario analysis basing EDSS disease management costs on alternative literature sources. The ERG was aware of other relevant sources including a relatively recent study by Thompson et al. (2018)[5] that re-examined the financial impact associated with RRMS in the UK. As an exploratory analysis the ERG conducted a scenario analysis using this alternative study to estimate disease management costs. See section 6.1.1.9 further description and results.

In the NICE appraisal of beta interferons and glatiramer acetate (TA527),[11] the assessment group preferred costs used in the appraisal of dimethyl fumarate (TA320),[56] which used costs from the UK MS survey in 2005 (subsequently reported by Tyas et al.[69]). As such, the ERG considered the use of direct costs from Tyas et al.[69] to be an appropriate source for use within the base case analysis.

The ERG noted that disease management costs were the same for both the ITT and HA RRMS populations. From Tyas et al.[69] it was unclear what proportion of participants (if any) had HA RRMS. Clinical advice to the ERG was that disease management costs are likely to be higher for people with HA RRMS, as people will have more relapses. The company conducted a one-way sensitivity analysis that varied disease management costs in RRMS and SPMS. ITT results were not overly sensitive to this analysis, however the ERG noted that in the HA RRMS subgroup, varying disease management costs for SPMS did have a material impact on results. The ERG acknowledged that the lack of robust EDSS disease management costs for HA RRMS (particularly in SPMS) is an area of uncertainty, however in the absence of relevant cost data for this subgroup, the use of Tyas et al. was considered reasonable.

Table 38: Modelled disease management costs

	RRMS	**SPMS**
EDSS 0	£998.74	NA
EDSS 1	£1,039.11	£1,386.86
EDSS 2	£760.70	£1,108.45
EDSS 3	£4,165.75	£4,512.46
EDSS 4	£2,018.19	£2,364.90
EDSS 5	£3,422.64	£3,771.42

	RRMS	SPMS
EDSS 6	£4,569.38	£4,916.10
EDSS 7	£12,027.36	£12,374.08
EDSS 8	£29,293.73	£29,641.48
EDSS 9	£23,439.95	£23,788.74
Relapse costs		
0-9	£2,243.81	£2,243.81

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

Costs associated with relapse

As noted in Section 4.2.2, in the model people were capable of experiencing relapse whilst in any EDSS state. The source of relapse cost used was the NICE appraisal of peginterferon beta 1a (TA624)[54]. Relapse costs within the appraisal were inflated from previous values published within dimethyl fumarate (TA320);[56] i.e. Tyas et al.[69] The company inflated costs to 2019 levels using the HCHS index and the PSSRU as appropriate. The cost of relapse in the model was estimated to be £2,243.

Although Tyas et al.[69] had been used previously in the NICE appraisal of fingolimod (TA254)[14], ocrelizumab (TA533)[53] and peginterferon beta 1a (TA624)[54], the ERG noted that there was a lack of granularity surrounding the cost of relapse estimated in the study; i.e. it was unclear what proportion of people were assumed to require hospitalisation. To explore uncertainty surrounding the cost of relapse, the company conducted a one-way sensitivity analysis that varied the cost using upper and lower bound percentiles. Base case results were not sensitive to this analysis.

The ERG identified that an alternative source by Dee et al.[70] had been used in several previous NICE appraisals including teriflunomide (TA303)[55] and alemtuzumab (TA312)[2]. Dee et al.[70] was an Irish study that assessed the budget impact of natalizumab. The study, which was conducted from a Health Service Executive (HSE) perspective, included people with RRMS deteriorating on one of the first line DMTs. The average cost of relapse was derived using a database that reported length of stay (LoS) data for neurology bed MS admissions from six large neurology centres. The average LoS for people requiring admission was reported to be 10.71 days. The average cost of relapse was estimated to be €3,696, based on 20% of people requiring an inpatient stay and 80% requiring a day case visit. For completeness, the ERG conducted a scenario analysis using the average relapse cost as reported by Dee et al.[70], inflated to 2020

GBP costs (see Section 6.1.1.10 for discussion and results). However it should be noted that clinical opinion to the ERG noted that the majority of relapses in the UK are treated in an outpatient setting via GP. Therefore resource use data from Dee et al. may overestimate the cost of relapse.

Similar to EDSS health state costs, the company assumed that relapse costs were the same for both people with HA RRMS. Based on clinical input to the ERG, this assumption may be reasonable, however it could be plausible for highly active groups to experience more severe relapses and therefore higher costs. Overall, the ERG considered that the company's base case approach to estimating the cost of relapse was reasonable. Based on sensitivity analysis conducted by the company and the ERG, cost of relapse was not considered to be a key driver of cost effectiveness in the model.

Costs associated with adverse events

The model included costs associated with both non-serious and serious adverse events (see Document B, p138). The ERG considered that adverse event costs were reasonable to include, given that most people receiving DMTs experience AEs, either mild or serious, and that the rates and types of AE vary across each DMT. Resource use estimates were primarily based on previous NICE TAs including ocrelizumab (TA533)[53], with costs reflecting PSSRU 2019 and NHS reference costs, as appropriate. However, as noted in the CS (Document B, p138), the company needed to make several assumptions surrounding resource utilisation with respect to alopecia, diarrhoea, dyspnoea, hypertension and nausea, due to a lack of data.

The ERG acknowledged that the majority of unit costs were relatively minor, with the exception of non-fatal and fatal progressive multifocal leukoencephalopathy (PML). PML was associated with a relatively high cost compared to other modelled adverse events. Adverse event costs ranged from £5.78 (for treatment of nausea) to £19,391 (for treatment of PML). However, PML costs only applied to a small proportion of people receiving natalizumab in the model, as PML incidence rates for all other DMTs were 0%.

From the base case results provided by the company, the ERG noted that there were differences in total adverse event costs between treatments due to variation in modelled incidence rates between treatments, however adverse event costs were not considered a key driver of incremental costs. The company conducted one-way sensitivity analysis which varied

the cost of adverse events using upper and lower bound percentiles, however this did not have a material impact on results.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

The company provided base case cost effectiveness results for both the ITT population and HA RRMS subgroup (see Document B, Sections B.3.27-28).

5.1.1.1. ITT population

The company's base case results are provided in Table 39 below.

[redacted] The ERG noted that incremental savings were largely due to lower drug acquisition costs and disease management costs, whilst the incremental QALY gained associated with ponesimod stemmed primarily from improved relative treatment efficacy. Compared to interferon beta 1a 22 mcg and peginterferon beta 1a 125 mcg, ponesimod resulted in ICER of [redacted] and [redacted] respectively. Compared to ocrelizumab and ofatumumab, ponesimod resulted in [redacted].

Table 39: Company base case results (ITT population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Company deterministic base case					
Ponesimod	[redacted]	[redacted]	-	-	-
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Interferon beta-1b 250mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125mcg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years

5.1.1.2. HA RRMS subgroup

The results of the company's subgroup analysis, shown in Table 40, showed that ponesimod was [redacted]. Compared to fingolimod and ozanimod, [redacted]. The results further showed that ponesimod resulted in a [redacted].

Table 40: Company base case results (HA RRMS population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Company deterministic base case					
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

5.2. Company's sensitivity analyses

The company conducted a variety of sensitivity analyses including one-way sensitivity analysis, scenario analyses and probabilistic sensitivity analyses. The results of these analyses are appraised in the following sections (Sections 5.2.1, 1.1.1 and 5.2.3).

5.2.1. One-way sensitivity analysis

In the CS (Document B, Section 3.31), the company provided the results of a one-way sensitivity analysis for comparisons between ponesimod and teriflunomide, in the ITT population, and fingolimod in the HA RRMS population. One-way sensitivity analysis results comparing ponesimod to the remaining comparators were included in an appendix. The results for the twelve most noteworthy parameters are displayed via tornado diagrams in ***[redacted]2 and

[redacted]3 below. The ICER for the ITT population was relatively robust with respect to most of the model parameters; though it was highly sensitive to the EDSS progression hazard ratio for teriflunomide, and was also sensitive to the EDSS progression hazard ratio and annual discontinuation rate for ponesimod. Varying the baseline conversion to SPMS progression, the annual discontinuation rate for ponesimod, and the relapse rate ratios and EDSS progression hazard ratios for both comparators had the biggest impact on the ICER for the HA RRMS subgroup.

[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years; EDSS, Expanded Disability Status Scale; OWSA, one-way sensitivity analysis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

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Abbreviations: EDSS, expanded disability status scale; HA, highly active; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

5.2.2. Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty when the model parameters were varied as per the respective distributions (CS, Document B, Section 3.10.1). The PSA was run for 5,000 iterations (see PSA results in Document B, p159, Table 62).

The PSA results are presented in Table 41 for the ITT population and in Table 42 for the HA RRMS subgroup, along with the deterministic ICERs (for reference). The cost effectiveness acceptability curves (CEAC) in ***[redacted]5 and ***[redacted]7 indicated that the probability of ponesimod being cost-effective at a £30k threshold was [redacted] for the ITT population and [redacted] for the HA RRMS subgroup. The cost-effectiveness scatterplots in ***[redacted]4 and

*[redacted]6 suggested that there was significant uncertainty around the results, especially for the HA RRMS subgroup.

[redacted]

5.2.2.1. ITT population

Table 41: PSA results (ITT population)

Outcomes Ponesimod vs Comparator	Incremental costs (£)	Incremental QALYs	Probabilistic ICER (£/QALY)	Deterministic ICER (£/QALY)
Teriflunomide 14 mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fuarate 240 mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg IM	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0 mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years

4

[redacted]

Abbreviations: ITT, intention-to-treat; QALYs, quality adjusted life years

5

Abbreviations: ITT, intention-to-treat; QALYs, quality adjusted life years

5.2.2.2. HA RRMS subgroup

Table 42: PSA results (HA RRMS subgroup)

Outcomes Ponesimod vs Comparator	Incremental costs (£)	Incremental QALYs	Probabilistic ICER (£/QALY)	Deterministic ICER (£/QALY)
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HA, highly active; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

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Abbreviations: HA, highly active; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

7

Abbreviations: HA, highly active; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

5.2.3. Scenario analyses

The company conducted a range of scenario scenario analyses for both the ITT and HA RRMS populations (see Table 43 and Table 44), the results of which are reported in Table 45 and Table 46 below. Total costs and QALYs for each treatment are reported in the CS (Document B, p171).

Table 43: Scenario analyses conducted by the company (ITT population)

Number	Parameter	Scenario
S1	Discounting	1.5% for both costs and outcomes
S2	Population characteristics	UK RSS data set
S3	Natural history transition matrix between EDSS health states	Dimethyl fumarate and London Ontario data source
S4	Disease progression to higher EDSS	Treatment effect based on 6 month data
S5	Treatment waning effect	a) No waning effect
		b) 50% loss after 10 years
S6	Care giver disutilities	Disutility based on Gani et al.[65]
S7	Mortality	Pokorski et al.[62] without interpolation
S8	Treatment discontinuation	5% discontinuation for all treatments
S9	Post treatment discontinuation	100% of people move to cladribine

Abbreviations: EDSS, Expanded Disability Status Scale; ITT, intention-to-treat; RSS, risk sharing scheme

Table 44: Scenario analyses conducted by the company (HA RRMS population)

Number	Parameter	Scenario
S10	Population	Highly active RRMS subgroup from OPTIMUM
S11	Disease progression to higher EDSS	Treatment effect based on 6-month data
S12	Treatment waning effect	a) No waning (backed up with Phase 2 long term data)
		b) 50% loss after 10 years
S13	Treatment discontinuation	5% discontinuation for all treatments
S14	Post treatment discontinuation	100% of people move to natalizumab

Abbreviations: EDSS, Expanded Disability Status Scale; HA highly active; RRMS, relapsing remitting multiple sclerosis

5.2.3.1. ITT population

Based on the company's scenario analyses, results for the ITT population were most sensitive to using an alternative EDSS natural history transition matrix (derived from the London Ontario

and dimethyl fumarate dataset), disease progression based on six-month CDA, and a post-treatment discontinuation assumption that assumed that 100% of people received cladribine after first-line treatment.

[redacted]

Table 45: Company scenario analysis results (ITT population)

Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
Base case	Incremental QALYs											
	Incremental Costs											
	ICER											
S1: Discounting	Incremental QALYs											
	Incremental Costs											
	ICER											
S2: UK RSS	Incremental QALYs											

Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
population	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3: EDSS health states	Incremental QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4: Disease progression	Incremental QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5a: Treatment waning (no waning)	Incremental QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5b: Treatment waning (50% loss at 10 yrs)	Incremental QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
S6: Caregiver disutilities	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7: Mortality	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8: Treatment discon	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
tinu-ation	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S9: Post-treatment discon tinu-ation	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DMF, Dimethyl fumarate 240mg PO; EDSS, Expanded Disability Status Scale; GA, Glatiramer acetate 20mg SC; ICER, incremental cost-effectiveness ratio; IFNB-1a 22 µg, interferon beta-1a 22 µg subcutaneously; IFNB-1a 30 mcg, interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg, interferon beta-1a 44 µg subcutaneously three times weekly; ITT, intention-to-treat; OCR, ocrelizumab 600 mg every six months; Ofatumumab 20mg SC; Ozanimod 1.0mg PO; PBO, placebo; PEG, Peginterferon beta-1a 125mcg subcutaneously; PON, ponesimod 20 mg once daily; QALYs, quality adjusted life years; RSS, risk sharing scheme; TER, teriflunomide 14 mg once daily

5.2.3.2. HA RRMS

A complete list of scenario analyses undertaken by the company can be found in the CS (Document B, p168). Based on the company's scenario analyses, results for the HA RRMS population were most sensitive to a scenario that assumed 100% of people would receive alemtuzumab post-treatment discontinuation.

[redacted] **Table 46: Company scenario analysis results (HA RRMS population)**

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
S10: Population	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S11: Disease progression	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S12a: Treatment waning (no waning)	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S12b: Treatment waning (50% loss at 10yrs)	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S13: Treatment	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
discontinu-ation	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S14: Post-treatment discontinu-ation	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; FIN, fingolimod 0.5 mg once daily; HA, highly active; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OCR, ocrelizumab 600 mg every six months; Ofatumumab 20mg SC; Ozanimod 1.0mg PO; PBO, placebo; PON, ponesimod 20 mg once daily; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

5.3. Model validation and face validity check

The ERG did not identify any errors in the company's original model. The results outlined below are based on the company's revised model (submitted during clarification), which included ozanimod and ofatumumab.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1. Exploratory and sensitivity analyses undertaken by the ERG

As noted throughout the report, the ERG identified a number of uncertainties surrounding the clinical efficacy parameters used in the economic analysis, the model assumptions and choice of literature sources. The ERG conducted scenario analyses in order to explore the potential impact of these uncertainties. See Section 6.1.1 for description of each scenario and Section 6.2 for the impact on the ICER. Please note that the results below incorporate the PAS discount for ponesimod, but do not include PAS discounts for comparator treatments.

6.1.1. ITT and HA RRMS populations

6.1.1.1. Scenario analysis 1: Six-month CDA used to model disease progression

The ERG considered that the use of three-month CDA in the economic model to estimate clinical effectiveness was not appropriate, given that six-month CDA is a more robust measure of disease progression and has been preferred by NICE in previous MS appraisals (see Section 4.2.6.1). This scenario analysis explored the impact of using six-month CDA data from the NMA to estimate hazard ratios and treatment-specific transition probabilities in both the active and highly active RRMS populations.

[redacted]. Overall, results from this analysis indicated that using the six-month CDA had a material impact on base case cost effectiveness results versus three key comparators (see Section 6.2).

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results i.e.

[redacted] (See Section 6.2)

6.1.1.2. Scenario analysis 2: 25% of SPMS group assumed to receive siponimod and 75% receive BSC

The ERG noted that siponimod had been recommended by NICE for the treatment of people with SPMS (see Section 4.2.6). Clinical experts to the ERG estimated that between 12.5% and 50% of people will receive siponimod after progressing to SPMS. To explore the potential impact of subsequent treatment with siponimod, this scenario analysis assumed that 25% of people who converted to SPMS in the model went on to receive siponimod, whilst 75% received BSC. Please note that for this scenario only the costs for siponimod were considered; i.e. siponimod was not assumed to have a treatment effect. Given the lack of robust long-term clinical effectiveness data for siponimod, this approach was considered to introduce less uncertainty into the analysis and provide indicative results based on treatment cost only.

Based on this analysis, the cost effectiveness of ponesimod improved versus all comparator DMTs in the ITT population.

[redacted] see Section 6.2).

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results; i.e.

[redacted] see Section 6.2).

6.1.1.3. Scenario analysis 3: Participant characteristics based on UK RSS population

As noted in Section 4.2.3, clinical opinion to the ERG was that characteristics from participants in OPTIMUM were likely to be generalisable to the UK population. For completeness, this scenario analysis (conducted in the ITT population only) used characteristics from people in the UK RSS dataset; i.e. mean age, sex and EDSS distribution. The ERG noted that the UK RSS dataset included people with RRMS and did not outline the proportion of participants with HA RRMS, therefore the ERG did not consider it appropriate to conduct a scenario analysis for the HA RRMS population based on UK RSS characteristics. The ERG also considered that the UK RSS dataset may not be fully generalisable to the target population, as clinical advice to the ERG was that it included people with SPMS, and participants generally had longer disease duration without access to DMT.

Based on this analysis,

[redacted] (see Section 6.2). The ERG did not consider baseline population characteristics to be a key source of uncertainty in this analysis.

6.1.1.4. Scenario analysis 4: Alternative subsequent treatment assumptions

The ERG accepted the company's base case assumption surrounding the use of BSC as the primary subsequent treatment option for people who discontinued treatment (see Section 4.2.6). Furthermore, the ERG acknowledged the company's attempt to explore uncertainty surrounding the impact of subsequent treatment use by including scenario analyses that assumed 100% of people who discontinue treatment go on to receive cladribine and natalizumab in the ITT and HA RRMS populations, respectively. However based on clinician feedback to the ERG, subsequent treatment will depend primarily on the rationale for stopping first-line treatment; i.e. if a person discontinues due to adverse events then they will likely go on to receive a treatment with a more favourable adverse event profile. As such the ERG considered that the selection of cladribine and natalizumab as the primary subsequent treatments for this scenario (as outlined in CS Document B, p125-126) was overly simplistic.

In this alternative exploratory scenario the ERG opted to use teriflunomide and alemtuzumab as the subsequent treatments in the respective ITT and HA RRMS populations. It should be noted that only the costs associated with these treatments were considered; i.e. drug acquisition costs, administration costs and monitoring costs only, and the efficacy of these treatments for health outcomes were not considered. The ERG opined that including subsequent treatment effects on the basis of the company's NMAs would introduce additional uncertainty, due to the limitations surrounding these results (see section 3.4 and 3.6). The alternative treatments selected by the ERG therefore explored the impact of using subsequent treatments with different acquisition costs.

The ERG noted that ITT population results were not overly sensitive to this scenario analysis. Most notably, ponesimod went from being [redacted] to resulting in a minor ICER of [redacted] and [redacted] compared to glatiramer acetate and interferon beta 1b 250 mcg respectively. Compared to peginterferon beta 1a 125mcg and interferon beta 1a 22mcg, ponesimod became more cost effective resulting in reduced ICERs (see Section 6.2).

In the HA RRMS population, this scenario primarily impacted the cost effectiveness results against alemtuzumab, as ponesimod went from being [redacted], to being [redacted]. The ERG noted that this scenario may lack validity as it assumed that people continued to receive alemtuzumab, despite not responding to alemtuzumab as a first line treatment (see Section 6.2).

6.1.1.5. Scenario analysis 5: No difference in discontinuation rates (assumed 5% for all treatments)

As noted in Section 4.2.6, the use of treatment specific all-cause discontinuation rates in the company's base case was considered to be reasonable. However, the ERG noted that there is uncertainty surrounding the validity of the NMA estimates due to the limitations outlined in Section 3.4. This scenario analysis explored the impact of variation in discontinuation rates by assuming no difference in rates between treatments; i.e. a discontinuation rate of 5% is applied to all treatments.

Based on this analysis [redacted] See Section 6.2.

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results; i.e. [redacted] See Section 6.2.

6.1.1.6. Scenario analysis 6: No waning in treatment effect (applies to all treatments)

The ERG considered the company's base case assumption surrounding treatment waning to be broadly acceptable (see Section 4.2.6). However, due to the lack of long term data surrounding treatment efficacy over time, this scenario analysis explored the impact of removing the treatment waning assumption used in the base case for all treatments. Please note that although this scenario analysis was useful in exploring uncertainty, the ERG did not consider it to reflect clinical practice and therefore it may lack plausibility.

Based on this analysis, cost effectiveness results for ponesimod compared to each comparator improved; i.e.

[redacted] See Section 6.2. In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to most base case results; i.e.

[redacted] However, the ERG noted that compared to fingolimod, [redacted]. See Section 6.2.

6.1.1.7. Scenario analysis 7: Alternative modelled clinical effectiveness parameters

In Sections 3.4 and 3.6, the ERG noted there to be uncertainty surrounding the clinical effectiveness estimates used in the economic model, which were derived from the NMAs. This scenario analysis estimated alternative clinical effectiveness estimates by adopting a positioning-based approach; i.e. DMTs were stratified into 3 groups according to their approximate position within the treatment pathway (see Table 47 below). For CDA and ARR, each treatment group was compared to BSC and the median efficacy estimate (hazard ratio and rate ratio) was selected for each. For treatment discontinuation, each group was compared to ponesimod (which was not included in Group B) and the median odds ratio was selected for each. This analysis was considered exploratory in nature, however it helped to demonstrate the sensitivity of base case results to a change in key treatment efficacy parameters.

Table 47: Treatment groups according to positioning

Group A	Group B	Group C
Interferon beta 1a (22mcg, 30mcg, 44mcg)	Ponesimod (except for treatment discontinuation)	Alemtuzumab
Interferon beta 1b	Ozanimod	Fingolimod
Peginterferon beta 1a	Ofatumumab	Cladribine
Glatiramer acetate	Teriflunomide	
Dimethyl fumarate	Ocrelizumab	

Table 48: Median efficacy effect estimates for positioning-based groups (ITT population)

Group	ARR Rate Ratio	3-month CDA HR	6-month CDA HR	Premature Treatment Discontinuation OR
A	[redacted]	[redacted]	[redacted]	[redacted]
B	[redacted]	[redacted]	[redacted]	[redacted]
C	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; HR, hazard ratio; ITT, intention-to-treat; OR, odds ratio

Table 49: Median efficacy effect estimates for positioning-based groups (HA RRMS)

Group	ARR Rate Ratio	3-month CDA HR	6-month CDA HR	Premature Treatment Discontinuation OR
A	[redacted]	[redacted]	[redacted]	[redacted]
B	[redacted]	[redacted]	[redacted]	[redacted]
C	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDA, confirmed disability accumulation; HA, highly active; HR, hazard ratio; ITT, intention-to-treat; OR, odds ratio; RRMS, relapsing remitting multiple sclerosis

Based on this analysis, in the ITT population [redacted] In the HA RRMS population, results were sensitive to this scenario analysis; i.e. [redacted] Notably, ponesimod was [redacted] by ozanimod and fingolimod. See Section 6.2.

6.1.1.8. Scenario analysis 8: Increased monitoring costs for ponesimod in Year 1

As noted in Section 4.2.8.1, the ERG highlighted some uncertainty surrounding monitoring costs for ponesimod in year one. In order to explore the impact of increased monitoring costs, this scenario assumed that ponesimod would require monitoring equivalent to that of fingolimod in year 1. The ERG noted that for both the ITT and HA RRMS populations, results were not considered sensitive to this scenario (see Section 6.2).

6.1.1.9. Scenario analysis 9: Alternative EDSS health state costs

Tyas et al.[69] was considered to be an appropriate source for deriving EDSS disease management costs in the base case (see Section 4.2.8.2). This scenario analysis was

conducted to determine the impact of using an alternative literature source to derive EDSS health state costs. Based on direct health care costs, community services costs and investment costs from Thompson et al.[63], the mean annual EDSS disease management cost per person was estimated to be £6,369, £7,994 and £13,325 for EDSS states 0-3, 3-6 and 6-9, respectively. The ERG noted that the RRMS costs reported by Thompson et al.[63] are somewhat limited, given that values were reported for mild, moderate and severe disease (and not individual EDSS health states).

The ERG noted that results for the ITT population were not overly sensitive to this scenario analysis. Most notably, [redacted]. See Section 6.2.

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results; i.e. [redacted] See Section 6.2.

6.1.1.10. Scenario analysis 10: Alternative cost associated with relapse

The ERG acknowledged that the cost of relapse used in the company's base case analysis was largely appropriate (see Section 4.2.8.2). This scenario explored the impact of using a higher cost of relapse in the model for both the ITT and HA populations, based on an Irish study by Dee et al.[70]. For this analysis costs were converted from euros into GBP and inflated to 2020 values, resulting in a cost per relapse of £3,451. The ERG accepted that this study may be associated with generalisability concerns given that it is non-UK based and there are likely to be differences in healthcare resource utilisation for RRMS groups between Ireland and the UK.

The ERG noted that results were not overly sensitive to this scenario analysis and slightly improved the cost effectiveness of ponesimod compared to other DMTs in the ITT population. This scenario analysis resulted in minor incremental cost and QALY changes, however base case results remained largely unchanged (see Section 6.2).

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results i.e.

[redacted] See Section 6.2.

6.1.1.11. Scenario analysis 11: Alternative EDSS health state utilities.

Overall the ERG considered Orme et al.[51] to be an appropriate source for estimating EDSS health state utilities (see Section 4.2.7.1). To test uncertainty surrounding the utility value source, the company provided a scenario analysis that used an alternative values reported by Gani et al.[65] (for the active RRMS population). Results were not considered overly sensitive to these alternative values (see Section 5.2.3). For completeness this scenario analysis applied utility values from an additional UK study by Thompson et al.[63] (see Table 50 below) to the ITT and HA RRMS populations. It should be noted that in the absence of robust HRQol data, utility values for the SPMS population were estimated by applying the -0.045 utility decrement from Orme et al.[51] to the RRMS values from Thompson et al.[63].

The ERG noted that results were not overly sensitive to this analysis, as utility values were broadly similar to Orme et al.[51]. In the ITT population [redacted] Compared to interferon beta 1a 22 mcg and peginterferon beta 1a 125 mcg, ponesimod resulted in an ICER of [redacted] and [redacted] respectively. Compared to ocrelizumab and ofatumumab, ponesimod resulted in [redacted].

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results; i.e. [redacted] See Section 6.2.

Table 50: Utility values from Thompson et al.[63]

	EDSS									
	0	1	2	3	4	5	6	7	8	9
RRMS	0.898	0.787	0.695	0.573	0.605	0.569	0.48	0.373	0.157	-0.111
SPMS	N/A	0.742	0.650	0.528	0.560	0.524	0.435	0.328	0.112	-0.156

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

6.1.1.12. Scenario analysis 12: Alternative annual conversion probabilities (from RRMS to SPMS)

As noted in Section 4.2.6, the ERG was aware that alternative SPMS conversion probabilities had been used previously in the NICE appraisal of peginterferon (TA624)[54]. To explore the sensitivity of results to a change in this modelled parameter, this scenario used the annual EDSS baseline probabilities of converting to SPMS reported in peginterferon (TA624)[54], which were lower than the estimates used by the company in their base case.

The ERG noted that ITT results were highly sensitive to this analysis. Notably the ICER compared to interferon beta 1a 22 mcg increased from [redacted] to [redacted]. Compared to teriflunomide, dimethyl fumarate and ozanimod, ponesimod was no longer dominant, resulting in [redacted]. For the comparison with peginterferon beta 1a 125 mcg, ponesimod went from being the [redacted] treatment to being [redacted]. See Section 6.2.

In the HA RRMS population, this scenario had an impact on the incremental costs and QALYs for all treatments, but did not result in material changes to the base case results; i.e. [redacted] See Section 6.2.

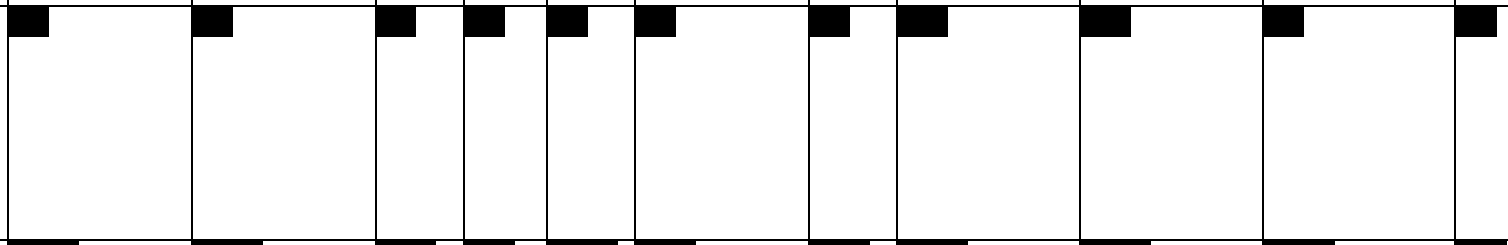
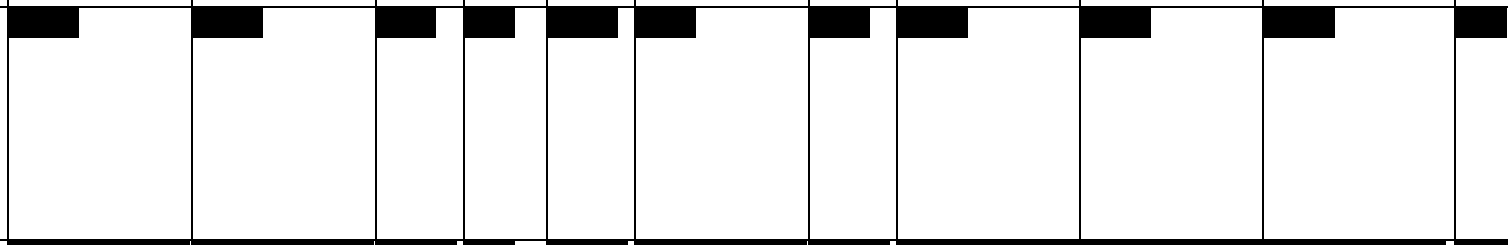
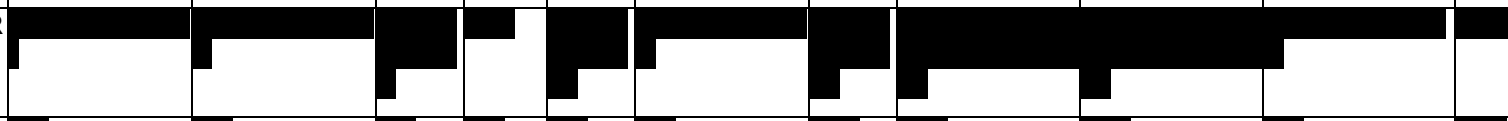
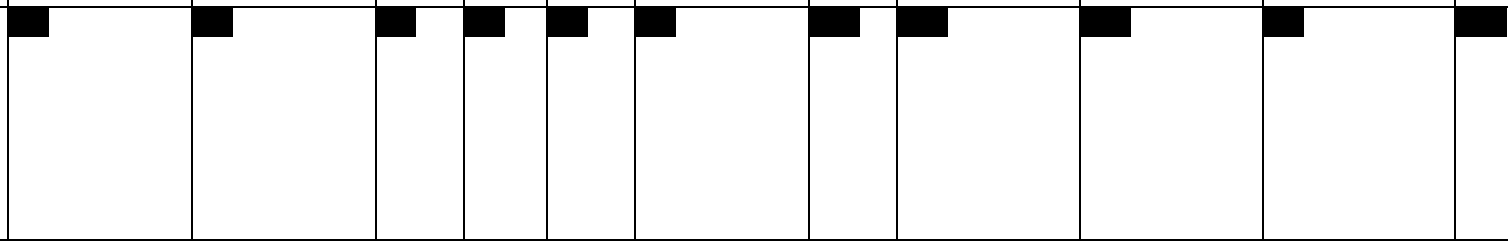
6.2. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results of the ERG's one-way sensitivity analyses are reported in Table 51 (ITT) and Table 52 (HA RRMS). A full description of the analyses undertaken is provided in Sections 6.1.1.1 - 6.1.1.12. The scenarios that had the most impact on the base case results were:

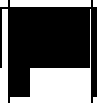
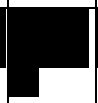
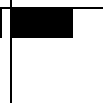
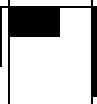
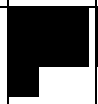
- Using six-month CDA for EDSS progression in the model, rather than 3-month CDA (ITT population)

- Using a positioning-based approach to estimate treatment effect (ITT and HA RRMS populations)
- Using an alternative set of annual conversion probabilities, from RRMS to SPMS (ITT population)
- No waning in treatment effect (HA RRMS population)

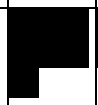
Table 51: ERG scenario analysis results (ITT population)

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
Company base case	Incremental QALYs											
	Incremental Costs											
	ICER											
S1: CDA-6	Incremental QALYs											

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S2: 25% population receive siponimod	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	ICER											
S3: UK RSS population	Incremental QALY											
	Incremental Costs											
	ICER											
S4: Alternativ	Incremental											

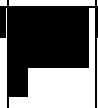
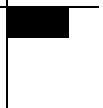
ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
e subsequent treatments	QALY											
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5: 5% discontinue-ation rate	Incremental QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	Costs											
	ICER											
S6: No treatment waning	Incremental QALY											
	Incremental Costs											
	ICER											

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
S7: Alternative modelled clinical effectiveness parameters	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8: Monitoring costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	Incremental Costs	[redacted]										
	ICER	[redacted]										
S9: EDSS health state costs	Incremental QALYs	[redacted]										
	Incremental Costs	[redacted]										

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S10: Relapse costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S11: EDSS healt	Incremental	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
h state utilities	QALYs											
	Incremental Costs											
	ICER											
S12: Conversion to SPMS	Incremental QALYs											
	Incremental											

ERG Scenario	Outcome PON vs. comparator	TER	DMF	GA	IFNB-1a 22 mcg	IFNB-1a 30 mcg	IFNB-1a 44 mcg	IFNB-1b	OCR	OFA	OZA	PEG
	Costs											
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DMF, Dimethyl fumarate 240mg PO; EDSS, Expanded Disability Status Scale; ERG, Evidence Review Group; GA, Glatiramer acetate 20mg SC; ICER, incremental cost-effectiveness ratio; IFNB-1a 22 µg, interferon beta-1a 22 µg subcutaneously; IFNB-1a 30 mcg, interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg, interferon beta-1a 44 µg subcutaneously three times weekly; ITT, intention-to-treat; OCR, ocrelizumab 600 mg every six months; Ofatumumab 20mg SC; Ozanimod 1.0mg PO; PBO, placebo; PEG, Peginterferon beta-1a 125mcg subcutaneously; PON, ponesimod 20 mg once daily; QALYs, quality adjusted life years; SPMS, secondary progressive multiple sclerosis; TER, teriflunomide 14 mg once daily

Table 52: ERG scenario analysis results (HA RRMS subgroup)

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
Company HA subgroup analysis	Incremental QALYs						
	Incremental Costs						
	ICER						
S1: CDA-6	Incremental QALYs						
	Incremental Costs						
	ICER						
S2: 25% population	Incremental QALYs						

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
receive siponimod	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3: UK RSS population	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4: Alternative subsequent treatments	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
S5: 5% discontinu-ation rate	Incremental QALYs						
	Incremental Costs						
	ICER						
S6: No treatment waning	Incremental QALYs						
	Incremental Costs						
	ICER						
S7: Alternative modelled clinical effectiveness	Incremental QALYs						
	Incremental Costs						

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
parameters	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8: Monitoring costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S9: EDSS health state costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S10: Relapse costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs. comparator	OCR	OFT	OZA	ALE	CLA	FIN
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S11: EDSS health state utilities	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S12: Conversion to SPMS	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; EDSS, Expanded Disability Status Scale; ERG, Evidence Review Group; FIN, fingolimod 0.5 mg once daily; HA, highly active; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OCR, ocrelizumab 600 mg every

six months; Ofatumumab 20mg SC; Ozanimod 1.0mg PO; PBO, placebo; PON, ponesimod 20 mg once daily; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

6.3. ERG's preferred assumptions

The ERG considered that several of the company's base case assumptions were inappropriate, and alternatives to these were used in the ERG base case. The ERG's preferred assumptions are outlined in Table 53 for both the ITT and HA RRMS populations. The ICERs presented in Table 54 and Table 55 below incorporate all of the ERG's preferred assumptions.

Table 53: ERG preferred base case assumptions (ITT and HA RRMS)

Preferred assumption	Report Section
Company base-case	*5.1.1*
6 month CDA used to model disease progression	4.2.6.1 and 6.1.1.1
25% of people receive BSC after converting to SPMS, 75% receive Siponimod	4.2.6 and 6.1.1.2

Abbreviations: BSC, best supportive care; CDA, confirmed disability accumulation; ERG, Evidence Review Group; HA, highly active; ITT, intention-to-treat; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

6.3.1. Deterministic analysis

Table 54: ERG's preferred base case results (ITT population)

Outcomes **Ponesimod vs** **Comparator**	**ERG base case**			**Company base case**
	Incremental QALYs	**Incremental costs (£)**	**ICER (£/QALY)**	**ICER (£/QALY)**
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30mcg IM	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes Ponesimod vs Comparator	ERG base case			Company base case
Interferon beta-1a 44mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125mcg SC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; QALY, quality-adjusted life year

Table 55: ERG's preferred base case results (HA RRMS population)

Outcomes Ponesimod vs Comparator	ERG base case			Company base case
	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	ICER (£/QALY)
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes **Ponesimod vs** **Comparator**	**ERG base case**			**Company base case**
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; HA, highly active; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RRMS, relapsing remitting multiple sclerosis

6.3.2. One-way sensitivity analysis

In order to test the impact of parameter uncertainty on results (based on the ERG's preferred assumptions), one-way sensitivity analyses were conducted, to vary key parameters using low and high values. Tornado diagrams are presented below for comparisons with teriflunomide and fingolimod for the ITT and HA RRMS populations, respectively. Due to the large number of comparators within this appraisal, the rest of the results have been included in Appendix D.

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Abbreviations: EDSS, expanded disability status scale; ERG, Evidence Review Group; HA, highly active; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis;

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years; EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

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Abbreviations: EDSS, expanded disability status scale; ERG, Evidence Review Group; HA, highly active; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis;

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; HA RRMS, highly active relapsing remitting multiple sclerosis

6.3.3. Probabilistic sensitivity analysis

The ERG's preferred probabilistic ICERs comparing ponesimod to each comparator are presented below (alongside the company's deterministic ICER for each comparison). The ERG's probabilistic results were broadly similar to the company's deterministic results, which seemed reasonable, given that the ERGs base case only included two different assumptions.

6.3.3.1. ITT population

Table 56: ERG PSA results (ITT population)

Outcomes Ponesimod vs Comparator	Incremental costs (£)	Incremental QALYs	Probabilistic ICER (£/QALY)	Deterministic ICER (£/QALY)
Teriflunomide 14 mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fuarate 240 mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg IM	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250 mcg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0 mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes **Ponesimod vs** **Comparator**	**Incremental costs (£)**	**Incremental QALYs**	**Probabilistic ICER (£/QALY)**	**Deterministic ICER (£/QALY)**
125 mcg SC				

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years

[redacted] 10

Abbreviations: ERG, Evidence Review Group; ITT, intention-to-treat; QALY, quality-adjusted life year

11 [redacted]

Abbreviations: ERG, Evidence Review Group; ITT, intention-to-treat; QALYs, quality adjusted life years

6.3.3.2. HA RRMS subgroup

Table 57: ERG PSA results (HA RRMS subgroup)

Outcomes Ponesimod vs Comparator	Incremental costs (£)	Incremental QALYs	Probabilistic ICER (£/QALY)	Deterministic ICER (£/QALY)
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; HA, highly active; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

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[redacted]

Abbreviations: ERG, Evidence Review Group; HA, highly active; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

13 [redacted]

Abbreviations: ERG, Evidence Review Group; HA, highly active; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

6.4. Conclusions of the cost-effectiveness section

Based on the ERG's preferred assumptions in the ITT population [redacted] Compared to interferon beta 1a 22 mcg ponesimod resulted in an ICER of [redacted]. Ponesimod resulted in [redacted] compared to ocrelizumab and ofatumumab (the latter currently under appraisal by NICE); [redacted]. ERG preferences had the most impact on the results versus Interferon beta-1b 250mcg SC and peginterferon beta-1a 125mcg, with ponesimod becoming the [redacted] treatment.

In the HA population, using the ERG's preferred assumptions did not have a material impact on the base case results; i.e. ponesimod remained [redacted] when compared to [redacted] Compared to fingolimod and ozanimod, ponesimod [redacted] treatment. As in the company's base case, cladribine [redacted] ponesimod.

The ERG considered that the company had broadly used the best available evidence to inform the data and modelled assumptions, and most modelled parameters and assumptions were informed by sources used and accepted in previous NICE MS appraisals. However, the ERG nevertheless considered that these were subject to a high degree of uncertainty. In most cases the ERG were unable to identify improved sources, though tested the sensitivity of the ICERs to variations in each of the uncertainties. These analyses identified that ICERs were broadly robust to most assumptions, with the exception of clinical efficacy estimates (CDA, ARR, and discontinuation rates). As discussed in Section 3, the ERG identified considerable limitations surrounding NMAs for both the ITT and HA RRMS populations, and the true estimates for each of the included treatments could vary considerably. Sensitivity analyses showed that even small variations in clinical efficacy estimates could materially change the ICERs. This was particularly true in the HA RRMS population.

Finally, NICE should be aware that comparators in both the ITT and HA RRMS populations have patient access scheme discounts (PASs). The inclusion of comparator PAS discounts had a substantial impact on the base case cost effectiveness results (see addendum to this report).

7. END OF LIFE

The ERG considered that ponesimod does not meet NICE end of life criteria as the treatment is not indicated for people with a short life expectancy (normally defined as less than 24 months).

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Appendix A: Additional searches conducted by the ERG

Additional Medline search strategy for multiple sclerosis NMAs

This was a partial (modified) update of the searches used in Melendez-Torres (2018)[44], limited to papers published in 2016 onwards. The search was also translated into Embase.

1. exp Multiple Sclerosis/

2. multiple sclerosis.tw.

3. 1 or 2

4. (metaanalys* or "meta analys*" or "meta-analys*").tw.

5. meta analysis.pt.

6. 4 or 5

7. 3 and 6

8. limit 7 to yr="2016 -Current"

Additional Medline strategy for adverse events

This search uses the broad adverse effects expert search filter from Ovid (Adverse Effects - Medline – Broad[45]) without any study type filter. The search was also translated into Embase using the equivalent Ovid search filter (Adverse Effects – Embase – Broad[45]).

1. exp "Drug-Related Side Effects and Adverse Reactions"/ or adverse.ti,ab,kf. or side effect?.ti,ab,kf. or adverse effects.fs. or exp drug overdose/ or overdos*.ti,ab,kf. or exp drug misuse/ or misus*.ti,ab,kf. or exp Substance-Related Disorders/ or abus*.ti,ab,kf. or exp pregnancy/ or pregnan.ti,ab,kf. or exp pregnancy complications/ or exp lactation/ or exp lactation disorders/ or exp breast feeding/ or (exp milk, human/ and exp secretion/) or exp fertility/ or exp infertility/ or exp reproduction/ or exp fetus/ or exp embryonic structures/ or terat*.ti,ab,kf. or drug efficacy.ti,ab,kf. or therapeutic efficacy.ti,ab,kf. or drug withdrawal.ti,ab,kf. or exp medication errors/ or exp death/ or death*.ti,ab,kf. or fatal*.ti,ab,kf. or exp drug interactions/ or exp carcinogens/ or carcinogen*.ti,ab,kf. or mutagen*.ti,ab,kf. or exp "Off-Label Use"/ or exp occupational exposure/ or toxicity.fs. or toxic*.ti,ab,kf. or pharmacotox*.ti,ab,kf. or

neurotox*.ti,ab,kf. or cardiotox*.ti,ab,kf. or nephrotox*.ti,ab,kf. or immunotox*.ti,ab,kf. or hepatotox*.ti,ab,kf. or cytotox*.ti,ab,kf. or immunocytotox*.ti,ab,kf. or intoxicat*.ti,ab,kf. or exp "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/ or drug treatment failure.ti,ab,kf. or drug toxicity.ti,ab,kf. or exp case report/ or case report?.ti,ab,kf. or exp environmental exposure/ or treatment contraindication.ti,ab,kf. or exp contraindications, drug/ or exp "Wounds and Injuries"/ or suicid*.ti,ab,kf. or exp poisoning/ or poisoning.fs. or exp drug tolerance/ or exp treatment failure/ or exp drug resistance/ or exp substance-related disorders/

2. Ponesimod/ or (ponesimod$2 or "act 128800" or act128800 or act-128800 or "rg 3477" or rg3477 or 854107-55-4).ti,ab,kw,du,rn.

3. 1 and 2

Additional Medline strategy for cost effectiveness (adding four additional technologies)

This was the search as used in the CS but with the existing drug terms removed and the four missing drug terms (for siponimod, ozanimod, ofatumumab and ponesimod) added. The search was also translated into Embase.

1. exp multiple sclerosis/ or (multiple sclerosis or ((primary or progressive or secondary) and (relapsing or remittent or (relapsing and remitting)) and multiple and sclerosis) or ppms or spms or rrms).tw,kw.

2. ("health utilit$" or "health state utility$" or "utility score$" or "utility valu$").tw,kw.

3. ("standard gamble" or "time trade-off" or "time tradeoff" or tto or "visual analog$ scale$" or "patient preference$" or preference$).tw,kw.

4. (eq-5d or eq5d or euroqol or "health utility$ index" or hui or sf-6d or "short form 6d" or "quality of well-being scale$" or "utility assessment" or qaly$ or "quality adjusted life year$" or utility$).tw,kw.

5. 2 or 3 or 4

6. exp economics/ or exp cost control/ or exp cost of illness/ or exp drug costs/ or exp hospital costs/ or exp health care costs/ or exp socioeconomic factors/ or exp health care economics and organizations or exp fee and charges/ or exp budgets/

7. (fiscal or funding or financ$ or economic$ or pharmacoeconomic$ or pric$).tw,kw.

8. 6 or 7

9. exp patient acceptance of health care/

10. ("health care use" or "healthcare use" or "health service$ use" or "health care utili?ation" or "healthcare utili?ation" or "health resource utili?ation" or "health service$ utili?ation" or "resource use" or "medical leave" or "work disability").tw,kw.

11. exp absenteeism/ or absenteeism.tw,kw.

12. exp retirement/ or retirement.tw,kw.

13. exp sick leave/

14. exp workers' compensation/

15. ("disability absence" or "illness day" or "sick day" or "work absence" or "work day loss" or "work incapacity" or "work loss" or "work time loss" or "workmans compensation" or "workers compensation" or "productivity loss" or "work impairment" or "sickness absence" or "lost days" or "productivity").tw,kw.

16. or/9-15

17. ("cost minimi?ation analys$" or ("cost-minimi?ation" adj analys$)).tw,kw.

18. exp cost benefit analysis/

19. (("cost benefit" or "cost-benefit") adj analys$).tw,kw.

20. (("cost utility" or "cost-utility" or "cost-effective$") adj analys$).tw,kw.

21. exp cost utility analysis/ or exp economic evaluation/

22. (cost adj effective$ adj analys$).tw,kw.

23. or/17-22

24. ((economic or pharmacoeconomic) adj (evaluation or assessment or analys?s or stud$)).tw,kw.

25. (cea or cma or cba or cua or cca).tw,kw.

26. exp decision theory/ or exp decision trees/

27. "decision tree".tw,kw.

28. ((economic or cohort or transition) adj model).tw,kw.

29. (markov or deterministic).tw,kw.

30. ((transition adj probability$) or (health adj stat$) or (sensitivity adj analys$) or (health adj outcome) or (("patient level" or "patient-level" or "discrete event" or "discrete-event") adj simulat$)).tw,kw.

31. (incremental-cost or icer or qaly or daly or wtp or tto).tw,kw.

32. or/24-31

33. 5 or 8 or 16 or 23 or 32

34. Ponesimod/ or (ponesimod$2 or "act 128800" or act128800 or act-128800 or "rg 3477" or rg3477 or 854107-55-4).ti,ab,kw.

35. (siponimod$2 or 1230487-00-9 or 1230487-85-0 or "baf 312" or baf312 or mayzent$2 or nvpbaf312nx).ti,ab,kw.

36. (ozanimod$2 or 1306760-87-1 or 1618636-37-5 or “rpc 1063” or rpc1063 or Zeposia$2).ti,ab,kw.

37. (ofatumumab$2 or arzerra$2 or "gsk 1841157" or gsk1841157 or "humac CD20" or "HuMax CD20" or HuMax-CD20 or HuMaxCD20 or "omb 157" or omb157 or 679818-59-8).ti,ab,kw.

38. or/36-39

39. 1 and 33 and 38

Appendix B: NMA methods used in the HA RRMS population in previous NICE appraisals

A brief overview of the included trials and methodology used to evaluate treatments for RRMS in the HA population in previous appraisals and publications of NMAs is provided in Table 58 below.

Table 58: NMA methods used to evaluate treatments for HA RRMS in previous NICE HTA appraisals

Appraisal (NMA publications)	Included publications (*reporting on HA MS; ^included in NMA)	Included treatments (note that not all treatments were included in all analyses)	Definition of HA	Assumptions
Alemtuzumab [TA312] 2013[2]	FREEDOMS*^ CARE-MS: II*^ TRANSFORMS *^ TENERE TEMSO & TOWER TEMSO & TENERE & TOWER	Terifuonimide 7mg Terifuonimide 14mg Interferon 44mg* Interferon 1a 30mg* Alemtuzumab 12mg* Fingolimod 0.5mg* Fingolimod 1.25mg Placebo	HA despite interferon use, although various trial definitions accepted	In their response to ACD, the company conducted NMAs in the highly active population. Treatments relevant to HA populations were included, along with treatments and evidence in the ITT population that were added to complete the networks where necessary. The ERG noted that heterogeneity in population definitions and the inclusion of indirect evidence increased uncertainty in the effect estimates.
Ocrelizumab [TA533] 2018[53]	CARE-MS II (ALE)*^ CONFIRM & DEFINE (pooled) (DMF) *^ TRANSFORMS (FIN) *^ FREEDOMS & FREEDOMS II (pooled) (FIN) *^ OPERA I & II (pooled) (OCR) *^	IFNB-1b 250 µg SC EOD IFNB-1a 22 µg TIW Glatiramer acetate 20 mg QD IFNB-1a 30 µg IM QW IFNB-1a 44 µg SC TIW Fingolimod 0.5 mg QD Alemtuzumab 12 mg Ocrelizumab 600 mg Daclizumab 150 mg Q4W	Populations treated with INFBs or GA for at least one year with (1) ≥ 1 relapse(s) in previous year, (2) ≥ 1 Gd+ lesion on brain MRI at baseline, or (3) ≥ 9 T2 hyperintense lesions on brain MRI at baseline	Networks for the HA population were disconnected. To connect the networks, ITT data from studies investigating ABCR treatments (IFNB-1a [Avonex], IFNB-1b [Betaferon], glatiramer acetate [Copaxone], and IFNB-1a [Rebif]) were included. In addition, where studies did not report CDA-6 data from CDA-3 was used to complete the network. The ERG suggested that the results of the HA analyses be interpreted with caution. Furthermore, the committee stated a preference for evidence for CDA-3 in the ITT population to be excluded where evidence for CDA-6 in the same comparison was not also available.

Appraisal (NMA publications)	Included publications (*reporting on HA MS; ^included in NMA)	Included treatments (note that not all treatments were included in all analyses)	Definition of HA	Assumptions
	TEMSO & TOWER (pooled) (TER) *^ SELECT (DAC) *^ DECIDE (DAC) *^ N=12*			All-cause discontinuation rates were assumed to be the same as the whole RRMS population. Unlicensed doses and treatment regimens were excluded.
Cladribine [TA616] 2017[67] *Need access to appendix D of CS*	AFFIRM*^ CONFIRM*^ DEFINE *^ FREEDOMS*^ TOWER*^ TRANSFORMS*^ CLARITY*^ CAMMS223*^ CARE-MS*^ PRISMS*^ CARE-MS I*^	Alemtuzumab dimethyl fumarate fingolimod glatiramer acetate 20mg IFN-β-1a 30 µg IFNβ-1a 44 µg Natalizumab teriflunomide 7 mg/14 mg Cladribine	Two definitions were explored: HA (licensed population): 1 relapse in the previous year while on treatment and ≥1 T1 Gd+ lesion or ≥9 T2 lesions OR populations with ≥2 relapses in the previous year whether on treatment or not Sub-optimally treated: Populations with ≥1 relapses in the prior year whether on treatment or not. A 2nd (very limited NMA) is reported for 'sub-optimally treated MS' – relapse despite treatment.	Assumed that subgroups in CLARITY were comparable to those in other trials despite differences in definitions of subgroups from previous NICE guidance. NMA conducted for HA population but not for the sub-optimally treated, due to small number of populations in relevant cladribine trials that met this criteria, and the paucity of evidence available from other trials. In the HA population NMA, it was assumed that outcomes were comparable between trials despite differences in outcome measures in CLARITY and clinical trials for other treatments. While the ERG expressed concerns about the validity of this approach, the committee accepted that the results were sufficiently similar. A meta-regression was conducted to estimate effect sizes for the sub-optimally treated population adjusted by baseline disease severity. This analysis assumed a linear relationship between baseline severity and treatment efficacy. The ERG recognised that this approach was used to address heterogeneity across trials; however, noted that the analysis was still subject to the other limitations associated with the company's NMA. The ERG also flagged indications that

Appraisal (NMA publications)	Included publications (*reporting on HA MS; ^included in NMA)	Included treatments (note that not all treatments were included in all analyses)	Definition of HA	Assumptions
				the reported effect sizes were influenced by other effect modifiers, thus undermining the validity of the analysis.
Fingolimod [TA254] 2011[14]	AFFIRM EVIDENCE FREEDOMS INCOMIN MSCRG IFNB MS Study Group PRISMS TRANSFORMS BEYOND BECOME REGARD Hurwitz 2008 Etemadifar 2006 Wroe 2005 Saida 2005 Johnson 1995 Comi 2001 Bornstein 1987	fingolimod 0.5 mg* natalizumab 300mg* interferon beta-1a* 22mcg interferon beta-1a* 44mcg interferon beta-1a* 30mcg interferon beta-1b* 250mcg glatiramer acetate 20mg placebo Interferon 1b 50mcg Interferon 1b 500mcg	Populations who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (including RES RRMS). The company suggested that the populations included in the indirect comparison were populations with RRMS regardless of previous treatment, rather than from those whose disease had a suboptimal response to disease-modifying therapy.	Fingolimod was the first DMT to be recommended specifically in the HA population. The company conducted a NMA using the active RRMS population, though this was not used to inform the economic analysis for the HA population due to indirectness/heterogeneity of the trial poplations. Instead, an indirect comparison between fingolimod and placebo was generated from two of the included trials (FREEDOMS and TRANSFORMS). As fingolimod was the first treatment to be recommended by NICE for the HA population, and so no NMA was conducted in the HA population. The results of the NMA in the active population were not used in the model. Notably for this appraisal, discontinuation due to AEs was evaluated instead of all-cause discontinuation, due to variability in the reasons for exclusion used across trials. Unadjusted data was used, also due to variability in covariates applied in the included trials. For the CDA analysis, the company excluded three trials that didn't report CDA-3, but these were included in a sensitivity analysis.

Appraisal (NMA publications)	Included publications (*reporting on HA MS; ^included in NMA)	Included treatments (note that not all treatments were included in all analyses)	Definition of HA	Assumptions
Ozanimod [TA1294] 2021[12]; note that information reported is based on documents published following AC2 (May 2021)	NA	NA	Those with an unchanged or increased relapse rate, or ongoing severe relapses compared with the previous year despite treatment with at least one DMT	No separate NMA conducted for the HA population, and the company did not present evidence for comparators used in the HA population, as ozanimod was not originally positioned for these populations. In the active population, the ERG did not consider that heterogeneity across the included trials to have a major impact on the results of the analyses. The company conducted an analysis combining CDA-3 and CDA-6, to account for older trials that did not report CDA-6. However, the ERG considered that the assumption of a proportional relationship between the CDA-3 and CDA-6 hazard ratios for ozanimod appeared to have been violated.
Ofatumumab [TA1677][13] 2021; note that information reported is based on documents published following AC1 (April 2021)	NA	NA	-	The company's feasibility assessment concluded that it was not possible to conduct NMAs in the HA or RES populations, due to heterogeneity between the trials and the paucity of data in completing the network. In the ACD, it was reported that clinical experts had suggested that HA and RES definitions may not be used in practice, but rather clinicians would consider treatment and relapse history. On that basis, the committee concluded that it was reasonable to consider the RRMS in full.

Abbreviations: ABCR, immunomodulators; ACD, appraisal consultation document; ALE, alemtuzumab; CDA, confirmed disability accumulation; CS, Company Submission; DAC, daclizumab; DMF, dimethyl fumarate; EOD, every other day; ERG, Evidence Review Group; FIN, fingolimod; GA, Glatiramer acetate; HA, highly active; HTA, health technology assessment; IFNB interferon beta; ITT, intention-to-treat; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; NICE, National Institute for Health and Care Excellence; NMA, network meta analysis; OCR, ocrelizumab; QD, once a day; QW, weekly; RES, rapidly evolving severe; RRMS, relapsing remitting multiple sclerosis; SC subcutaneous; TER, teriflunomide, TIW, three times weekly

Appendix C: Comparison of relative effects in ITT and HA populations

Table 59: Comparison of relative effects on annualised relapse rate between the highly active and intention-to-treat populations in the NMA

Comparison	HA subgroup [a,b]	ITT subgroup [a,b]	Difference [c]	Ratio [d]
OCR vs ALE	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs CLA	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs PON	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs TER	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs CLA	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs PON	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs TER	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs PON	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs TER	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
PON vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
PON vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
PON vs TER	[redacted]	[redacted]	[redacted]	[redacted]
PON vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
PON vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs TER	[redacted]	[redacted]	[redacted]	[redacted]

Comparison	HA subgroup [a,b]	ITT subgroup [a,b]	Difference [c]	Ratio [d]
FIN vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
IFNB 1a 44 vs TER	[redacted]	[redacted]	[redacted]	[redacted]
IFNB 1a 44 vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
IFNB 1a 44 vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
TER vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
TER vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
PBO vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; FIN, fingolimod 0.5 mg once daily; HA, highly active; IFNB-1a 30 µg , interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; ITT, intention-to-treat; NMA, network meta-analysis; OCR, ocrelizumab 600 mg every six months; PBO, placebo; PON, ponesimod 20 mg once daily; TER, teriflunomide 14 mg once daily

Notes:

[a] Data are point estimates of relative risk (lower 95% confidence interval; upper 95% confidence interval)

[b] Cells with grey shading denote significant results

[c] Difference of HA point estimate – ITT point estimate

[d] Ratio of HA point estimate/ITT point estimate

Table 60: Comparison of relative effects on confirmed disability accumulation at 3 months between the highly active and intention-to-treat populations in the NMA

Comparison	HA subgroup [a,b]	ITT subgroup [a,b]	Difference [c]	Ratio [d]
CLA vs OCR	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs PON	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs TER	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs PON	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs TER	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]

Comparison	HA subgroup [a,b]	ITT subgroup [a,b]	Difference [c]	Ratio [d]
OCR vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
PON vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
PON vs TER	[redacted]	[redacted]	[redacted]	[redacted]
PON vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
PON vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
PON vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs TER	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs IFNB 1a-44 µg	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs IFNB 1a-30 µg	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
TER vs IFNB 1a-44 µg	[redacted]	[redacted]	[redacted]	[redacted]
TER vs IFNB 1a-30 µg	[redacted]	[redacted]	[redacted]	[redacted]
TER vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
IFNB 1a-44 µg vs IFNB-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
IFNB-1a 30 µg vs PBO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CLA, cladribine 3.5 mg/kg once daily; FIN, fingolimod 0.5 mg once daily; HA, highly active; IFNB-1a 30 µg , interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; ITT, intention-to-treat; NMA, network meta-analysis; OCR, ocrelizumab 600 mg every six months; PBO, placebo; PON, ponesimod 20 mg once daily; TER, teriflunomide 14 mg once daily

Notes:

[a] Data are point estimates of hazard ratios (lower 95% confidence interval; upper 95% confidence interval)

[b] Cells with grey shading denote significant results

[c] Difference of HA point estimate – ITT point estimate

[d] Ratio of HA point estimate/ITT point estimate

Table 61: Comparison of relative effects on confirmed disability accumulation at 6 months between the highly active and intention-to-treat populations in the NMA

Comparison	HA subgroup [a,b]	ITT subgroup [a,b]	Difference [c]	Ratio [d]
CLA vs ALE	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs OCR	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs PON	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs TER	[redacted]	[redacted]	[redacted]	[redacted]

Comparison	HA subgroup [a,b]	ITT subgroup [a,b]	Difference [c]	Ratio [d]
CLA vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
CLA vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs OCR	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs PON	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs TER	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
ALE vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs PON	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs TER	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
OCR vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
PON vs FIN	[redacted]	[redacted]	[redacted]	[redacted]
PON vs TER	[redacted]	[redacted]	[redacted]	[redacted]
PON vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
PON vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs TER	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
FIN vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
TER vs IFNB-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]
TER vs PBO	[redacted]	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg vs PBO	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; FIN, fingolimod 0.5 mg once daily; HA, highly active; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; ITT, intention-to-treat; NMA, network meta-analysis; OCR, ocrelizumab 600 mg every six months; PBO, placebo; PON, ponesimod 20 mg once daily; TER, teriflunomide 14 mg once daily

Notes:

[a] Data are point estimates of hazard ratios (lower 95% confidence interval; upper 95% confidence interval)

[b] Cells with grey shading denote significant results

[c] Difference of HA point estimate – ITT point estimate

[d] Ratio of HA point estimate/ITT point estimate

Appendix D: ERG One-way sensitivity analysis

This section contains additional tornado plots displaying the results of one-way sensitivity analyses conducted by the ERG for ponesimod as compared to its comparators. Due to the large number of comparators included within this appraisal, the ERG opted only include the one-way sensitivity analysis results versus teriflunomide and fingolimod in the main report (for the ITT and HA RRMS populations respectively). The remaining results, have been included here for completeness.

ITT population

14)

Abbreviations: EDSS, expanded disability status scale; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

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Abbreviations: EDSS, expanded disability status scale; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

16 [redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

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Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[redacted]19[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

20

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

21 [redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

22 [redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

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Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

HA RRMS subgroup

[redacted]24[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

25 [redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[redacted]28[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[redacted]29[redacted]

[redacted]

Abbreviations: EDSS, expanded disability status scale ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ponesimod for treating relapsing multiple sclerosis [ID1393]

The ERG response to the issues raised by the company during the factual accuracy check (FAC) is provided in the tables below.

Issue 1 Highly active and Rapidly Evolving Severe (RES) RRMS definitions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to clarify the definitions of RRMS subgroups in the OPTIMUM phase 3 trial: while NHS England (NHSE) considers highly active (HA) RRMS and rapidly evolving severe (RES) RRMS as distinct mutually exclusive subgroups, the OPTIMUM trial pre-specified a single subgroup of patients with highly active disease. The definition of highly active RRMS within OPTIMUM was less restrictive than that used by NHSE, and also includes patients	On page 18, Janssen suggests the following revisions to the text of the ERG report: • The ERG notes the "company stated that the trial definition of highly active RRMS is less restrictive than that used by NHSE and likely includes patients with RES RRMS, as defined by NHSE." On page 49, Janssen suggests the following revisions to the text of the ERG report: • The definition of HA RRMS used in OPTIMUM is a broader than that used by NHSE and includes people with HA	Janssen have stated in the company submission (CS) that compared to the NHSE definition, highly active RRMS in several clinical trials (including OPTIMUM) has been more broadly defined, encompassing patients defined as RES RRMS by NHSE. Janssen would like to note that the OPTIMUM definition of highly active is similar to the trial definition used in both the cladribine (TA616) and alemtuzumab (TA312) company submissions, which were accepted	This is not a factual inaccuracy. The ERG also note that the wording of the ERG report was advised and reviewed by clinical experts to the ERG before submission.

that may be defined as RES RRMS as per the NHSE definition. Note that all analyses of RES RRMS from the OPTIMUM trial were conducted post hoc and the trial was not powered to evaluate differences between the treatment arms for RES RRMS patients only (as defined by NHSE). **Page 18 – Section 1.3: key issue 1** The ERG notes the "*company stated that people with RES RRMS were included within its definition of highly active (HA) RRMS*". **Page 49 – section 3.2.2: relevance of trial populations to target population** The ERG states *that "the definition of HA RRMS used in OPTIMUM included people with RES RRMS*".	RRMS as well as people with RES RRMS.	by NICE. The inaccuracy is minor but could contribute to a misunderstanding of how the highly active disease population was defined in OPTIMUM.	

Issue 2 Ponesimod patient suitability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to clarify the following point regarding the suitability of ponesimod in patients with RRMS, which was based on a patient study in RRMS commissioned by Janssen. **Page 31 – Section 2.2.2: The technology** The ERG discuss: "*the company further suggest that ponesimod may be preferred by people who prefer an oral treatment and/or a treatment with a shorter half-life".* However, in the CS (section B.3.9) Janssen note that ponesimod may offer an alternative for patients who [redacted] and who prefer a DMT [redacted]	Janssen suggest the following change to the text of the ERG report: • "The company suggest that ponesimod may be preferred by people who [redacted] who prefer a [redacted].	In the CS Janssen highlighted the key benefits for patients in a summary in section B.3.9. These are the benefits which patients would first consider and would be most valuable to patients when discussing treatment options with their clinician, based on patient research conducted by Janssen. It is not expected this will have a material impact on ERG conclusions.	This is not a factual inaccuracy. The wording of the ERG report was selected to demonstrate the potential benefits of ponesimod that are demonstrable; i.e. the ERG did not consider that the company had demonstrated that ponesimod was a less aggressive treatment, or had an improved AE profile, compared to other treatments.

Issue 3 CDA-3 and CDA-6 outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to clarify a point regarding reporting of outcome data from the phase 2 trials. The outcomes referred to by the ERG	Janssen proposes the below revisions: • Delete "no data for these outcomes were reported in the	The results for disability that Janssen captured during the trials were reported in the CS. The original statement written by the	This is not a factual inaccuracy; the statement is factually correct, and the ERG report stated elsewhere that these data were

were not collected as part of the trial. Currently, the text reads as if Janssen have the data, but did not report it. **Page 59 - Section 3.2.4.2: Clinical efficacy** The ERG report states: "[redacted]. *No data for these outcomes were reported for the Phase 2 trial.*"	Phase 2 trial". • Suggest text be revised to read: "[redacted]. These outcomes were not evaluated in the core Phase 2 trial and therefore no data is available. However, CDA-6 was a pre-specified endpoint in the long-term extension Study B202. The Kaplan-Meier estimate for the percentage of patients in the ponesimod 20 mg dose group who had experienced CDA-6 at Week 432 was [redacted]"	ERG may be misinterpreted as a failure of Janssen to provide data that exists and are relevant for the submission. The proposed revision clarifies the fact that these data were not collected in the core trial. The change is not anticipated to have a material impact on the ERG conclusion.	not collected in the Phase 2 trial.

Issue 4 CDA-3 and CDA-6 outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to highlight some factual inaccuracies regarding disability accumulation data from the Phase 2 extension trial which may lead to erroneous conclusions about the long-term clinical effectiveness of ponesimod.	Please update the legend and data as follows: • 3-month CDA Risk (%) = NR • 6-month CDA Risk = [redacted]	These are factual inaccuracies since the Phase 2 long term extension study evaluated 24-week CDA (6-month CDA) and not 12-week CDA (3-month CDA). Janssen proposes revising the description from rate to risk to avoid misinterpretation that these numbers represent an annual rate of CDA events. The numbers reported are	The ERG thank the company for highlighting that the data point in Table 15 of the ERG report for 12-week CDA was in fact a measure of 24-week CDA; this data point has been removed (p.61). However, the [redacted] data point in the table (p.62) is correct and has been retained. This

Page 60, 61 - Section 3.2.4.2: Table 15 There is a factual error in the last row in Table 15 which reports the following data for the B201 extension study at follow-up 432 weeks: • *3-month CDA* *Rate (%) =* [redacted] • *6-month CDA* *Rate =* [redacted]		the Kaplan-Meier estimates for the percentage of patients receiving ponesimod 20 mg who had experienced a 6-month CDA event at the specified timepoint.	data point represents the cumulative rate of 24-week CDA across the three trial phases, as reported in the interim trial CSR. Accordingly, the 'rate' label in the table is correct. The ERG notes that KM-estimates for CDA are not included in this table of the ERG report, for brevity.

Issue 5 Adverse event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to highlight some factual inaccuracies with regards to data on infections and PML in the ERG report as these may lead to erroneous conclusions about the safety profile of ponesimod and other DMTs in RRMS. **Page 87 - Section 3.5.3: Table 25** Table 25 presents the following data for Infections, Non-fatal PML and Fatal PML. 	Table 25 should be updated to present the following data for Infections, Non-fatal PML and Fatal PML in line with the below. 	The source tables for these data in the CS included formatting errors, which resulted in the table columns to be 1 row out. Janssen apologises for this error and we have now provided a revised submission with the correct source data for table 25. It is anticipated that this inaccuracy will have a material impact upon the interpretation of results.	The ERG thanks the company for providing their corrected AE data. From the information provided by the company, the ERG understands that the error affected the columns in the table, not the rows as stated. Table 25 (p.88) of the ERG report has been updated to reflect the amended data. In brief, the ERG did not consider the change to have affected the ERG's conclusions regarding elevated ALT and AST (p.89) or infections (p.89); though these proportions are now reported to highlight the higher risk with fingolimod. Changes in the rates of PML are addressed

			under Issue 6, below.

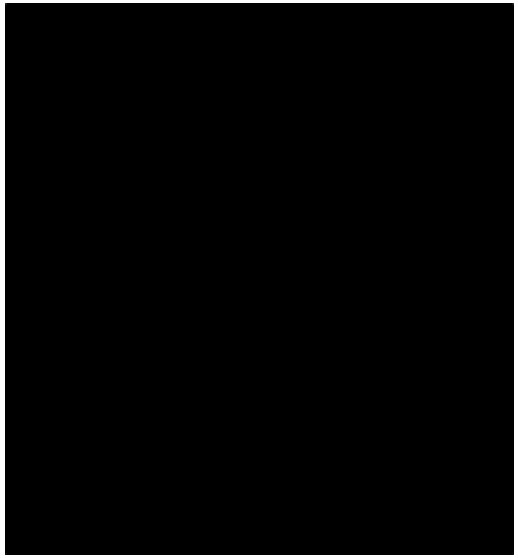
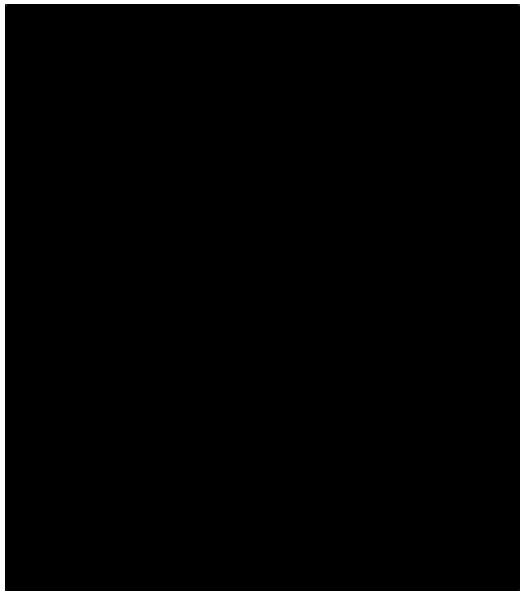
Issue 6 Adverse event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to highlight some factual inaccuracies with regards to data on infections and PML in the ERG report, related to Issue 5. These statements may lead to erroneous conclusions about the safety profile of ponesimod and other DMTs in RRMS **Page 88 - Section 3.5.3.1: Naïve comparison of AE rates for ponesimod vs. fingolimod** The ERG highlighted that "[redacted]. *In the absence of larger participant samples, however, it is uncertain whether* [redacted]." **Page 89 - Section 3.5.3.2: Naïve comparison of AE rates for ponesimod vs. other comparators** [redacted]	On page 88, Janssen proposes the following revisions to the text: • Based on real-world experience from the Novartis safety database (data cut off 28 February 2020), 37 cases of PML were associated with fingolimod treatment (Fox et al MS Virtual 2020, abstract FC02.02). The ERG noted that [redacted] On page 89, Janssen proposes the following revisions to the text: • [redacted]	The analysis described by the ERG was based on incorrect data in the CS. The corrected adverse event (AE) data tables have now been provided by Janssen as described in Issue 5 and revised text has been proposed to state the factual information. Janssen apologies for this error in the CS. There will be a material impact on the results reported by the ERG, due to the comparison or clinical data between ponesimod and fingolimod.	As above, the ERG thanks the company for providing the corrected data. The ERG report (p.90) has been amended to show that there were no cases of PML in either the fingolimod or ponesimod trials. In addition, the ERG report (p.90-91) has been amended to reflect no cases of PML in first or second line DMTs (excepting natalizumab). However, the ERG declines at this stage to include the new real-world data provided by the company, reporting rates of PML with fingolimod treatment. While the ERG consider that these data are informative, they were not presented in the CS, and therefore cannot be included retrospectively during the FAC. Moreover, the ERG consider that any additional data presented by the

[redacted] In line with issue 5 – the analyses provided by the ERG are based on incorrect data tables, due to a formatting error. Janssen apologises for this error.			company should be appraised by the ERG in full, including consideration of the methods used to identify the data. In its report, the ERG identified a key issue surrounding the need for more evidence to demonstrate the relative safety of ponesimod as compared to its comparators. The ERG would be interested in appraising such evidence during technical engagement.

Issue 7 Adverse event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to highlight some factual inaccuracies with regards to data on PML in the ERG report. These statements may lead to erroneous conclusions about the safety profile of ponesimod and other DMTs in RRMS	Janssen have concerns on the interpretation of Table 26, without the context of the submission and economic model. Based on this, we propose that table 26 is removed from the ERG report. However, if the ERG wishes to keep the	Janssen would like to clarify that the data in the table represents the proportion of AEs e.g., PML, headache etc, which can become a serious AE.	The ERG agrees that the content of Table 26 (p.88-89) could be misleading to readers, and therefore has amended the content and footnote as suggested.

Pages 87 & 88 - Section 3.5.3: Table 26 Table 26 presents the following data for Non-fatal PML and Fatal PML in the table of percentages of key adverse events that were serious for ponesimod and its comparators 	table, we propose that the table should be updated to present the following data for Non-fatal and Fatal PML. 	Due to the serious nature of PML, it was assumed that 100% of PML events (fatal or non-fatal) would be identified as a serious AE. However, table 26 does not represent if the patients experienced a serious AE, which only occurred in people receiving natalizumab. Therefore, the assumption does not apply to any other comparator, including ponesimod. While the current table is not incorrect, it could be misleading to the reader in this context, and therefore could be misinterpreted. We therefore have amended the table to show that PML (fatal or non-fatal) is not an applicable serious AE in any treatment, with the exception of natalizumab. Janssen have also updated this table in the revised version of form B. The updated revision will not have any material impact on the results but will ensure that there is clarity for the reader.	

Issue 8 Ponesimod search strategy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to clarify some points supporting the robustness of the search strategy for the SLR, which was used to inform studies used in the NMAs reported in the CS. **Page 92 – Section 4.1: ERG commentary on the company's review of cost-effectiveness evidence** In table 27 the ERG notes that "*the search strategy did not include any search terms for siponimod, ozanimod, ofatumumab or ponesimod. Therefore, few or no papers will have been identified for these interventions*". The search strategy that Janssen employed was aligned with TA624. However, we state explicitly in appendix G.1.1 (page 190) that "The key differences were the addition of recently introduced interventions (ponesimod, siponimod, and ozanimod) in the inclusion criteria".	Janssen propose that the paragraph is deleted as it does not accurately reflect what was undertaken.	Currently, the text in the ERG report is incorrect since all other sphingosine-1-phosphate receptor modulator (S1P) treatments were included as part of the updated search terms. Please see the original appendices submitted by Janssen (G.1.1 – page 190). The inaccuracy is not likely to have an impact on the conclusions; however, it could lead the reader to believe that Janssen did not consider the S1P modulators (including ponesimod) in its own submission.	The ERG has not amended this text. The ERG noted that the company stated in Section G.1.1 of the CS that three additional treatments (ponesimod, siponimod and ozanimod) were included as part of the search strategy. However, the search strategies shown in Tables 21-25 of the CS do not include these terms. These search strategies appeared to have been directly copied and pasted from the original databases, including the number of results for each search line on the date searched. Therefore the ERG had no evidence that the three additional treatments were actually included in the search strategies.

Issue 9 Cost-effectiveness analysis based on 6-month CDA to model disease progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to highlight the consistency of the cost-effectiveness analyses based on 3-month CDA vs those based on 6-month CDA to model disease progression. **Page 142 - Section 6.1.1.1: Scenario analysis 1 six-month CDA** The ERG report incorrectly concludes that "*Results from this analysis indicated that using the six-month CDA had a material impact on base case cost effectiveness results versus most comparators".* Where the term "most" could be misleading to the reader.	Janssen proposes the following revisions to the text in the ERG report • "Results from this analysis indicated that using the six-month CDA did not have a material impact on base case cost effectiveness results versus most comparators".	The ERG analysis finds that cost effective results are materially changed for only three out of the ten comparators (interferon beta 1a 22 mcg, interferon beta 1b 250 mcg and peginterferon beta 1a 125 mcg) while the results are consistent with those based on 3-month CDA for most comparators. The inaccuracy does not have an impact on the outcomes; however, it could be misleading to the reader leading them to believe that ponesimod in this scenario is not cost effective against nearly all or "most" comparators.	The ERG acknowledges the company's comment that this scenario had a material impact for three comparisons in the ITT population. As such the word 'most', has been removed from p.143 of the ERG report. The text has been amended to the following. *'Overall, results from this analysis indicated that using the six-month CDA had a material impact on base case cost effectiveness results versus three key comparators'.*

Issue 10 Treatment groups according to positioning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to seek clarification regarding the ERG's scenario analysis, in which it is unclear what basis the analysis is guided on, including the source of information which may be misleading and could lead to erroneous conclusions on the cost effectiveness of ponesimod vs other DMTs. **Page 146 – Section 6.1.1.7: scenario analysis 7 (model parameters)** The ERG discusses a scenario analysis conducted in the model related to treatment positioning, its highlighted that "*DMTs were stratified into 3 groups according to their approximate position within the treatment pathway*" and proceed to conduct an alternative scenario analysis on 3 groups of DMTs. However, there is no rationale or clinical basis provided for the group combinations.	Janssen is unsure of the rationale for the combination of treatments provided by the ERG, and it is not clear what the intention of this scenario analysis is. In the CS, Janssen provided ITT analysis based on approved active and highly active treatment in the NHS, based on the NHSE treatment algorithm and NICE approved treatments, as described in the final NICE scope. The clinical basis for this scenario is not clear and therefore we would suggest it is revised to align with the final NICE scope or deleted altogether.	No rationale for the combination of DMT groups A, B and C has been provided and the mixture of groups does not match any positioning described by NHSE or NICE. Janssen do not understand the rationale for the division of treatments across groups A, B and C as this was not described in the final NICE scope, ERG report, nor raised during discussion with NICE or the ERG. Furthermore, it is unclear how the treatment groups align with RRMS sub-populations described in the final NICE scope Without an understanding of the rationale of this scenario it is difficult to understand the basis for this scenario. However, the impact of this analysis is material and Janssen would like to understand further why each DMT has been grouped as stated.	This is not a factual inaccuracy. The ERG conducted this scenario analysis in order to explore the impact of varying the clinical effect estimates on the ICER. These analyses were undertaken due to a high degree of uncertainty in the clinical effects of ponesimod and its comparators. The ERG report stated that this analysis was exploratory in nature, and the ERG considered the groupings to be "approximate" groupings based on the NHSE treatment pathway reported in the CS (see p.147 of the CS). As noted by the ERG, NICE should consider this scenario analysis as exploratory only.

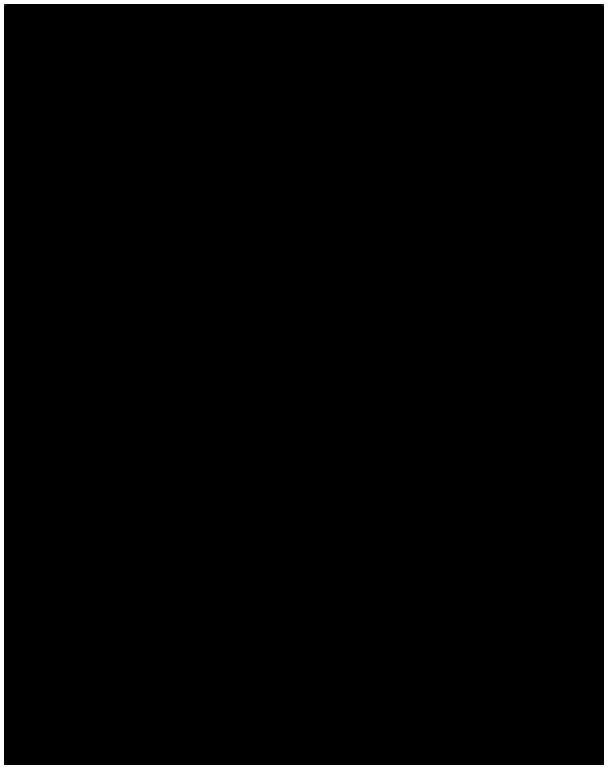
Issue 11 Minor typographical issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Janssen would like to note some minor typos detected in the ERG report.	1. Page 17 – hyphen missing in “positioning based” 2. Page 28 – “issues with cognitive issues” should read changed to “issues with cognition” 3. Page 31 – “RRMS/HAMS” where HAMS has not been previously defined and is not used again in the text 4. Page 39 – evidence synthesis section of table “company conducted several (number uncertain) of NMAs”, delete “of” 5. Page 49 – “ERG was that DMT within the”, insert “use” 6. Page 52 – “which they stated in section B.2.50 for the CS” – replace “for” with “of” 7. Page 58 – “clinically meaningful34,35” likely referencing error 8. Page 63 – “and favoured terifunomide” – should read teriflunomide 9. Page 95 – “NICE TAs includig ocrelizumab” – should read “including” 10. Page 98 - with the exception of alemtumumab” – should read alemtuzumab 11. Page 98 – “potential limitations surrouding” – should read surrounding	Making these amendments will help with the readability of the report. However, there will be no material impact on correcting the error beyond this.	The ERG thanks the company for their careful review of the ERG report, and has made all suggested edits. Page numbers in the ERG version varied from those of the company, and therefore page references for the edits are as follows: 1. Page 18 2. Page 29 3. Page 32 4. Page 40 5. Page 50 6. Page 53 7. Page 59 8. Page 64 9. Page 96 10. Page 99 11. Page 99 12. Page 100 13. Page 100 14. Page 102

	12. Page 99 – “effect estimate to paramterise” – should read parameterise 13. Page 99 – “of an alterative natural history” – should read alternative 14. Page 101 – “rates for each treament” – should read treatment 15. Page 101 – “estimating anualised relapse rates” should read annualized 16. Page 106 – “there is precendent for using” – should read precedent 17. Page 106 – “the company’s justifcation for” – should read justification 18. Page 107 – “adjusted by appyling” – should read applying 19. Page 113 – “however it was unlikley” – should read unlikely 20. Page 125 – “the determinstic ICERs” – should read deterministic 21. Page 125 – “ponesimod vs. alemtuzamb” should read alemtuzumab 22. Page 143 – “was considered be introduce” revise from be to “to” 23. Page 146 – “Interferon bet 1a” – should read beta 24. Page 147 – “ponesimod was [redacted] ozanimod” – insert “by”		15. Page 102 16. Page 107 17. Page 107 18. Page 108 19. Page 114 20. Page 126 21. Page 126 22. Page 144 23. Page 147 24. Page 148 Two additional typos were corrected on Page 97

Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Janssen would like to highlight some data that are no longer considered AIC in the submission **Page 33, 34**	The data marked as AIC in Table 8 have now been published (Kappos et al 2021) [redacted]	Please see screenshot below for revised markups **Rationale if different from the final NICE scope** The decision problem is focused on a sub-population of people with MS because there is limited evidence available for ponesimod in SPMS for health technology evaluation. The evidence presented in the submission is based on a RCT (OPTIMUM) that evaluated ponesimod compared to teriflunomide in people with RMS. At study entry, most people in the trial were diagnosed with RRMS (97.4%). The trial included only a small proportion of people with SPMS (2.6%). Phase 3 data for people with RRMS is more robust in people with active RRMS and highly active RRMS (35% of trial population) and so the submission focuses on these two subgroups ~~i.e.~~ not in people with RES RRMS. The OPTIMUM trial included only 2.6% SPMS population, therefore it was deemed that there is insufficient evidence for this population	The ERG thanks the company for the update on the publication of these data; the ERG has updated the mark-up accordingly.

Page 47, 48	The following baseline characteristics in Table 12 have been marked as AIC, however, these have been published in Kappos et al and are no longer AIC - Age (SD) - Female % - DMT received in 2 years prior to randomisation - Years since first symptoms at randomisation - Mean relapses in year prior to study entry - Disease subtype - Presence of Gd+ T1 lesions - Volume of T2 lesions - Mean FSIQ-RMS weekly symptoms score - % highly active - White race - Mean relapses in last year	Please see screenshots below for revised markups 	As above, the ERG has altered the mark-up to reflect the publication of these data.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

Deadline for comments 5:00pm, Friday 16 July 2021

Thank you for your time.

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

Notes on completing this form

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

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

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

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

About you

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

Key issues for engagement

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

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	Yes	**Janssen will not be actively seeking to position ponesimod for use in people with rapidly evolving severe (RES) RRMS and have provided additional analyses on the highly active (HA) RRMS population based on the NICE/NHSE definition to support the generalisability of the OPTIMUM trial HA population within the NHS. Positioning of ponesimod in active and highly active RRMS only.** The ERG sought clarity regarding Janssen's positioning of ponesimod within the NHS England (NHSE) treatment algorithm for relapsing remitting multiple sclerosis (RRMS), in particular for people with rapidly evolving severe (RES) RRMS. The ERG did not believe that the evidence presented by the company was sufficient to evaluate the effectiveness of ponesimod in the RES RRMS population; however, they noted that further clinical input and evidence may help to resolve this issue. Janssen would like to note that we do not seek to position ponesimod in RES RRMS. Ponesimod is most appropriately positioned in active and highly active RRMS based on clinical trial data and expert opinion. Janssen have conducted an additional analysis of the highly active population in the phase 3 OPTIMUM trial based on the NICE/NHSE definition and concluded that people in the HA subgroup based on this definition have consistent outcomes to the HA population defined in the OPTIMUM trial, which supports the generalisability of results to patients treated for HA disease in the NHS. While the final NICE scope for this appraisal and NHSE treatment algorithm specify RES RRMS as a separate population,(1) no clinical trials have been conducted specifically on patients with RES RRMS, nor

		has any trial prespecified RES RRMS as a distinct subgroup. The evidence base for this subgroup is known to have a high degree of uncertainty as acknowledged in the recent appraisals of ocrelizumab (TA533) and ofatumumab (TA699), both of which were recommended by NICE for RES RRMS based on evidence from the respective overall trial populations.(2, 3) Clinical experts have also confirmed that multiple sclerosis (MS) exists as a spectrum of disease activity rather than rigidly defined stages, with RES RRMS as broadly representative of patients at the more active end of the disease spectrum.(4) RES RRMS was not pre-specified as a separate subgroup in the OPTIMUM trial and these patients were considered within the context of the prespecified highly active subgroup due to a broader trial definition of highly active than what is currently used in the NHS. For completeness, we have included the results of the post hoc analysis conducted by Janssen which were presented in the response to clarification questions. This analysis demonstrated that [redacted]% of patients enrolled in the core phase 3 trial were RES RRMS based on the NICE definition (or [redacted]% of HA RRMS patients). In addition, [redacted]% of all patients (or [redacted]% of HA RRMS patients) rolled over into the long-term extension (LTE) could be defined as RES RRMS (See Appendix B for all data tables related to the post hoc analyses from Phase 3 ponesimod trials). As expected, the baseline disease activity was higher in RES RRMS subgroup vs overall HA group (OPTIMUM definition) (Baseline EDSS, mean [SD] = [redacted]) with a higher proportion of patients with active inflammation (Gd+ T1 lesions reported in [redacted] patients). Janssen notes that a high T2 lesion load (≥9 T2 lesions) is reported in similar proportions of patients in the two groups ([redacted]). These analyses indicate that the results for RES RRMS were consistent with those observed in the intention to treat (ITT) population, and the prespecified HA subgroup, with improvements reported in a greater proportion of patients receiving ponesimod vs teriflunomide. This is especially true for the long-term outcome of 6-month confirmed disability accumulation (CDA), where the Hazard Ratio (HR) (95% CI) for ponesimod vs teriflunomide in the ITT, HA (OPTIMUM definition) and RES subgroups was [redacted], [redacted] and [redacted] respectively. (5) At this time, Janssen has no additional direct evidence for the effectiveness of ponesimod in the RES subgroup. Janssen also notes that an indirect treatment comparison against other treatments

		recommended for RES RRMS is not feasible due to a lack of published subgroup data for these treatments and proposes using the ITT network and the highly active subgroup network meta-analysis (NMAs) presented in the company submission (CS) for decision making, similar to previous appraisals.(2, 3) Janssen is therefore not actively seek a NICE recommendation for RES RRMS given the limited evidence base for this population and the likely use of ponesimod in NHSE clinical practice where clinicians have suggested its primary benefit as an additional treatment option in active and highly active disease. **The prespecified highly active subgroup in the OPTIMUM trial is generalisable to people with highly active RRMS in the NHS and demonstrates consistent results in the NMA and economic results regardless of the definition of highly active used.** The OPTIMUM phase 3 trial definition of highly active RRMS includes a broader population than that defined by NHSE. There is no single universal definition of HA RRMS and definitions have varied across MS trials. The OPTIMUM trial definition for HA RRMS aligns with that used in the CLARITY trial and includes all patients defined as HA RRMS by NHSE, but it is broader in that it also includes patients with high disease activity that may be defined by the NHSE as RES RRMS. At technical engagement, the ERG raised concerns regarding the generalisability of the evidence for the prespecified HA subgroup from OPTIMUM around whether it would accurately reflect the treatment effect for patients with HA RRMS as defined by NHSE. The ERG understood that while there may be some similarities in presentation between people with HA and RES RRMS in terms of the speed of disease progression, there are differences in the populations: specifically, HA RRMS is disease that progresses despite treatment ('breakthrough disease'), and RES is a "separate, rare phenotype of the disease". Janssen acknowledges the definition of HA RRMS as "breakthrough disease"; however, the ERG statement implies that RES RRMS is a condition not associated with disease progression while on treatment and Janssen was unable to find any published literature to support this assumption. If disease progression on previous treatment is indeed the distinguishing factor between HA RRMS and RES RRMS, Janssen would like to highlight that among OPTIMUM trial patients defined post hoc as RES RRMS, [redacted] reported disease progression at baseline despite receiving disease modifying therapies (DMTs). These

data suggest that HA RRMS and RES RRMS may not be mutually exclusive groups as described in the NHSE treatment algorithm, and indeed represent a spectrum of patients with high disease activity. For this reason, Janssen proposes that the prespecified HA RRMS-subgroup from the OPTIMUM trial may be generalisable to HA RRMS and to some degree, also to RES RRMS as defined by NHSE.

To address the generalisability issue, Janssen have provided post hoc analyses to identify the proportion of patients within the ponesimod phase 3 trials that can be defined as HA RRMS by either OPTIMUM or NHSE definitions. The analysis shows that approximately [redacted]% vs [redacted]% of patients in the core OPTIMUM trial (or [redacted]% vs [redacted]% in OPTIMUM-LT) can be defined as HA RRMS based on OPTIMUM vs NHSE definitions, respectively. In addition, baseline disease characteristics (provided in Appendix B) and key clinical outcomes of ARR, 3-month CDA and 6-month CDA in the core trial are consistent across patients defined by either definition (Table 1), indicating that the trial subgroup results are generalisable to HA RRMS patients in NHSE clinical practice.

Table 1: OPTIMUM: Subgroup analysis results for treatment effect in patients with highly active RRMS per OPTIMUM and NICE criteria

	PON 20 mg		TER 14 mg		PON 20mg vs. TER 14 mg
Confirmed relapses up to EOS; Subgroup analysis (99% CL); Full analysis set					
	N	**Mean rate (99% CL)**	**N**	**Mean rate (99% CL)**	**RR (99% CL)**
HA RRMS (OPTIMUM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HA RRMS (NICE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to 12-week Confirmed Disability Accumulation up to EOS: Full analysis set					

	N	No of events (%)	N	No of events	HR (95% CI)
HA RRMS (OPTIMUM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HA RRMS (NICE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to 24-week Confirmed Disability Accumulation up to EOS: Full analysis set					
	N	**No of events (%)**	**N**	**No of events**	**HR (95% CI)**
HA RRMS (OPTIMUM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HA RRMS (NICE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Since the NMAs and economic analysis for HA RRMS in the original company submission (CS) were informed by evidence from the HA RRMS (OPTIMUM definition), Janssen wanted to allay any further concerns regarding the generalisability of the HA RRMS subgroup and have rerun the NMAs for HA RRMS using the treatment effects for HA RRMS (NICE definition) to inform the analysis. The outputs of these new NMAs were then used to inform the revised economic model, using the ERG's preferred assumptions to demonstrate clinical and cost effectiveness of ponesimod in HA RRMS, as defined by NICE/NHSE.

The NMA methods and results for the revised highly active subgroup are described in detail in Appendix D3. The key results for ARR, 3-month CDA and 6-month CDA are presented below in Figures 1, 2 and 3, respectively. These results indicate that ponesimod is comparable to other oral treatments for all three outcomes, with wide credible intervals that cross 1. Consistent with the previously submitted results, the effect estimates for all outcomes favoured ponesimod for the comparison to fingolimod. With regard to the

		other NICE-recommended treatments for HA RRMS, the effect estimates favoured the monoclonal antibody treatments over ponesimod with the notable exception of 6-month CDA, where ponesimod was more favourable than ofatumumab.

		Figure 1: NMA results for ARR of the updated highly active subgroup analyses (based on HA RRMS (NICE)) 

		Figure 2: NMA results for 3-month CDA of the updated highly active subgroup analyses (based on HA RRMS (NICE)) 

		Figure 3: NMA results for 6-month CDA of the updated highly active subgroup analyses (based on HA RRMS (NICE))  Revised economic analyses based on post hoc data for HA RRMS (NICE definition) from OPTIMUM trial are consistent with those based on the prespecified HA RRMS (OPTIMUM definition) and demonstrates cost effectiveness of ponesimod versus fingolimod for people with HA RRMS. Results of the updated NMAs based on HA RRMS (NICE definition) informed treatment effects of NICE-recommended DMTs for HA RRMS within the economic model and forms the new base case for HA RRMS. The revised economic model demonstrated that ponesimod dominates fingolimod and ozanimod, consistent with the outcomes presented in the original submission. For the comparisons to monoclonal antibody treatments, ponesimod is less costly and less effective vs ocrelizumab and ofatumumab

suggesting an efficient use of resources in patients who are risk averse and may prefer a treatment option with a more favourable safety profile.

The updated economic analysis for people with HA RRMS is presented in Table 2.

Table 2: Updated CEM results for the highly active subgroup

	PON	OCR	OFA	OZA	ALE	CLA	FIN
Economic outcomes							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related (pre-discontinuation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Cost-effectiveness							
		ICER, ponesimod vs. comparator (£ per QALY)	NA	[redacted] Less costly and less effective	[redacted] Less costly and less effective	[redacted] Dominates	[redacted] Dominated	[redacted] Dominated	[redacted] Dominates
Key issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	Yes	Additional NMAs have been conducted following the technical engagement that reduce the uncertainty in the comparator evidence base and allow for appropriate and improved confidence in relative efficacy comparison of ponesimod to established DMTs. The MS evidence landscape is heterogeneous due to a lack of consistency in definitions and evolving subgroups over time, in addition to changing clinical practices. A number of the core trials were conducted over 10 to 20 years ago and variations in MS diagnosis and endpoint measurements are a source of substantial uncertainty in the overall MS evidence base. The ERG raised this issue as a concern during technical engagement but expressed satisfaction that the evidence presented by the Janssen is representative of the known treatment effects for ponesimod and its comparators. They noted that until further evidence is available (more direct head-to-head trials, trials with longer follow-up, and evidence							

		identifying whether treatment effects vary according to the sources of heterogeneity in the evidence base), uncertainty surrounding the treatment effects of DMTs is a key issue in all appraisals of treatments for RRMS. After the technical engagement call, Janssen have tried to further address this issue with comparator trial evidence base and have presented two additional NMA analyses (interferon class effect NMA and NMA excluding ADVANCE and INCOMIN trials. The latter being consistent with the recent NICE appraisal of ofatumumab TA699. Both NMAs help to explore further the clinical uncertainty in the evidence base and to support appraisal committee decision making. Janssen have provided all available and relevant data from the head-to-head trials of ponesimod and from the ongoing phase 2 and phase 3 extension studies. While the treatment effects of DMTs have been a key issue in the appraisals of treatments for RRMS, clinical experts in MS have examined the clinical trial data and advised Janssen that ponesimod would be a suitable treatment option for patients with active RRMS as an alternative to existing low- or moderate-efficacy treatments and as a treatment option in highly active RRMS for patients who do not want to receive continuous high efficacy treatments (e.g. anti-CD20 therapies) or fingolimod.(6) Janssen would like to reiterate that the evidence package for ponesimod is based on an active comparator trial with more than 1,000 patients, and accompanied by approximately 9 years of long-term effectiveness data which shows consistent results in clinically relevant endpoints.. Janssen would like to note that in previous appraisals of disease modifying therapies DMTs for RRMS, the heterogeneity in the evidence base did not preclude decision making by NICE, and patients have gained access to additional treatment options that have offered them to select a treatment that suits their treatment goals. **Janssen have provided additional NMAs to reduce uncertainties in the MS comparative evidence base and increase confidence in the relative effectiveness of ponesimod** A major source of heterogeneity in the evidence base arises from variations in treatment effects from the interferon beta trials, which has been well acknowledged as lacking clinical validity. The results of selected clinical trials have suggested superiority of one interferon over the other (e.g., INCOMIN) or implausibly high results vs placebo (e.g., ADVANCE). However, this is inconsistent with clinical experience which has

established that individual interferon beta treatments have similar clinical effectiveness. These "outlier" trials have been reviewed in the literature (Vartanian et al 2003) as well as in previous NICE appraisals (TA699, 2021), and clinical experts have recommended exercising caution when interpreting the results of any analyses that include these trials.

As a result, Janssen conducted additional NMAs for the ITT population in an attempt to reduce the uncertainty due to inclusion of these trial results in the network following discussions with the ERG at technical engagement. Janssen would like to present new evidence for the outcomes of ARR, 3-month CDA, 6-month CDA and treatment discontinuation based on the following analyses:

- Interferon class-based NMA – These are sensitivity analyses for the previously submitted NMAs in which all interferon products are pooled as a single treatment node
- NMAs excluding ADVANCE and INCOMIN trials – These are sensitivity analyses for the previously submitted NMAs excluding the two outlier trials similar to the network presented in the ofatumumab appraisal (TA699).

Both NMAs are ways of addressing the clinical uncertainty associated with the interferon beta trials. Janssen's preference is for the interferon class based NMA, based on discussion with the ERG. We have updated our base case for active disease to use this NMA accordingly in the economic model, as this retains clinical trial data from the evidence base. But also acknowledge that the NMA excluding ADVANCE and INCOMIN is now consistent with committee decision making in TA699 and have also presented updated analysis using that data. The results of the class based and INCOMIN and ADVANCE excluded NMAs are presented below in figure 4 -7 and 8-11 respectively. The results are also included in appendix D.

Results of the updated network meta-analyses: Interferon class based NMA

ARR: Interferon class based NMA

Pooling of the interferons as a class did not have a material impact on the results of the NMAs. Consistent with the previously submitted NMAs, ponesimod was found to have a [redacted] probability of reducing relapses compared with [redacted] and performed

		similarly to [redacted]. In line with the analyses presented in their company submissions to NICE, [redacted] performed better than [redacted] for this outcome. **Figure 4 NMA Results for ARR, considering interferon regimens as a class (Fixed effects).** [redacted] Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferons, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide, TIW = three times per week.

3-month CDA: Interferon class-based NMA

In line with the previously submitted NMAs, ponesimod was comparable to [redacted] with wide credible intervals crossing 1, and the effect estimate favouring ponesimod for all comparisons except the monoclonal antibody treatments.

Figure 5 NMA Results for 3-month CDA, considering interferon regimens as a class (fixed effects).

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide.

		6-month CDA: Interferon class-based NMA Pooling of the interferon trials had no material impact on the outcomes of 6-month CDA, and ponesimod was comparable to [redacted] with credible intervals crossing 1, and the effect estimate favouring ponesimod for all comparisons except the monoclonal antibody treatments. The effect estimates were nearly equivalent for the comparisons of ponesimod to fingolimod. **Figure 6 NMA Results for 6-month CDA, considering interferon regimens as a class (fixed effects).** [redacted]

		Treatment discontinuation: Interferon class based NMA Pooling of the interferons had very little impact on the results compared to the previously submitted NMAs, with the exception that interferons as a class had a greater odds of treatment discontinuation vs ponesimod. **Figure 7 NMA Results for treatment discontinuation, considering interferon regimens as a class (random effects).** 

		Results of the updated network meta-analyses: excluding ADVANCE and INCOMIN **ARR: excluding ADVANCE and INCOMIN** The results of a network that excluded the ADVANCE and INCOMIN trials were also consistent with the previously submitted NMAs. However, no comparisons can be made between ponesimod and peginterferon beta 1a, since the latter DMT could not be included in the network. Once again, ponesimod was found to have a [redacted] probability of reducing relapses compared with [redacted] and performed similarly to [redacted] while [redacted] performed better than [redacted].

		Figure 8 NMA Results for ARR, excluding ADVANCE and INCOMIN (Fixed effects).  **3-month CDA: excluding ADVANCE and INCOMIN** Results for 3-month CDA NMAs after excluding the ADVANCE trial had no impact on the comparative efficacy of ponesimod vs other [redacted] Due to the exclusion of ADVANCE, peginterferon could not be included in the network and no comparison was possible versus this DMT.

		Figure 9 NMA Results for 3-month CDA, excluding ADVANCE and INCOMIN (Fixed effects).  **6-month CDA: excluding ADVANCE and INCOMIN** Exclusion of the ADVANCE trial had no material impact on the outcomes of 6-month CDA, and ponesimod was comparable to [redacted] with credible intervals crossing 1, and the effect estimate favouring ponesimod for all comparisons except the monoclonal antibody treatments. The effect estimates were nearly equivalent for the comparisons of ponesimod to fingolimod and interferon beta 1a 44mg.

		Figure 10 NMA Results for 6-month CDA, excluding ADVANCE and INCOMIN (Fixed effects).  **<u>Treatment discontinuation: excluding ADVANCE and INCOMIN</u>** Exclusion of the outlier trials had little impact on the outcomes on the NMA results and the effect estimates for ponesimod vs all other DMTs were consistent with those reported from the previously submitted NMAs.

		Figure 11 NMA Results for treatment discontinuation, excluding ADVANCE and INCOMIN (random effects).  **<u>Janssen have provided additional details on the methods of feasibility assessment and risk of bias tool employed when conducting the NMA's to reduce uncertainty noted by the ERG</u>**

		The ERG asked for more details surrounding the feasibility assessment and risk of bias tool as these were not fully described in the original submission. The ERG critique of the submission also noted that the methods to identify evidence relevant to the decision problem would be useful for assessment (Table 9 of ERG Report). The ERG wanted to see the risk of bias assessment for the long-term trial extensions to OPTIMUM or the phase 2 trial and also that it would be useful to have the feasibility assessment. In response to the above points, Janssen has submitted additional details around feasibility assessment, which clarifies how the feasibility assessment for the NMAs were conducted for the main analysis and highly active subgroup in the core clinical outcomes for ARR, 3-month CDA, 6-month CDA and all-cause treatment discontinuations, which is detailed in appendix C. Also detailed in appendix C, is the risk of bias assessment for long term extension, which clarifies how attrition and other biases were assessed and also notes that there was no double-counting of risk of bias issues.
Key issue 3: Insufficient comparative evidence for the safety of ponesimod	Yes	**Janssen have provided additional trial and NMA evidence to mitigate any concerns surrounding the safety of ponesimod relative to its comparators, ponesimod has a safety profile consistent with NICE recommended DMTs** The ERG commented that there was insufficient evidence to draw conclusions about the relative safety of ponesimod vs other DMTs and expressed concerns about the lack of evidence regarding rare serious adverse events. Janssen acknowledges these concerns and have provided additional analyses comparing overall adverse events and serious adverse events of MS DMTs based on RCT data. Janssen have also provided a summary of relevant safety data highlighted in the summary of product characteristics for ponesimod and fingolimod, that would guide clinical practice. These data demonstrate that ponesimod has a safety profile consistent with other NICE-recommended DMTs. The safety profile of ponesimod is based on experience in 1,148 patients with MS who were treated with ponesimod 20 mg. As of April 2020, this included a treatment exposure of up to 9.9 years in the phase 2 extension study and up to 2.8 years of treatment in the ongoing phase 3 extension study. Ponesimod has a safety profile that is comparable to other NICE-approved oral and injectable DMTs. Safety signals relevant

		to S1P receptor modulators such as elevated liver enzymes, cardiac events and macular oedema were reported at frequencies lower than or comparable to those reported for fingolimod. **Janssen have provided additional NMAs related to adverse events and serious adverse events to reduce uncertainty in the comparative safety data vs. other DMTs** It was noted overall that additional comparative safety evidence would be useful to aid decision making for the safety of ponesimod. The ERG noted that in the original submission no NMA evaluating the relative safety of ponesimod was reported. Janssen would like to submit additional NMAs comparing ponesimod vs NICE-recommended DMTs for the outcomes of adverse events (AEs) and serious adverse events (SAEs) in a supplement. Appendix D includes the details of the input data, network diagrams for the forest plots presented in Figure 12 -15. Janssen have conducted two sets of analyses, comparing ponesimod vs all NICE-recommended DMTs (full network), or ponesimod vs other S1P receptor modulators (S1P network). In the latter analysis, additional DMTs were included in order to ensure full network connectivity and allow comparison across S1P class of treatments.

		Figure 12: NMA results for Adverse events (Full network; Random Effects with vague priors) 

		Figure 13: NMA results for Serious adverse events (Full network; Random Effects with vague priors) 

		Figure 14: NMA results for Adverse events (S1P network; Random Effects with vague priors) 

		Figure 15: NMA results for Serious adverse events (S1P network; Random Effects with vague priors)  The results of these analyses suggest that the overall safety profile of ponesimod is comparable to those of other NICE-recommended DMTs, with credible intervals crossing 1 suggesting overall similarity of these treatments in the evidence base. Results of the NMAs for AEs in either full or S1P network indicate that ponesimod is equivalent to or has more favourable effect estimates vs fingolimod, a comparison that would be relevant for patients with highly active RRMS.

		Similar results were observed with regards to SAEs; however, the credible intervals were substantially wider given the low event numbers from each trial. Therefore, Janssen would recommend exercising caution when interpreting the results for the NMAs for SAEs, since they may lead to erroneous conclusions of the comparisons. **Ponesimod has one of the longest data collection periods (over 9 years) to capture safety data of all the DMTs apprised by NICE** In line with the request for additional safety endpoints from the ERG, it was noted that there was insufficient evidence provided on the safety of ponesimod. The ERG additionally noted that with regards to rare serious adverse events, it was uncertain whether ponesimod provides an improved safety profile due to the lack of data in a large enough group of participants. The ERG commented that higher quality evidence for the safety of ponesimod, including long-term real-world evidence in larger groups of people, would give a more informed insight into the safety of ponesimod, particularly in terms of rare serious adverse events, such as progressive multifocal leukoencephalopathy (PML). With regards to rare serious adverse events, Janssen acknowledges the concerns raised by the ERG. However, we would like to note that in contrast to previous appraisals in MS, safety profile for ponesimod is based on comparatively longer periods of treatment (treatment exposure of up to 9.9 years in the phase 2 extension study and up to 2.8 years of treatment in the ongoing phase 3 extension study). In previous appraisals for MS DMTs, committee decisions have been guided by safety data based on shorter exposure periods and concerns about rare serious events did not preclude decision making. **Janssen have submitted additional NMA evidence to directly address comparative safety concerns raised by the ERG** To reduce uncertainty in the safety concerns raised by the ERG, Janssen have provided additional NMAs to evaluate the overall safety of ponesimod. The ERG noted that a further NMA evaluating the relative risk of discontinuation due to AEs as compared to other available DMTs would contribute to an understanding

		of the overall safety of ponesimod. While this NMA would also be limited by heterogeneity in the trials, discontinuation gives an overall picture of tolerability, and may be more consistently measured across trials. Janssen have submitted additional NMAs for AEs and SAEs to directly address questions regarding the comparative safety of ponesimod. Janssen acknowledges the ERG comment to compare treatment discontinuation rates as a surrogate for safety; however, these would be an indirect measure of safety and may include events of mild or moderate severity that would normally be resolved in clinical practice or discontinuation due to events unrelated to safety (e.g., pregnancy). It was not immediately clear from comparator trial publications if treatment discontinuation frequencies reported were purely due to safety (physician decision) or also tolerability (patient decision). As discussed, the results of the newly conducted NMAs for AEs and SAEs indicate that ponesimod is comparable to other NICE-recommended DMTs for RRMS. **Plotting safety vs efficacy demonstrates that ponesimod has a comparable or more favourable benefit-risk profile vs most NICE-recommended DMTs** The ERG asked Janssen to graphically plot the safety vs efficacy of ponesimod and comparator DMT: "Moreover, published NMAs of treatments for RRMS often present a graph plotting the relative safety vs. efficacy of all available treatments, which would be useful to aid decision-makers in identifying the most appropriate positioning for ponesimod". Janssen would like to submit graphs plotting the relative safety vs. efficacy of all available treatments, to aid decision-making as suggested by ERG. In these graphs, the effect estimates of ponesimod vs individual regimens have been plotted for ARR on the Y-axis and overall AEs on the X-axis (Figure 16). These results indicate that ponesimod has a comparable or more favourable benefit-risk profile vs most NICE-recommended DMTs, including fingolimod and may be a more suitable treatment option in eligible patients.

		Figure 16: Full network analyses of ARR and AEs: Effect estimates for treatments versus placebo  In the corresponding analysis of ARR vs SAEs (Figure 17), ponesimod is still equivalent to or positioned higher than most NICE recommended DMTs; however as stated in point 1 above, the NMAs for the outcome of SAE have very wide credible intervals, and these results should be interpreted with caution.

		Figure 17: Full network analyses of ARR and SAEs: Effect estimates for treatments versus placebo  **<u>Janssen advise caution against drawing conclusions from the naïve safety comparison of ponesimod vs fingolimod conducted by the ERG</u>** The ERG conducted a naïve comparison of ponesimod vs fingolimod to try to understand the relative safety between the two S1P modulator treatments, specifically to understand the safety of ponesimod as an alternative to fingolimod in patients with highly active disease. With respect to the naïve comparison

conducted by the ERG (Section 3.5.4), Janssen would advise caution using such methods to directly compare the safety of ponesimod and fingolimod since these data have not been conducted in head-to-head trials and reflect different trial settings and protocols. For example, Janssen notes that the reference range for normal levels of liver enzymes was more conservative in OPTIMUM trial vs those published for fingolimod trials. Given the substantially lower threshold applied in OPTIMUM, a greater proportion of patients treated with ponesimod would appear to have elevated liver enzymes in a naïve comparison against patients treated with fingolimod. Applying a lower Upper Limit of Normal (ULN) (as was done in the OPTIMUM study) may have resulted in potentially greater proportion of patients having elevated liver enzymes than in the fingolimod study (assuming that these ranges were consistently applied across the fingolimod clinical development).

Table 3: Ranges of ULN and ALT in ponesimod and fingolimod trials

	Upper Limit of Normal (ULN) reference range	Incidence of elevated alanine aminotransaminase (ALT) informing ERG's naïve comparison
Ponesimod	ALT: 44 units/L for males 33 units/L for females	[redacted]
Fingolimod	ALT: ≥117 units/L for males ≥90 units/L for females	[redacted]

Rather, Janssen would advise consulting the summary of product characteristics (SmPC) of these two drugs to identify the key safety signals deemed noteworthy by regulatory authorities, and an overview of the frequencies and contraindications for these drugs. Janssen understands that the safety summary in the SmPC would be the primary source of information for practising clinicians when deciding the benefit-risk

		profile of a given DMT for individual patients. Janssen would therefore like to present a brief summary of relevant information for key safety signals for these two treatments below. **Liver safety**: **Ponesimod** • In the ponesimod clinical trials, treatment was discontinued if the elevation exceeded a 3xULN and the patient showed symptoms related to hepatic dysfunction. In contrast, in the fingolimod trials, treatment was discontinued if the elevation exceeded 5×ULN • In the OPTIMUM trial, most elevations occurred within 6–12 months of starting treatment and most cases of alanine aminotransaminase (ALT) increases ≥3×ULN resolved on continued ponesimod treatment ([redacted]), and the remaining cases resolved upon treatment discontinuation ([redacted]). It is not possible to obtain detailed data from the fingolimod trials. • Based on the individual case review, most ALT/AST (aspartate transaminase) increases ≥3×ULN occurred as single transient asymptomatic episodes resolving with continued treatment or after protocol-mandated treatment discontinuation. • The majority ([redacted]) of patients with ALT increases ≥3×ULN continued treatment with ponesimod with values returning to <3×ULN within approximately 2–4 weeks • As seen with other S1P receptor modulators elevations of ALT and/or Aspartate transaminase (AST) have been observed during ponesimod treatment. In Study B301, ALT increased to 3 and 5×ULN in 17.3% and 4.6% of ponesimod 20 mg-treated patients, respectively, compared to 8.3% and 2.5% of patients receiving teriflunomide 14 mg, respectively. • ALT increased to 8×ULN in 0.7% ponesimod 20 mg-treated patients, compared to 2.1% in patients receiving teriflunomide 14 mg. • The majority of elevations occurred within 6 or 12 months of starting treatment. The 2 ponesimod 20 mg-treated patients who met Hy's law laboratory criteria were both confounded by other medical conditions (pre-existing ALT >5×ULN or active chronic hepatitis C) • Due to most cases of ALT increase ≥3×ULN were single transient asymptomatic episodes, resolved on continued ponesimod treatment (and the rest resolved upon treatment

discontinuation). In the Ponesimod clinical trials, treatment was discontinued if the elevation exceeded a 3xULN and the patient showed symptoms related to hepatic dysfunction. This is reflected in the SMPC for Ponesimod. In contrast, in the fingolimod trials, treatment was discontinued if the elevation exceeded 5×ULN.

Fingolimod

- In the fingolimod clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in 8.0% of adult patients treated with fingolimod 0.5 mg compared to 1.9% of placebo patients.
- Elevations 5-fold the ULN occurred in 1.8% of patients on fingolimod and 0.9% of patients on placebo.
- In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN.
- Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod.
- In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months.
- Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod

Cardiac safety events: The following parameters have been described for selected cardiac measurements for the two S1P receptor modulators, based on the SmPC

Table 4: Cardiac safety events for ponesimod compared to fingolimod

	Ponesimod	Fingolimod
Heart Rate (HR) reduction from baseline (BL), beats per minute (bpm)	6	12-13

Patients with first degree atrioventricular (AV) block, %	3.4	4.7
Patients with second degree AV block or higher, %	None	<0.2 (2nd degree); 3rd degree observed in post marketing experience
Corrected QT interval which corrects for heart rate (QTc) prolongation, milliseconds (ms)	1.8 - 5.2 (20 mg dose)	14.0 (1.25 and 2.5 mg dose)

Ponesimod

- The 14-day up-titration regimen of ponesimod resulted in an overall low incidence of first-dose HR and rhythm adverse events of special interest (AESIs) (2.1%), with none reported as serious or leading to treatment discontinuation. The gradual up-titration has been shown to have successfully mitigated the risk of symptomatic bradycardia and high degree AV blocks due to first dose effects on heart rate and atrioventricular (AV) conduction. This is important as first dose monitoring is not required for all patients initiated on ponesimod unlike fingolimod where first dose monitoring is required for all patients.
- A total of 20.0% of patients at risk for symptomatic bradyarrhythmia had sinus bradycardia on Day 1. No AV blocks higher than first degree were reported for patients on ponesimod.
- Initiation of ponesimod treatment has been associated with transient AV conduction delays that follow a similar temporal pattern as the observed decrease in HR during dose titration. In the OPTIMUM study, the AV conduction delays manifested as first-degree AV block (prolonged PR interval (or the time from the onset of the P wave to the start of the QRS complex) on an electrocardiogram (ECG), which occurred in 3.4% of ponesimod-treated patients and in 1.2% of

		patients receiving teriflunomide 14 mg. No second-degree AV blocks, Mobitz type I (Wenckebach), were observed in OPTIMUM. The conduction abnormalities were typically transient, asymptomatic, resolved within 24 hours, and resolved without intervention, and did not require discontinuation of ponesimod treatment • No clinically relevant effect on QTc interval is expected for the therapeutic dose of Ponesimod 20 mgs. In the long-term pool, no treatment emergent adverse events (TEAEs) of torsade de pointes, ventricular tachycardia or ventricular tachyarrhythmia were noted • As it shows over 2 years, as opposed to just first dose monitoring, in the 2-year OPTIMUM study, ponesimod treatment was not associated with an increased risk of major adverse cardiac event (MACE). **Fingolimod** • In the fingolimod trials, the HR decrease starts within an hour after the first dose. On Day 1, the maximal decline in HR generally occurs within 6 hours and recovers, although not to baseline levels, by 8–10 hours post-dose. Because of physiological diurnal variation, there is a second period of HR decrease within 24 hours after the first dose. In some patients, the HR decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Fingolimod, not using initial up titration, requires first-dose observation for 6 hours to detect symptomatic bradycardia and AV blocks, unlike Ponesimod where first dose monitoring is required only in select patients for 4 hours. • Bradycardia was generally asymptomatic, but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, and/or palpitations, which resolved within the first 24 hours after treatment initiation [USPI & SmPC] • There are no head-to-head trials between ponesimod and fingolimod; direct comparisons cannot be made, and results should be interpreted with caution. Bearing in mind the transient and dose related decrease in heart rate with fingolimod, the overall cardiac safety of ponesimod is at least comparable to fingolimod if not more positive.

		Macular Oedema: **Ponesimod** • Macular edema was reported in 1.1% of ponesimod-treated patients compared with 0% of patients receiving teriflunomide. None of the events were severe or serious. • All events of macular edema in the ponesimod 20 mg group were considered related to study drug by the investigator and were recovered/resolved, except for one event, which was reported as recovered/resolved with sequelae. • Of the six patients in the ponesimod 20 mg group with macular edema AESIs, four had a medical history of or concomitant eye disorder; one patient had diabetes. **Fingolimod** • Macular edema with or without visual symptoms was reported in 0.5% of patients treated with fingolimod 0.5 mg and 0.1% of patients treated with placebo; it occurred predominantly in the first 3–4 months of therapy. • The incidence of macular edema is also increased in patients with MS who have a history of uveitis. The rate was 17% in patients with a history of uveitis vs. 0.6% in those without a history of uveitis in the combined experience with all doses of fingolimod [USPI & SmPC]. Within the S1P class, it is difficult to accurately compare the safety of S1P modulators to each other in broad patient populations. The variety of in S1P modulators highlights across different S1P receptors demonstrates the strengths of individual agents to address the unique needs of different MS patients. In summary, it is not appropriate to draw conclusions of the relative safety of ponesimod versus other treatments based on naïve comparisons of frequencies of individual safety events. The summary of data from the respective SmPCs of ponesimod and fingolimod should guide individualising treatment selection based on specific drug as recommended by physician and patient factors. Neurologists and MS specialists have been provided the relevant safety information, that has been reviewed and approved by regulatory authorities and no new safety signals are expected compared to those reported for fingolimod.

Key issue 4: Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model	Indirectly related to new NMAs, but not for 3 or 6-month CDA	**<u>Janssen acknowledges the committee preference for 6-month disability data in recent appraisals, however we feel that the committee should consider both 3-month and 6-month CDA outcome values given the limitations with both analyses</u>** The ERG notes that there is uncertainty surrounding the use of 3-month confirmed disability in the economic model and that 6-month confirmed disability outcomes should be used in the base-case model. We acknowledge that there are uncertainties with the 3-month disability timepoint, due to the ability of longer disability timepoints to reflect disability more accurately. However, we note that there is a paucity of data points for the 6-month disability timepoint and while the longer timepoint is arguably more appropriate, the lack of data from trials and missing values result in uncertainty surrounding 6-month data. Janssen would also like to reiterate, that the evidence network for the 3-month disability results, which informs the model was more robust than the 6-month data in that it had a larger number of closed loops than the 6-month CDA network. Additionally, a greater proportion of trials in the 3-month CDA network defined the outcome as either a primary or secondary endpoint, whereas 6-month CDA was more frequently defined as a secondary or exploratory endpoint across the identified trials. This is an issue that has been repeatedly highlighted in previous MS appraisals, and Janssen believes that decision making should not completely ignore higher quality evidence for the 3-month timepoint. Janssen have provided both 3-month and 6-month scenarios in the economic model from the initial submission, the new model base-case discussed in 'additional issue 2' accounts for the 3 and 6-month CDA results based on the new NMA, treating interferons as a class-effect rather than individual comparators. In line with the ERG's comments on 6-month CDA we have conducted additional analyses in the model with 6-month values as the base-case for consistency with previous appraisals. Based on the points described above, Janssen suggests the ERG and appraisal committee to also consider both the 3-month and 6-month CDA results in the model, since DMTs recommended on the basis of 3-month disability data in past appraisals have provided substantial benefit to patients with MS.

Key issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive best supportive care (BSC)	Yes	**There is uncertainty surrounding the number of patients who will receive siponimod when converting to SPMS from RRMS, but expert opinion indicates in the region of 15% to 30% of patients.** Until recently there were no approved treatments in secondary progressive multiple sclerosis (SPMS). However, at the end of 2020, NICE recommended siponimod for treating SPMS (TA656). The ERG noted that, given this update a proportion of patients in the economic should receive siponimod when transitioning from RRMS to SPMS. Clinical advice to the ERG estimated that approximately 12.5% to 50% of patients will receive siponimod when transitioning to SPMS, with the ERG selecting 25% as an average transition rate. After consulting four clinical experts, Janssen notes that an appropriate transition rate of SPMS and receiving siponimod is between 15% and 30%, but that 25% is appropriate. Janssen has consulted four clinical experts regarding siponimod use in NHS England for patients transitioning from RRMS to SPMS. Please see appendix A for full information. While clinicians have attested that siponimod use is currently limited, it is anticipated that use of siponimod across the NHS in England will be variable, where certain areas of the country will have different levels of use, based on NHS Trust, patient preferences and clinical experience. It is anticipated that approximately 25% of the incident SPMS population will be eligible for treatment due to the requirement for detection of new MRI activity for treatment eligibility, but that this figure could vary from approximately 15% to up to 30% use currently. At present, it is not known how widely siponimod will be used in the NHS after COVID-19 and once clinicians and patients gain more experience with siponimod. Janssen have conducted a set of scenario analyses which presents varied proportions of RRMS patients transitioning to Siponimod when converting to SPMS. In line with expert opinion, we have presented percentage increments of 15%, 25% and 40% conversion to Siponimod, based on Janssen and ERG clinical feedback for when a patient moves from RRMS to SPMS. However, the clinical experts we sought advice from agreed that the true value of patients receiving siponimod when converting to SPMS likely lies

		between 15% and 30%. The assumed base-case transition proportion is 25% in line with the ERG's original assumption. Detailed results of this analysis are presented in appendix G, but the overall results of this analysis show that for the scenarios where [redacted]

Additional issues

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

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Induction treatments (cladribine and alemtuzumab) as appropriate comparators	Discussed at ERG technical engagement call	Yes	**Higher efficacy treatments (in particular those used as "induction treatments") are not appropriate comparators to moderate efficacy treatments such as ponesimod, and the results should be interpreted with caution.** It was discussed during the technical engagement call that cladribine and alemtuzumab are induction therapies, which are of higher efficacy and are used as part of a treatment strategy referred to as '*induction therapy*', which has patients start on higher efficacy treatments and work down to lower efficacy treatments. This strategy is different to an escalation strategy, where treatments are initiated by starting from lower efficacy treatments and working up to higher efficacy treatments. Janssen noted that based on treatment strategy, a patient looking to receive a moderate efficacy treatment such as ponesimod is unlikely to ever consider a higher efficacy induction treatment such as alemtuzumab or cladribine as an alternative option. This is because a decision is made between the patient and their clinician which considers how risk averse the patient is, the mode of administration, and the efficacy and side effect profile of treatment options. Ponesimod compared to treatments such as cladribine, alemtuzumab and even other monoclonal antibody treatments such as ocrelizumab (that are also used to treat highly active patients) are unlikely to be comparators to ponesimod (if made available in highly active disease), despite multiple treatment options being available, patients generally consider

			options based on risk and efficacy. A more practical comparator to ponesimod in highly active RRMS would be fingolimod, as noted by the clinical experts we consulted (please see appendix A for further information). During technical engagement Janssen consulted four clinical experts, who noted that generally, in the highly active positioning the most appropriate comparator to ponesimod will be fingolimod, and that higher efficacy treatments are generally not comparators to moderate or lower efficacy treatments (at any positioning). The clinical experts discussed that it is important to have access to several treatment options to allow patients to choose the one that is best suited for their circumstance. Clinicians noted that they would welcome an alternative to fingolimod for patients with highly active RRMS, a position where risk averse patients have currently no alternative low- or moderate-safety options. Janssen suggest that the committee should appraise fingolimod as the most appropriate comparator to ponesimod in highly active RRMS, and caution should be exercised when reviewing induction treatments (cladribine and alemtuzumab) due to their short-term treatment length and the economic model's inability to capture treatment sequencing given the complexity of treatment options available. Induction treatments are prescribed as part of a limited treatment cycle and cannot be prescribed for more than a few years. In the economic model, cladribine and alemtuzumab treatments are stopped in most patients after 2 years, with patients phasing treatments out over a short period of time. In the economic model no patients remain on cladribine or alemtuzumab past a maximum of 5 years, in line with the economic models presented by the manufacturers in previous NICE appraisals. With only [redacted], [redacted] and [redacted] of patients receiving cladribine in years [redacted] respectively and [redacted]

			and [redacted] of patients receiving alemtuzumab in years [redacted] respectively. However, patients in the economic model receiving these treatments discontinue to best supportive care and cycle through the model for the remaining time horizon (up to 50 years), which is unlikely to occur in clinical practice. This provides the induction treatments in the model with an implausible advantage relating to cost effectiveness. As noted by the ERG it is difficult to look at treatment sequencing in the economic model, therefore we have looked at a shorter time horizon to better reflect clinically the comparison of the induction treatments to other DMTs. Janssen have included a scenario analyses of a 5 year 10-year and 15-year time horizon in the highly active population to accurately reflect treatment with either cladribine or alemtuzumab, since individual treatment sequencing is not possible in the model. For completeness we have also included the same scenario for the ITT population (please see appendix F). When the time horizon is reduced to 5, 10 and 15 years to more accurately reflect the use of cladribine and alemtuzumab, ponesimod is a less costly and less effect treatment to both comparators (ICERS are in the south-west quadrant). When the time horizon is reduced to 5, 10 and 15 years for cladribine, ponesimod is less costly and less effective treatment over years 5 and 10 but becomes dominated by 15 years (up to 10 years after treatment stops in the model). Overall, Janssen would like to note that the comparison of ponesimod to the induction treatments should be interpreted with caution, given that the model cannot accurately reflect real world treatment sequencing. Clinically, induction treatments are not relevant comparators to ponesimod in highly active disease and the most relevant established comparator in highly active RRMS is fingolimod. However, if the ERG and committee may wish to look at the

			analysis of ponesimod compared to cladribine and alemtuzumab, then, we propose reviewing the scenario where the time horizon has been updated to reflect treatment periods more commonly reflective of experience with induction therapies.

Additional issue 2: Plausibility of trials for interferon-beta-1B (INCOMIN) and peginterferon (ADVANCE) -class based NMA and model - ADVANCE and INCOMIN removed from model and NMA	Discussed at ERG technical engagement call	Yes	**<u>The INCOMIN and ADVANCE trials produce implausible results: Janssen have explored two methods to reduce the uncertainty and implausible results produced in the NMA and economic model, as noted in the response to Key Issue 2 above.</u>** During the technical engagement the ERG and Janssen discussed the implausible results produced by some of the interferon trials, in particular the trials for interferon-beta-1B (INCOMIN) and peginterferon (ADVANCE). The results of these trials suggested that some interferons are more effective than other interferons, which does not reflect clinical experience. During expert clinical feedback (appendix A) it was noted by all experts that generally the interferon treatments are seen as being comparable and therefore the fact that some interferons are significantly more effective lack clinical validity. During the technical engagement call, it was suggested that Janssen could explore options to reduce the uncertainty produced by these two comparators in particular. In line with this suggestion, Janssen have provided two updated model options with revised NMAs, these are: • A class based NMA, which treats all interferons as one comparator • Following the approach taken in the recent appraisal of ofatumumab (TA699), we have produced an NMA excluding evidence from INCOMIN and ADVANCE, which results in the exclusion of peginterferon and interferon-beta 1b from the economic model. Janssen would like to submit a revised economic model, with the base case for the ITT population based on the updated NMA with interferons pooled as a class-based comparator, while the second model excluding peginterferon and interferon-beta 1b provides justification of the outlier comparators and follows the approved methods outlines on the ofatumumab appraisal. Note that both

			submitted model versions include the revised highly active model base case as discussed in issue 1. Combining interferon trials and removing trials with implausible results produces more plausible ICERs in the economic model The new economic model base-case for the ITT population in active RRMS is proposed to include interferons as a combined comparator, based on an interferon class based NMA. Full results of the new economic models are provided in appendix G. This includes treatment effects, costs, QALYs and ICERs for: • Model 1: (new base case) results based on the interferon class effect • Model 2: (scenario) results with ADVANCE (peginterferon) and INCOMIN (interferon-beta 1b) removed Results of Model 1: Interferon class-based model - In the updated economic base case model (ITT population) including the interferons as a class effect, ponesimod dominates all treatments compared to all comparators list prices, with the exception of ocrelizumab and ofatumumab, in which ponesimod is less costly and less effective (south-west quadrant). Compared to the original model results submitted in the company submission the results are aligned; in the original model ponesimod dominated all treatments and was less costly and less effective that ocrelizumab (and ofatumumab when added in). In the original model ponesimod dominated interferons 1a 30mg and 44mg and was cost effective at £20,000 against peginterferon and interferon 1a 22mg. With the class effect input these results level out and ponesimod now dominates the new class effect interferon comparator.

			Results of Model 2: ADVANCE (peginterferon) and INCOMIN (interferon-beta 1b) removed.in the updated economic model scenario (ITT population) with peginterferon and interferon beta 1b removed, ponesimod dominates all treatments compared to all comparators list prices, with the exception of ocrelizumab and ofatumumab, in which ponesimod is less costly and less effective (south-west quadrant) and interferon beta 1a 322mg, where ponesimod is cost effective against at £30,000 per QALY threshold. Compared to the original model results submitted in the company submission the conclusions of the results are comparative to model 1 for the class-based interferons. In the original model ponesimod dominated interferon beta 1a 22mg but is now cost effective at a £30,000 per QALY threshold, this is due to the removal of INCOMIN and ADVANCE from the NMA. Overall, the two models are generally aligned in the result and reduce uncertainty present in MS data and older MS trials, such as with the interferon treatments.

Additional issue 3: NEDA-3 NMA results	Section 3.2.4.1-page 58		**No Evidence of Disease Activity (NEDA-3) as an outcome may provide further indication on disease progression of patients with MS. Ponesimod effectively prevents disease activity in RMS based on NEDA-3, similar to other oral DMTs.** In clinical practice, NEDA results may provide indication of how a patients MS disease is progressing. Janssen conducted an NMA based on NEDA-3 outcomes to provide additional evidence on the benefits of ponesimod and reduce clinical uncertainty (as noted in issue 2 but the ERG). Results indicated that ponesimod was significantly more effective than placebo, glatiramer acetate, and teriflunomide. Ponesimod was numerically superior to ozanimod, dimethyl fumarate and interferon β-1a. Natalizumab and ofatumumab were associated with higher odds of NEDA-3 than ponesimod. The ERG cited in their report that in the submission Janssen reported data from OPTIMUM for NEDA-3 as well as NEDA-4 (NEDA-3 criteria plus absence of brain atrophy). However, it was highlighted that neither outcome was considered as part of an NMA. Based on this response, Janssen have conducted an NMA for the outcome of NEDA-3 to provide supporting evidence for comparative effectiveness of ponesimod vs other DMTs. NEDA-3 was defined in the OPTIMUM trial as: absence of confirmed relapses, absence of 3-month CDA, and no new or enlarging MRI lesions. While some heterogeneity was noted in the outcome definitions across studies (e.g., use of 6-month CDA rather than 3-month CDA; differences in the types of included MRI lesions), these were deemed minor overall. Detailed methods are presented in Appendix F. It was not possible to conduct an NMA for NEDA-4 because it was not possible to connect any regimens to the OPTIMUM trial. There was no NEDA-4 data for

			teriflunomide, cladribine, peginterferon, dimethyl fumarate, fingolimod, interferon beta-1b, alemtuzumab, ocrelizumab, and ozanimod. In addition, there is no possible way of connecting fingolimod, glatiramer acetate, interferon beta 1a 30mg or placebo to the OPTIMUM trial. For these reasons an NMA of NEDA-4 could not be carried out. However, we have presented the results of a NEDA 3 analysis to provide further information to the ERG, NICE and the committee on No Evidence of Disease Activity. NEDA is a measure which is valuable in clinical practice and could potentially reduce the uncertainties on longer-term outcomes. • <u>Results for NEDA-3</u> In the fixed effects analysis (Figure 18), results indicated that patients have a higher probability of achieving NEDA-3 with ponesimod [redacted]. Only the [redacted] treatments were associated with a [redacted] than ponesimod

			Figure 18 NMA of NEDA-3: Fixed Effects  In the fixed effects analysis, results indicated that patients have [redacted]

			Figure 19 NMA of NEDA-3: Random Effects with Vague Priors  In the random effects analysis using vague priors,

			Generally, [redacted] Janssen suggest the committee consider the NEDA-3 evidence provided as supplementary, even though this cannot be considered in the economic model.

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

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

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	Treatment effects for ponesimod in the highly active subpopulation were based on evidence from the prespecified highly active subgroup from the OPTIMUM trial	Treatment effects for ponesimod in the highly active subpopulation are based on patients with highly active RRMS as defined by NICE/NHSE and obtained from post hoc analyses of the OPTIMUM trial	Please see Table 6 for details of changes in the base case ICER for the full set of comparators considered in this appraisal

Issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	Treatment effects for interferons were considered separately for each DMT in the ITT population	Treatment effects for interferons are considered as a pooled average of all DMTs, since all of these DMTs are considered to have equivalent clinical effectiveness	Please see Table 5 for details of changes in the base case ICER for the full set of comparators considered in this appraisal
Issue 4: Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model	3-month CDA was used as the primary measure of disease progression in the economic model	6-month CDA is used as the primary measure of disease progression in the economic model, in line with the ERG's preferred assumptions	Please see Table 5 and 6 for details of changes in the base case ICER for the full set of comparators considered in this appraisal
Issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	100% of patients that convert to SPMS will receive best supportive care (BSC)	25% of patients that convert to SPMS will receive siponimod, while 75% of patients will receive BSC, in line with the ERG's preferred assumptions and based on clinical expert feedback to Janssen	Please see Table 5 and 6 for details of changes in the base case ICER for the full set of comparators considered in this appraisal

Table 5: ICERs for ponesimod vs comparator DMTs in the ITT population: comparison of original base case and revised base case after technical engagement: deterministic results

	TER	DMF	GA	IFNB - 1a 22 mg	IFNB-1a 30 mg	IFNB-1a 44 mg	IFNB-1b	OCR	OFA	OZA	PEG
Original base case ICER	[redacted] Dominates	[redacted] Dominates	[redacted] Dominates	[redacted]	[redacted] Dominates	[redacted] Dominates	[redacted] Dominates	[redacted] Less costly and less effective	[redacted] Less costly and less effective	[redacted] Dominates	[redacted]
Revised base case ICER	[redacted] Dominates	[redacted] Dominates	[redacted] Dominates	[redacted] Dominates				[redacted] Less costly and less effective	[redacted] Less costly and less effective	[redacted] Dominates	[redacted]

Table 6: ICERs for ponesimod vs comparator DMTs in the highly active population: comparison of original base case and revised base case after technical engagement

	OCR	OFA	OZA	ALE	CLA	FIN
Original base case ICER	[redacted] Less costly and less effective	[redacted] Less costly and less effective	[redacted] Dominates	[redacted] Less costly and less effective	[redacted] Dominated	[redacted] Dominates
Revised base case ICER	[redacted] Less costly and less effective	[redacted] Less costly and less effective	[redacted] Dominates	[redacted] Dominated	[redacted] Dominated	[redacted] Dominates

Summary of changes to the company's cost-effectiveness estimate(s): Probabilistic Sensitivity Analysis Results (mean) compared with deterministic results

A probabilistic sensitivity analysis (PSA) was conducted for both of the two new models: 1) interferon class-based model and 2) minus ADVANCE and INCOMIN trials. This was also conducted for both the ITT and highly active populations for each mode to better understand the robustness of the cost-effectiveness estimates given uncertainty about model input values. Total costs and total QALYs from the PSA for each treatment are presented by mean (with 95% CI lower and 95% CI upper range), as well as a comparison of cost-effectiveness results (i.e., ICER) alongside deterministic results. The corresponding scatterplot with incremental costs by incremental QALYs for ponesimod vs. the comparators, and cost-effectiveness acceptability curves (CEAC) are also presented. Appendix G.2 presents the results for the interferon class-based model, while appendix G.4 presents results excluding INCOMIN and ADVANCE.

Overall, the results are generally consistent: for the ITT population in the interferon class-based model the conclusions drawn are the same between the deterministic and probabilistic results. Ponesimod dominates all treatments with the exception of ocrelizumab and ofatumumab, which are positioned in the south-west quadrant and are therefore more costly and more effective therapies than ponesimod. For the highly active subgroup, the results are again consistent between all deterministic and probabilistic results, with the exception of alemtuzumab, where ponesimod is positioned as less costly and less effective (south-west quadrant) in the probabilistic results but dominated in the deterministic results. For the remaining comparators, ponesimod dominates fingolimod and ozanimod, is dominated by cladribine and is less costly and less effective than ocrelizumab and ofatumumab. Further discussion is presented in additional issue 1 regarding the use of cladribine and alemtuzumab and their use in clinical practice as induction therapies.

The economic model results from the model excluding ADVANCE and INCOMIN produce very similar outcomes between deterministic and probabilistic results and also when compared to the interferon class-based model: for the ITT population all conclusions are the same between the deterministic and probabilistic ICERs, with the exception of interferon-1a 44mg dose, where probabilistically, ponesimod is less costly and less effective (south-west quadrant), but in the deterministic results ponesimod dominates interferon-1a 44mg. For the remaining treatments, ponesimod dominates all comparator therapies, with the exception of ocrelizumab and ofatumumab, where ponesimod is less costly and less effective.

In the highly active subgroup of the excluding ADVANCE and INCOMIN model, all probabilistic and deterministic results are consistent with one another and align to the results produced in the interferon class-based model, with the exception of the alemtuzumab deterministic result, as discussed above.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Technical Engagement Appendices

16th July 2021

File name	Version	Contains confidential information	Date
Ponesimod Technical Engagement Appendices AIC-CIC July update PSA v2 2021	1.0	Yes	16.07.2021

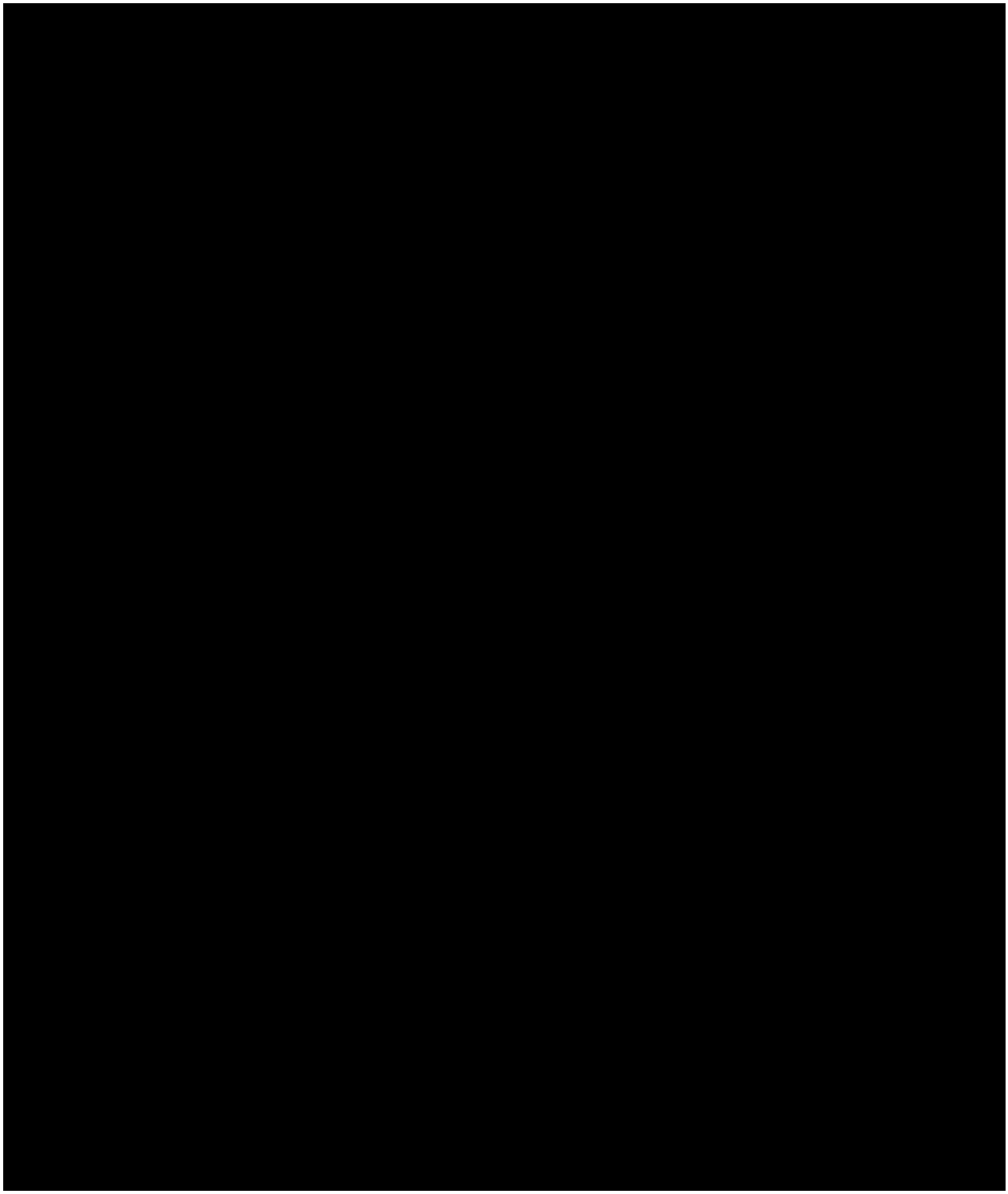
Contents

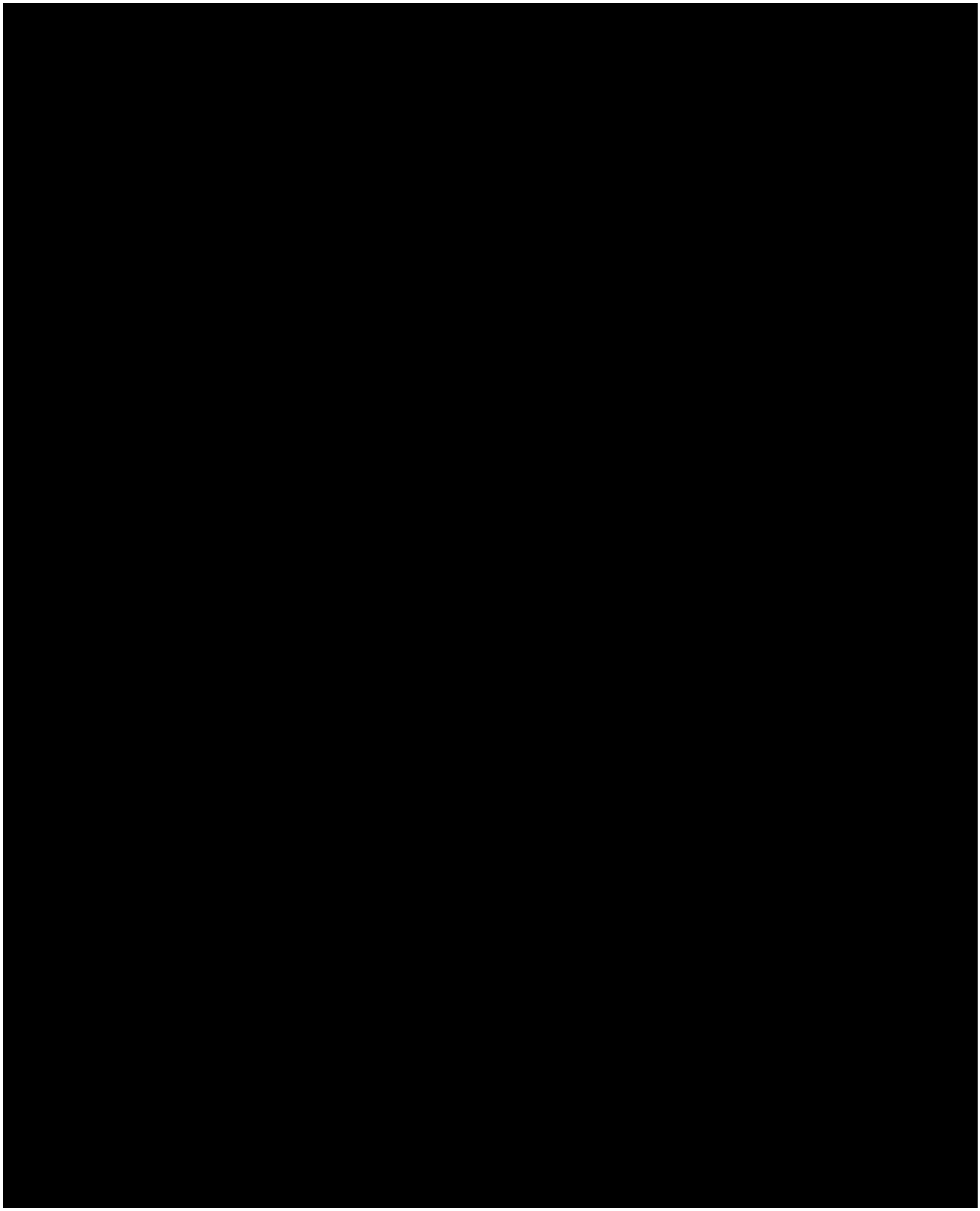
Tables

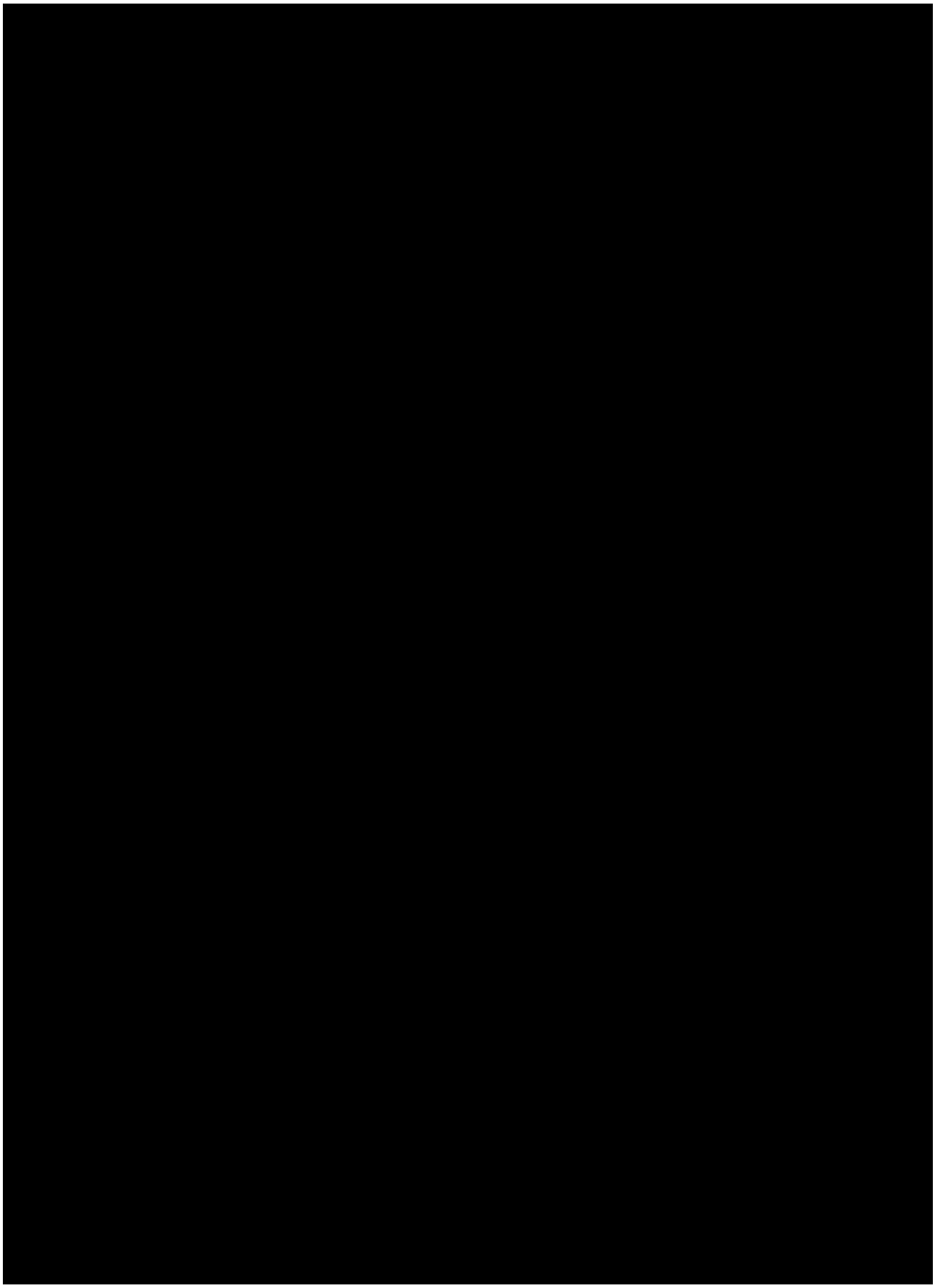
Figures

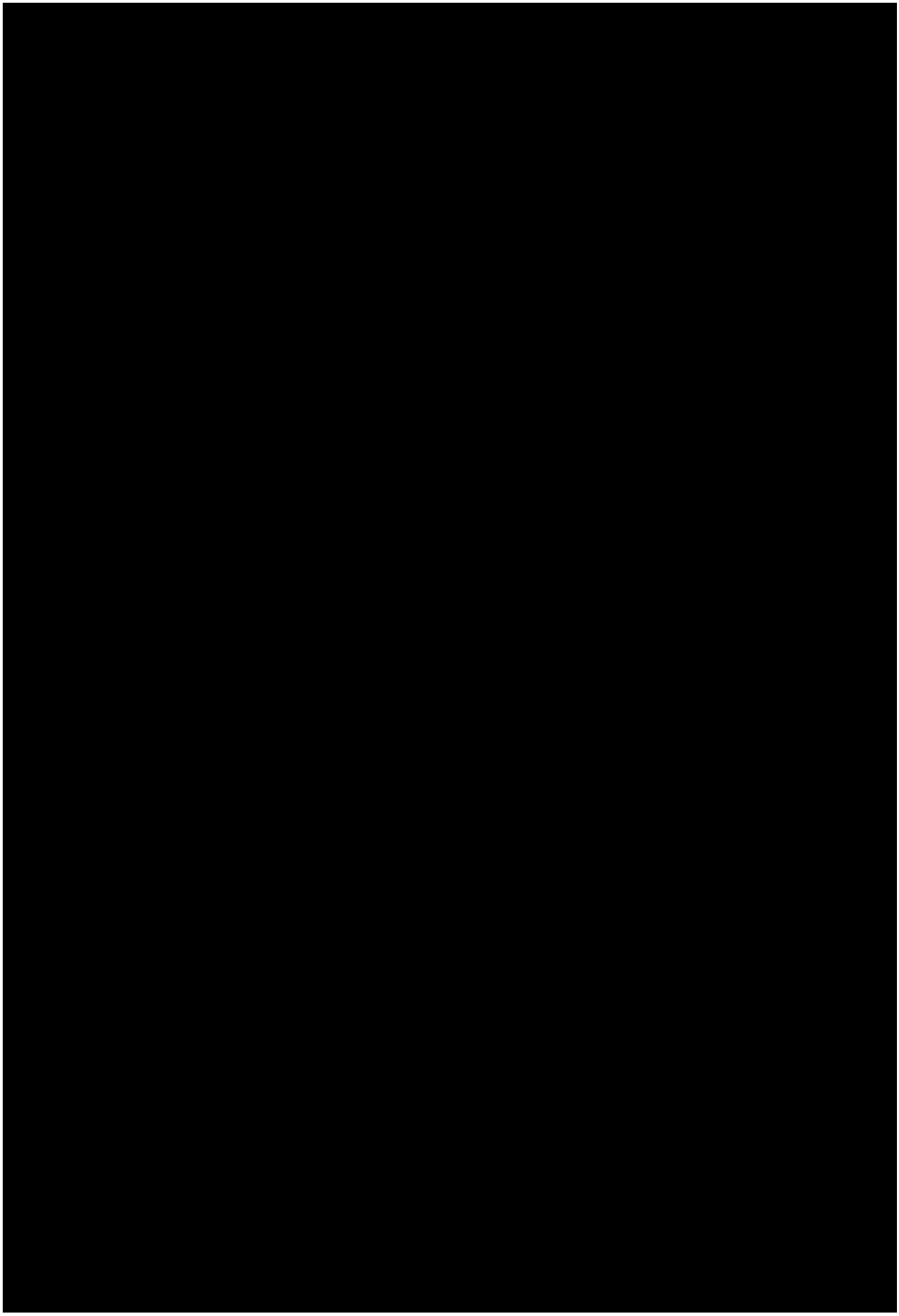
Appendix A: Clinical Expert Feedback following Technical Engagement

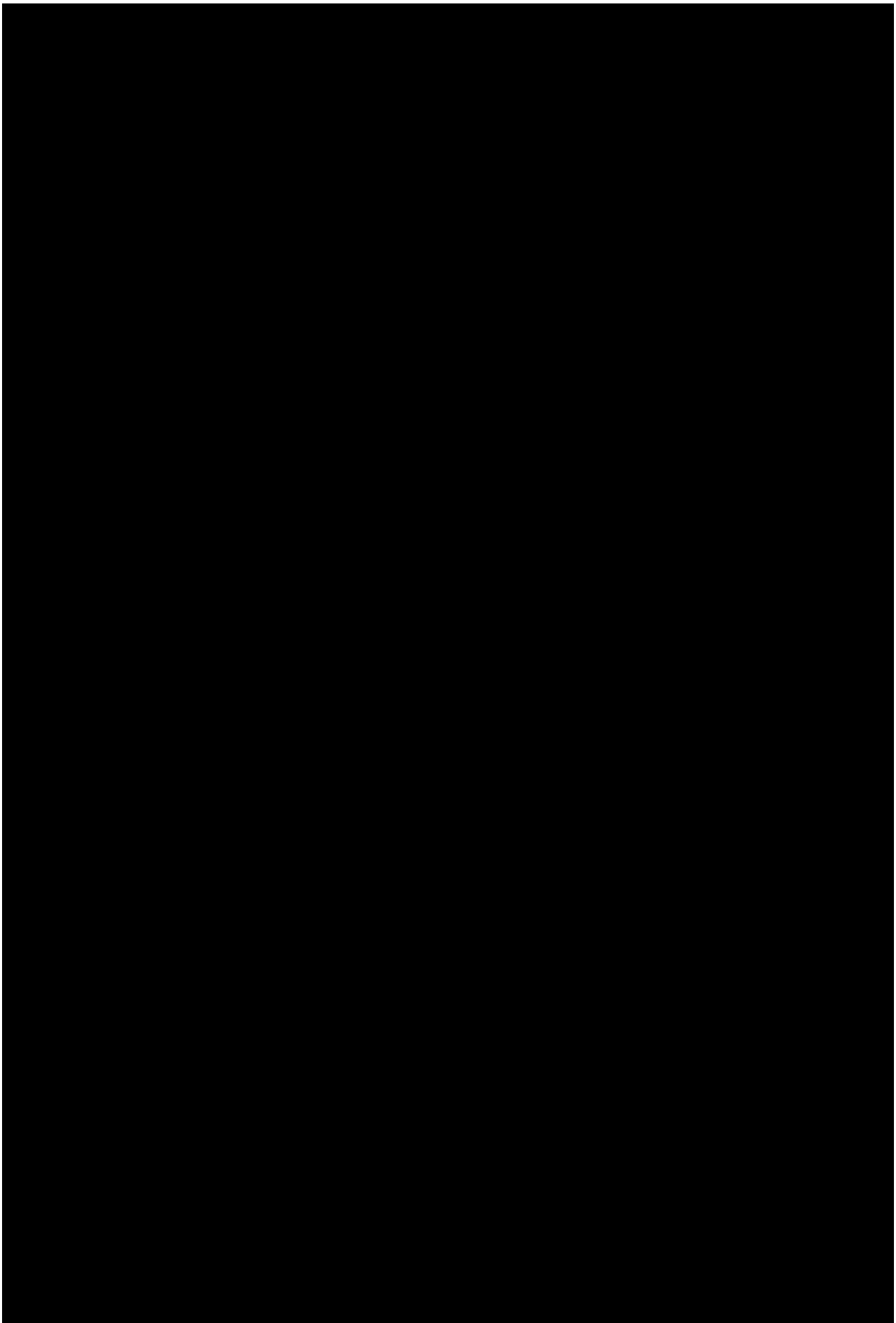
During the technical engagement call with NICE and the ERG it was agreed that it could be useful to gain further advice on clinical practice in the NHs and how and when Siponimod is used for new patients transitioning from relapsing remitting multiple sclerosis to secondary progressive multiple sclerosis and to address uncertainties.







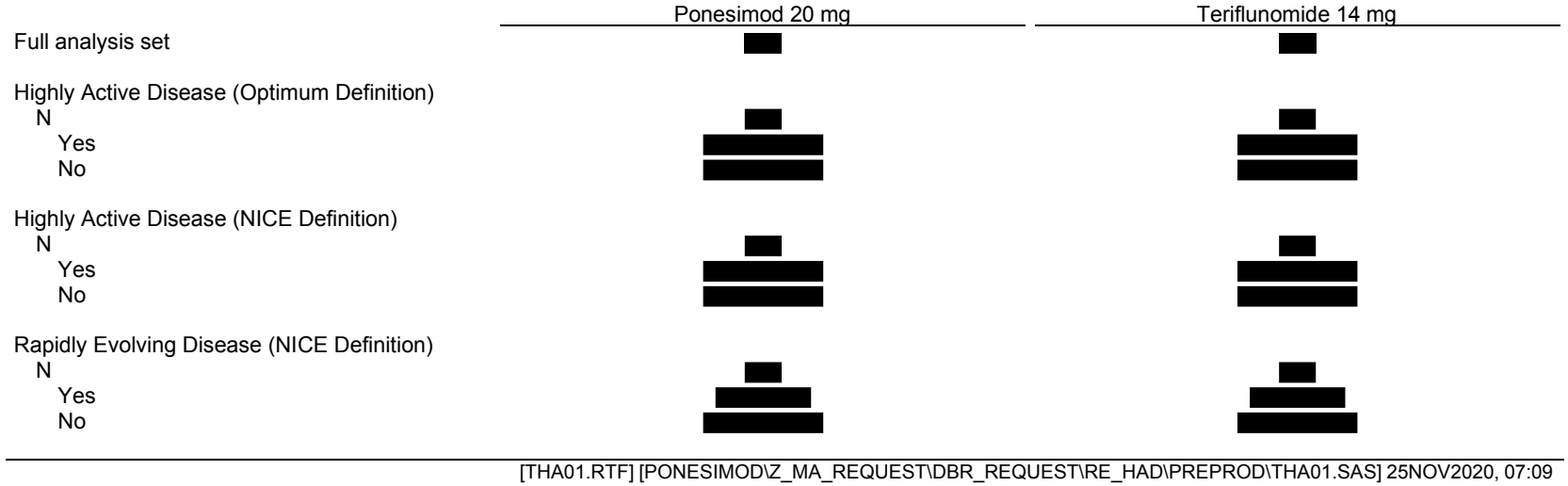




Appendix B: Post-hoc Analyses of Highly Active and RES RRMS

B.1 Proportion of patients with Highly Active and Rapidly Evolving RRMS as per OPTIMUM/ NICE definitions

Table 1 Number of Subjects with Highly Active and Rapidly Evolving Disease as per NICE Definition; Full analysis set (Study JNJ-67896153/AC-058B301)



[THA01.RTF] [PONESIMOD\Z_MA_REQUEST\DBR_REQUEST\RE_HAD\PREPROD\THA01.SAS] 25NOV2020, 07:09

Table 2 Number of Subjects with Highly Active and Rapidly Evolving Disease as per NICE Definition; Full analysis set (Study JNJ-67896153/AC-058B303)

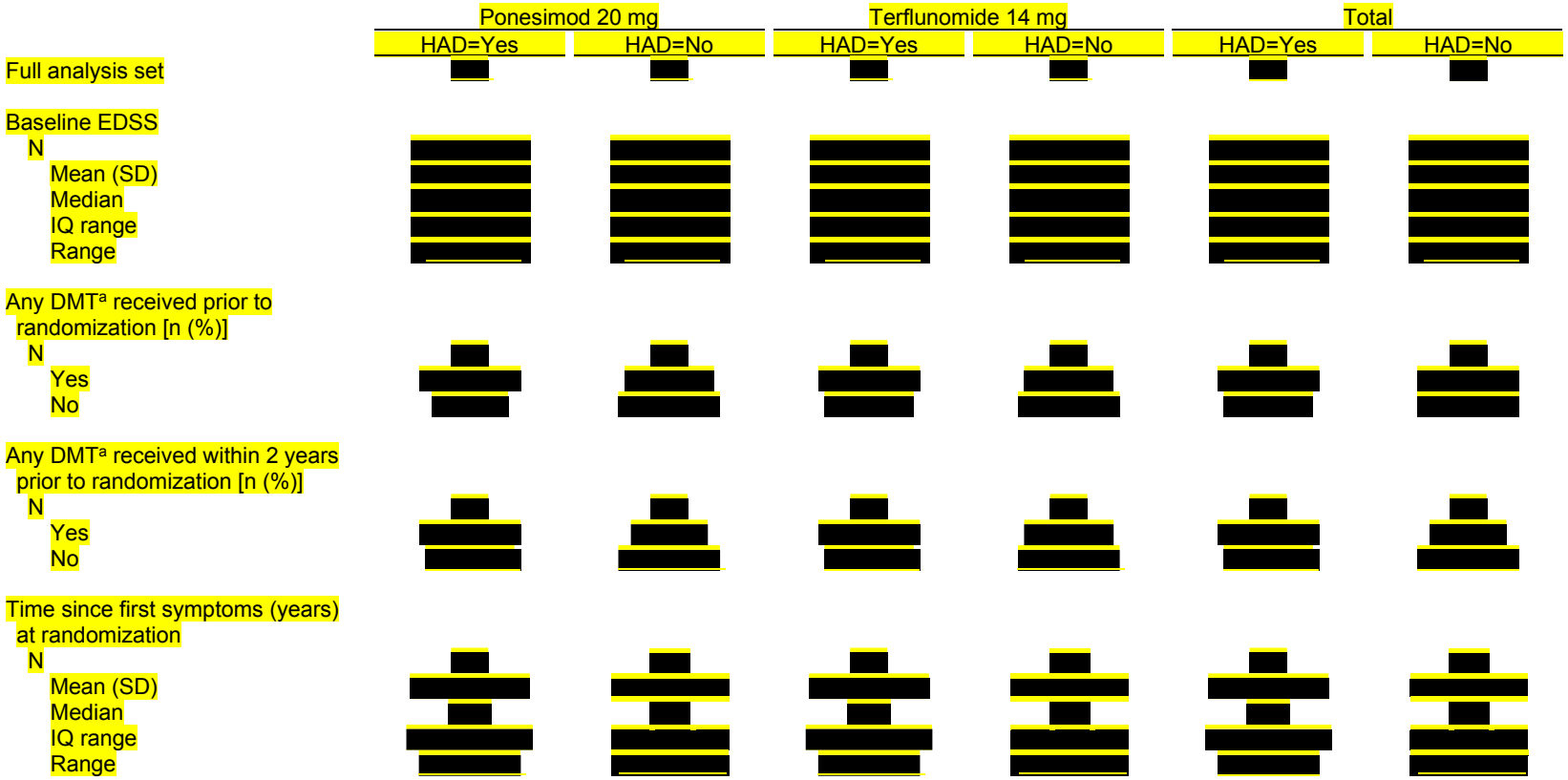
	Ponesimod 20mg/Ponesimod 20mg	Teriflunomide 14mg/Ponesimod 20mg
Full analysis set		
Highly Active Disease (Optimum Definition)		
N		
Yes		
No		
Highly Active Disease (NICE Definition)		
N		
Yes		
No		
Rapidly Evolving Disease (NICE Definition)		
N		
Yes		
No		

Treatment group displayed as AC-058B301 treatment/AC-058B303 treatment.

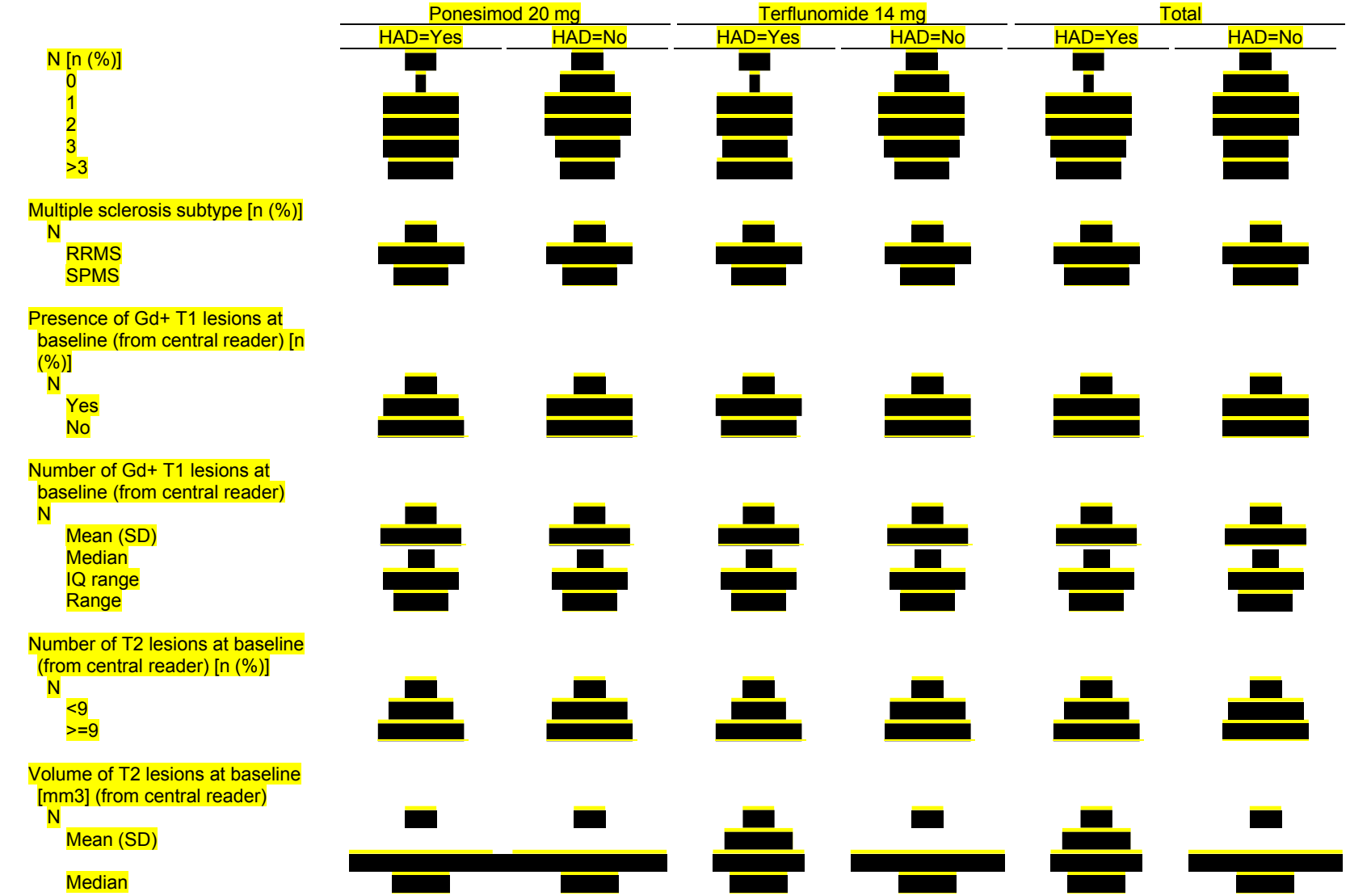
[THA01_COMB.RTF] [PONESIMOD\Z_MA_REQUEST\DBR_REQUEST\RE_FATIGUE\PREPROD\THA01_COMB.SAS] 30JUN2021, 19:12

B.2 Baseline disease characteristics by treatment for patients with Highly Active and Rapidly Evolving RRMS as per OPTIMUM / NICE definitions

Table 3 Baseline Disease Characteristics by Treatment and Highly Active Disease (HAD) [OPTIMUM Definition]; Full analysis set (Study JNJ-67896153/AC-058B301)



	Ponesimod 20 mg		Terflunomide 14 mg		Total	
	HAD=Yes	HAD=No	HAD=Yes	HAD=No	HAD=Yes	HAD=No
Time since initial diagnosis (years) at randomization						
N						
Mean (SD)						
Median						
IQ range						
Range						
Time since most recent relapse (months) at screening						
N						
Mean (SD)						
Median						
IQ range						
Range						
Number of relapses in last year prior to study entry						
N						
Mean (SD)						
Median						
IQ range						
Range						
N [n (%)]						
0						
1						
2						
3						
>3						
Number of relapses in last 2 years prior to study entry						
N						
Mean (SD)						
Median						
IQ range						
Range						



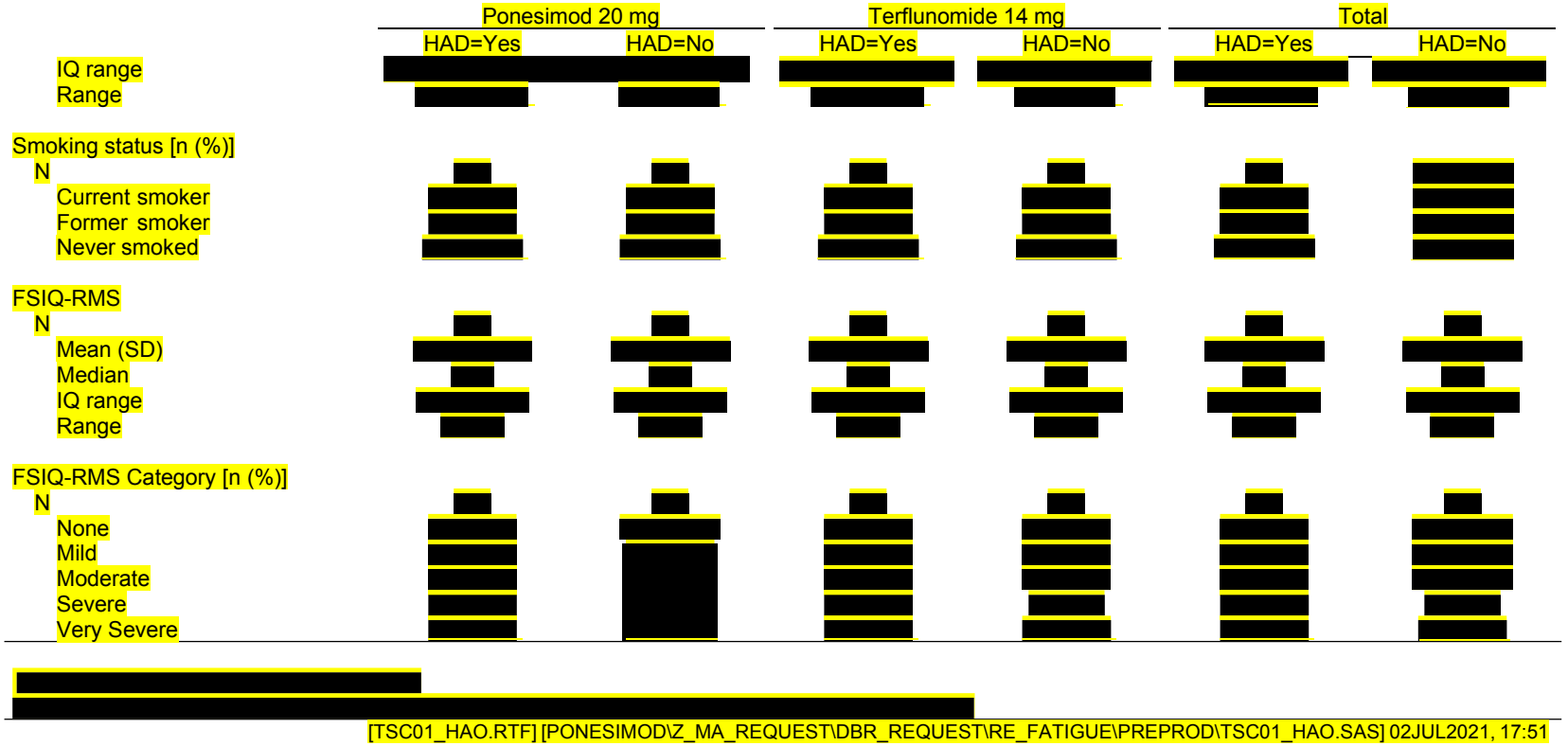
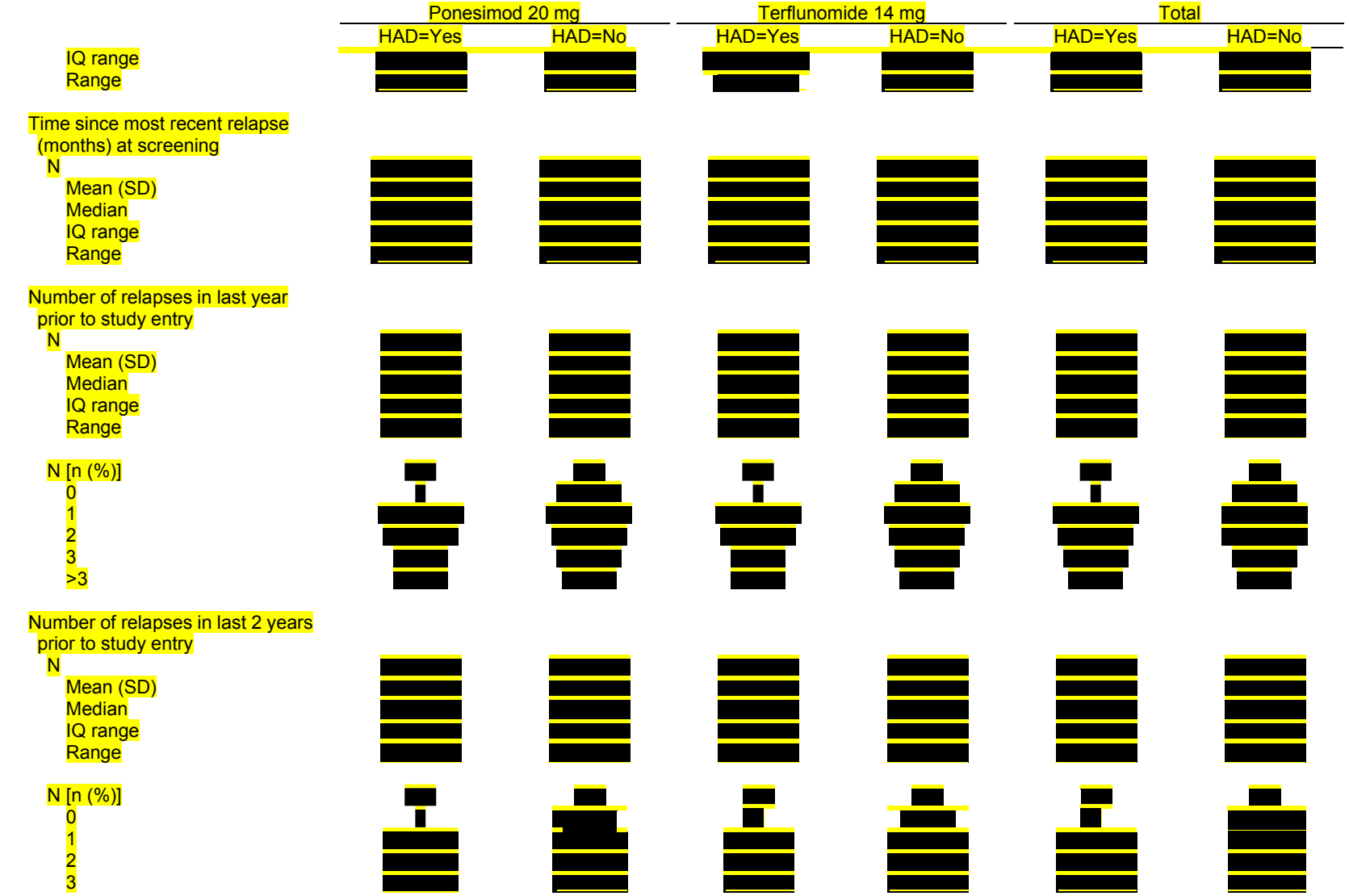


Table 4 Baseline Disease Characteristics by Treatment and Highly Active Disease (HAD) [NICE Definition]; Full analysis set (Study JNJ-67896153/AC-058B301)

	Ponesimod 20 mg		Terflunomide 14 mg		Total	
	HAD=Yes	HAD=No	HAD=Yes	HAD=No	HAD=Yes	HAD=No
Full analysis set						
Baseline EDSS						
N						
Mean (SD)						
Median						
IQ range						
Range						
Any DMT[a] received prior to randomization [n (%)]						
N						
Yes						
No						
Any DMT[a] received within 2 years prior to randomization [n (%)]						
N						
Yes						
No						
Time since first symptoms (years) at randomization						
N						
Mean (SD)						
Median						
IQ range						
Range						
Time since initial diagnosis (years) at randomization						
N						
Mean (SD)						
Median						




Ponesimod 20 mg
Terflunomide 14 mg
HAD=Yes
>3
Multiple sclerosis subtype [n (%)]
N
RRMS
SPMS
Presence of Gd+ T1 lesions at baseline (from central reader) [n (%)]
N
Yes
No
Number of Gd+ T1 lesions at baseline (from central reader)
N
Mean (SD)
Median
IQ range
Range
Number of T2 lesions at baseline (from central reader) [n (%)]
N
<9
>=9
Volume of T2 lesions at baseline [mm3] (from central reader)
N
Mean (SD)
Median
IQ range
Range
Smoking status [n (%)]
N
Current smoker

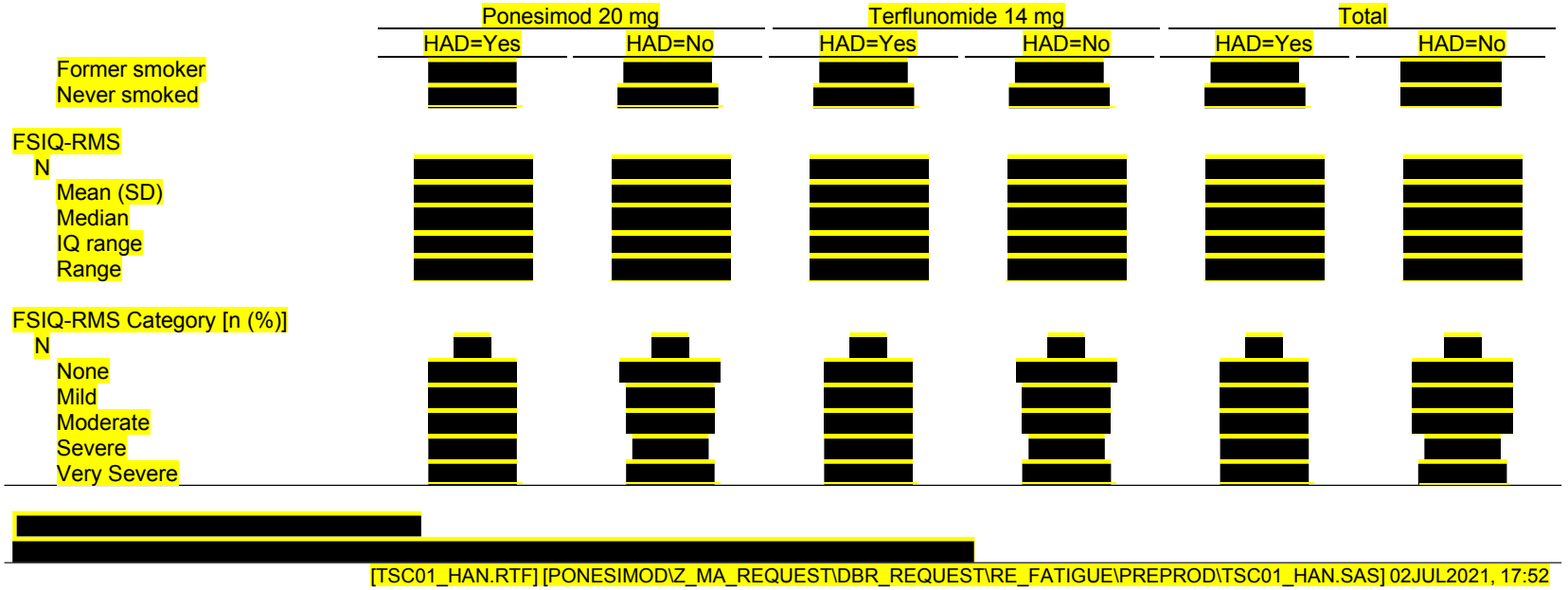
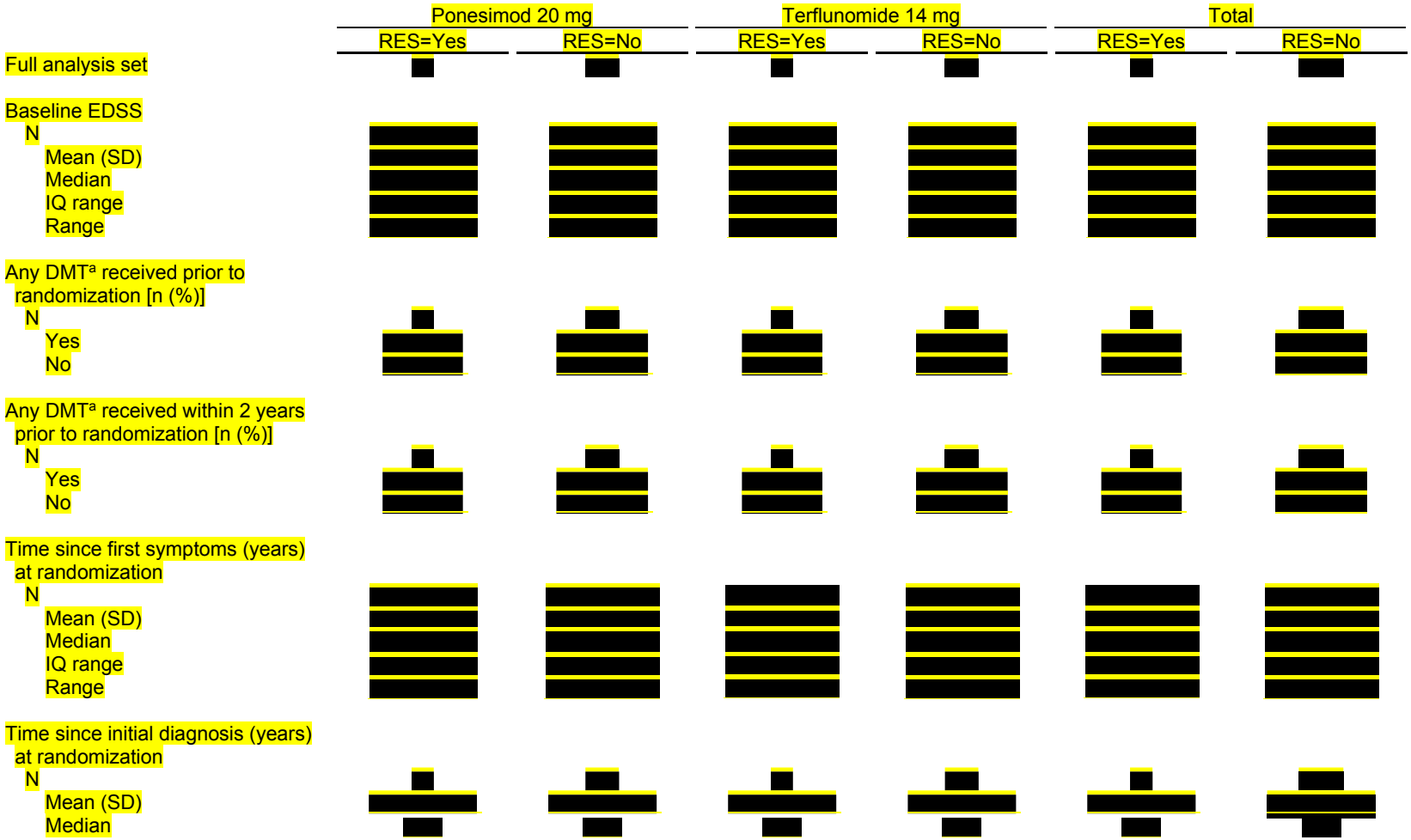
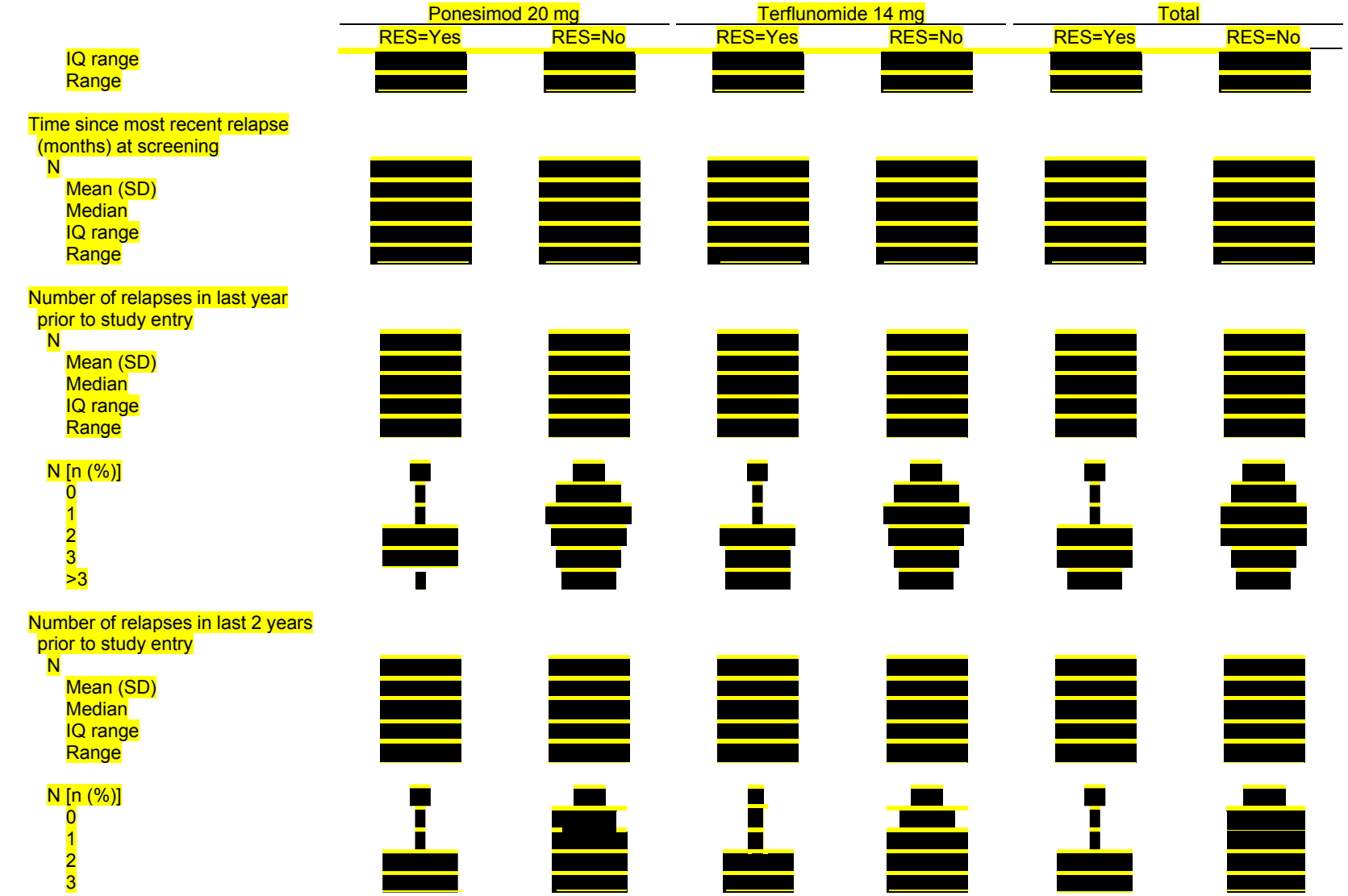
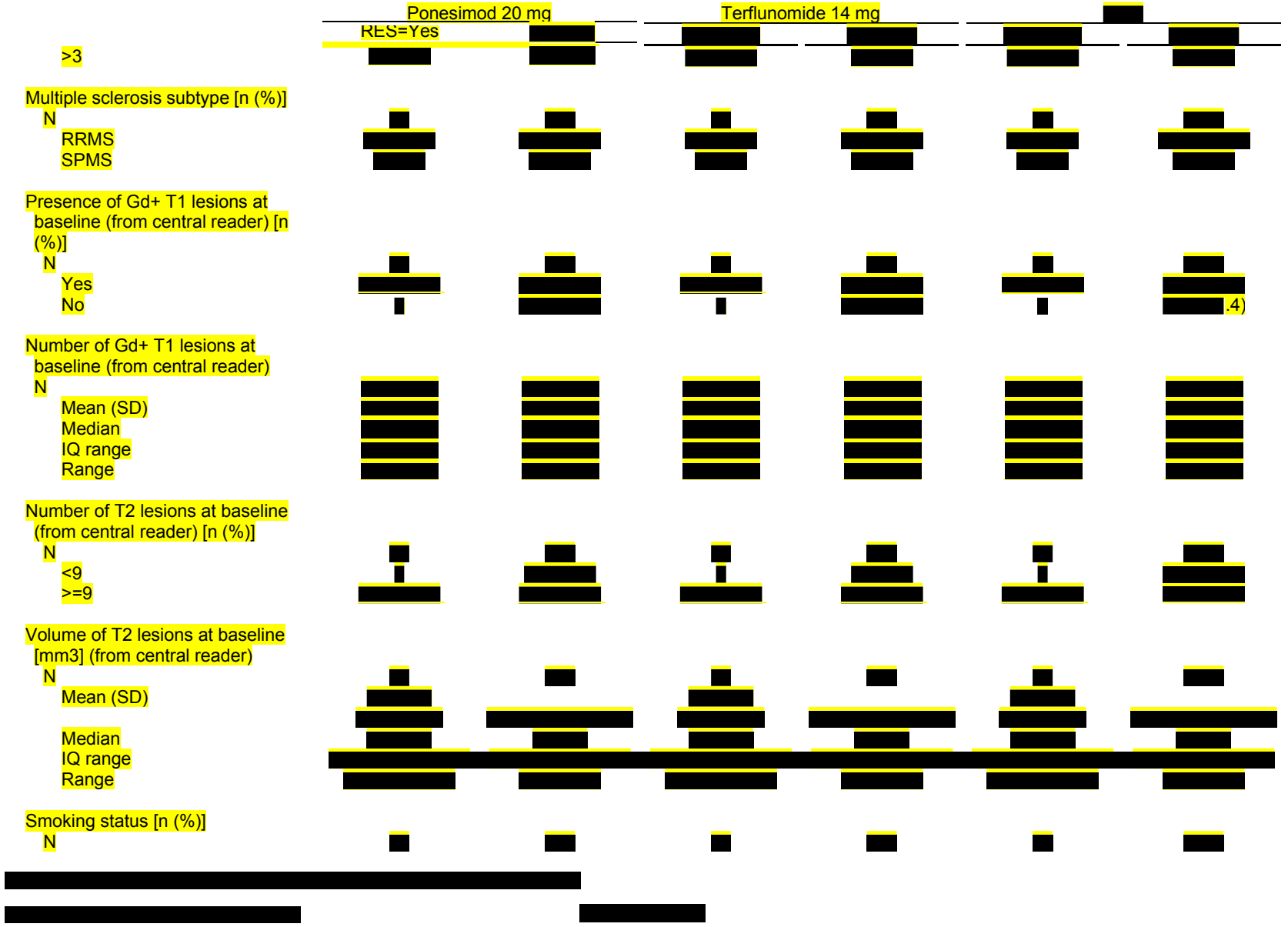
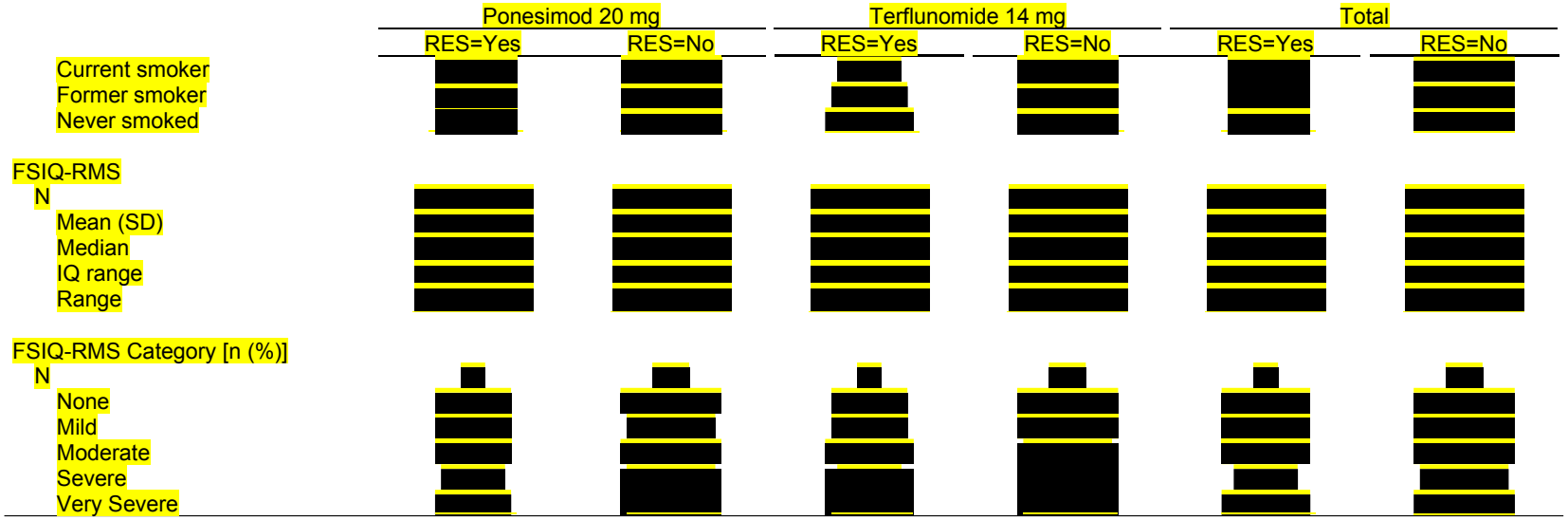


Table 5 Baseline Disease Characteristics by Treatment and Rapidly Evolving Severe (RES) [NICE Definition]; Full analysis set (Study JNJ-67896153/AC-058B301)






Ponesimod 20 mg
Terflunomide 14 mg
RES=Yes
>3
Multiple sclerosis subtype [n (%)]
N
RRMS
SPMS
Presence of Gd+ T1 lesions at baseline (from central reader) [n (%)]
N
Yes
No
.4)
Number of Gd+ T1 lesions at baseline (from central reader)
N
Mean (SD)
Median
IQ range
Range
Number of T2 lesions at baseline (from central reader) [n (%)]
N
<9
>=9
Volume of T2 lesions at baseline [mm3] (from central reader)
N
Mean (SD)
Median
IQ range
Range
Smoking status [n (%)]
N



[a]DMT = MS disease-modifying treatment.
RRMS = Relapsing-remitting multiple sclerosis, SPMS = Secondary progressive multiple sclerosis.

[TSC01_RESN.RTF] [PONESIMOD\Z_MA_REQUEST\DBR_REQUEST\RE_FATIGUE\PREPROD\TSC01_RESN.SAS] 02JUL2021, 17:53

B.3 Post hoc analyses of key clinical endpoints for patients with Highly Active and Rapidly Evolving RRMS as per OPTIMUM / NICE definitions

Table 6 Confirmed relapses up to EOS - Subgroup analysis (99% CL); Full analysis set (Study JNJ-67896153/AC-058B301

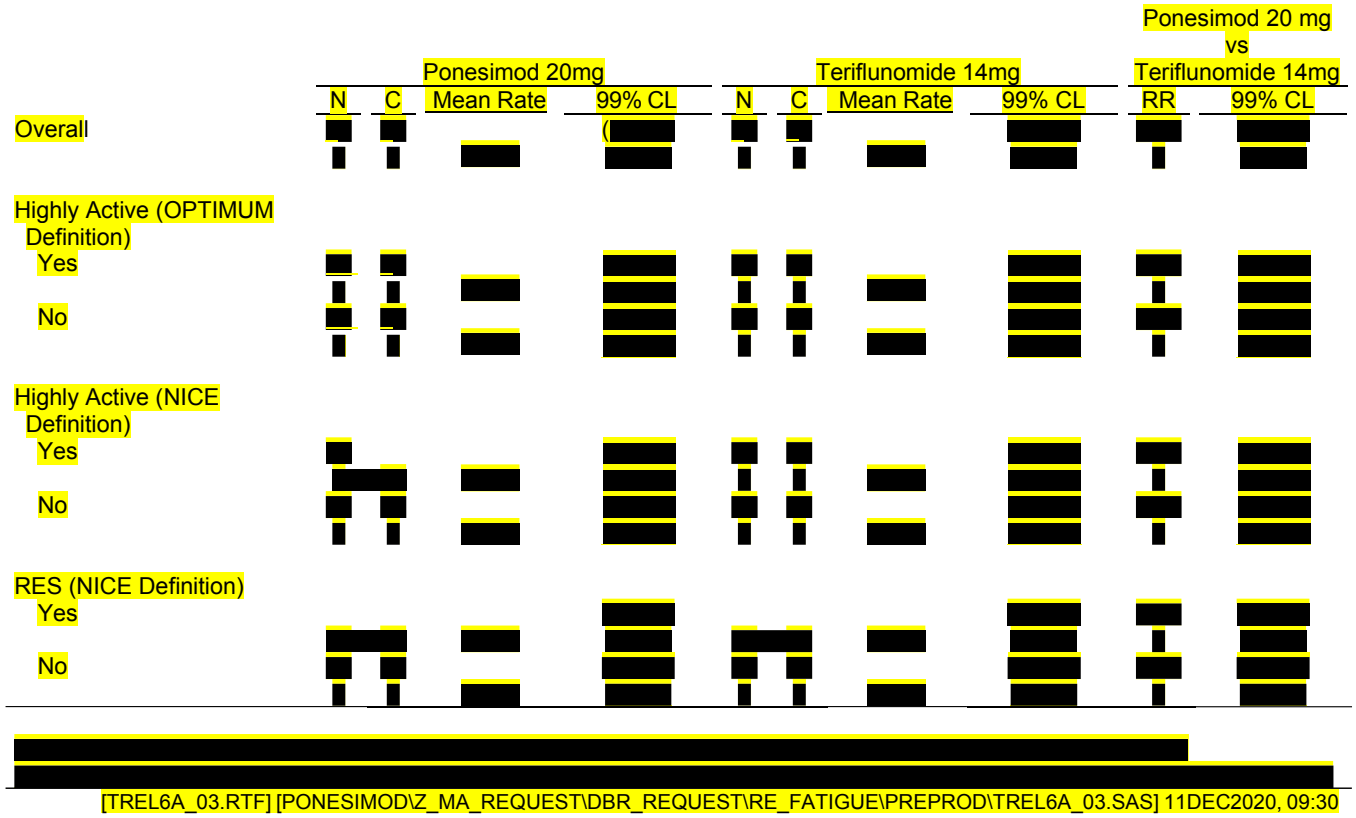


Table 7 Time to 12-week Confirmed Disability Accumulation up to EOS: Full analysis set (Study JNJ-67896153/AC-058B30)1

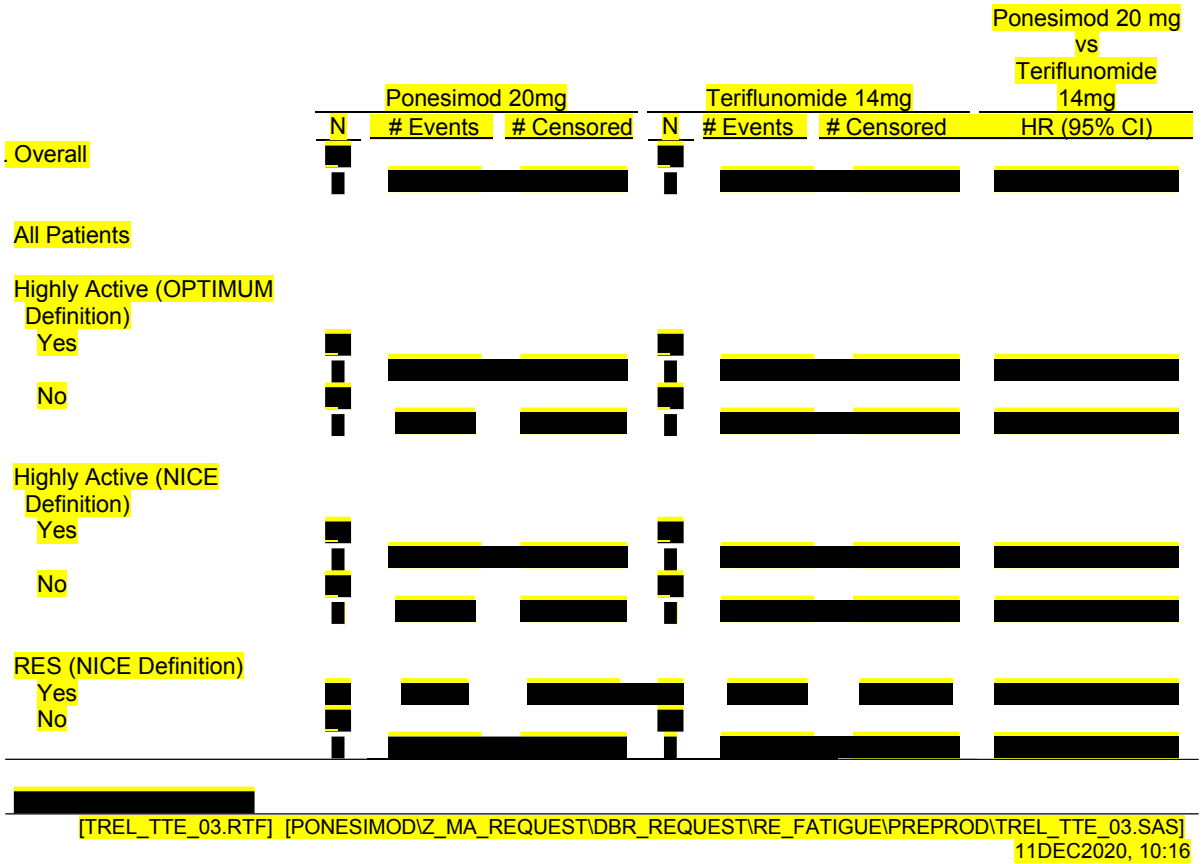
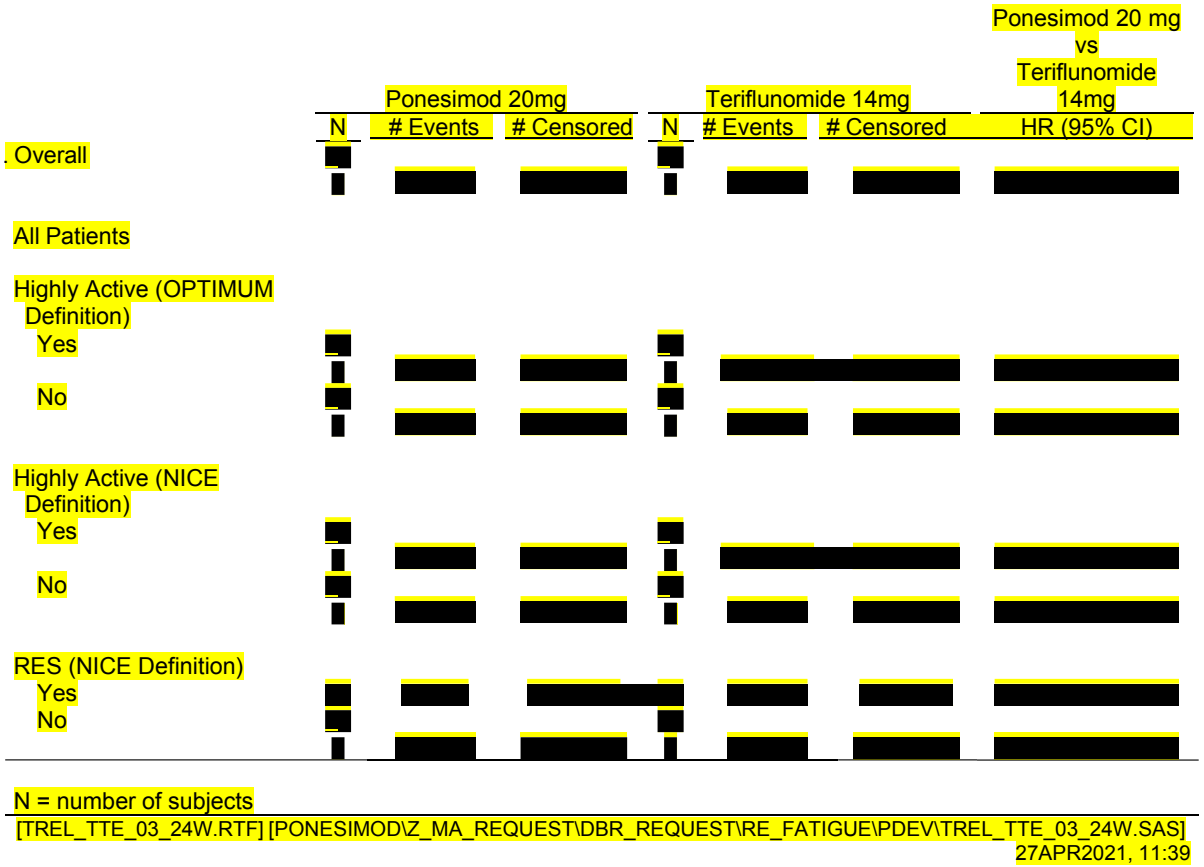


Table 8 Time to 24-week Confirmed Disability Accumulation up to EOS: Full analysis set (Study JNJ-67896153/AC-058B301)



Appendix C: Feasibility Assessment and Risk of Bias

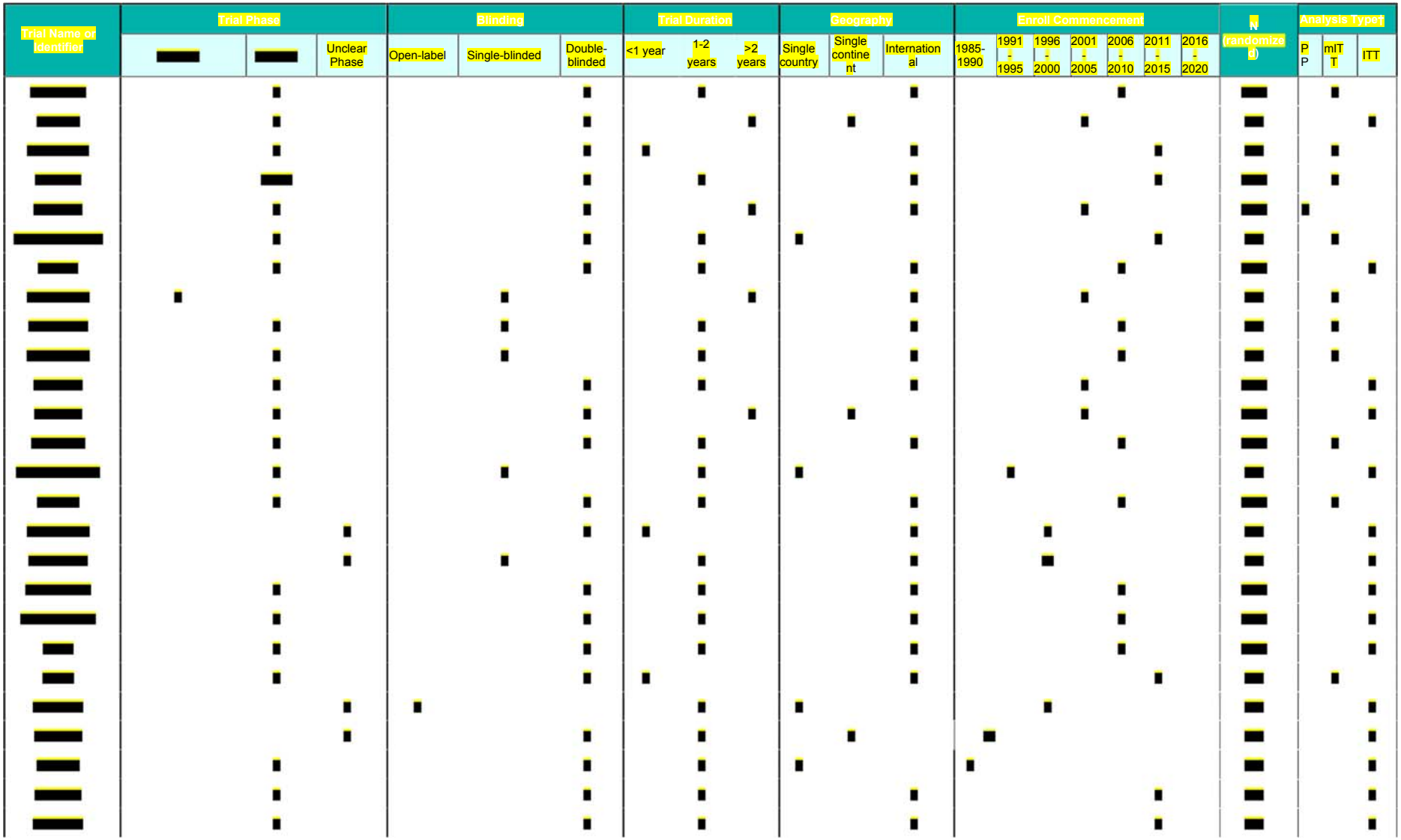
C.1 Feasibility Assessment

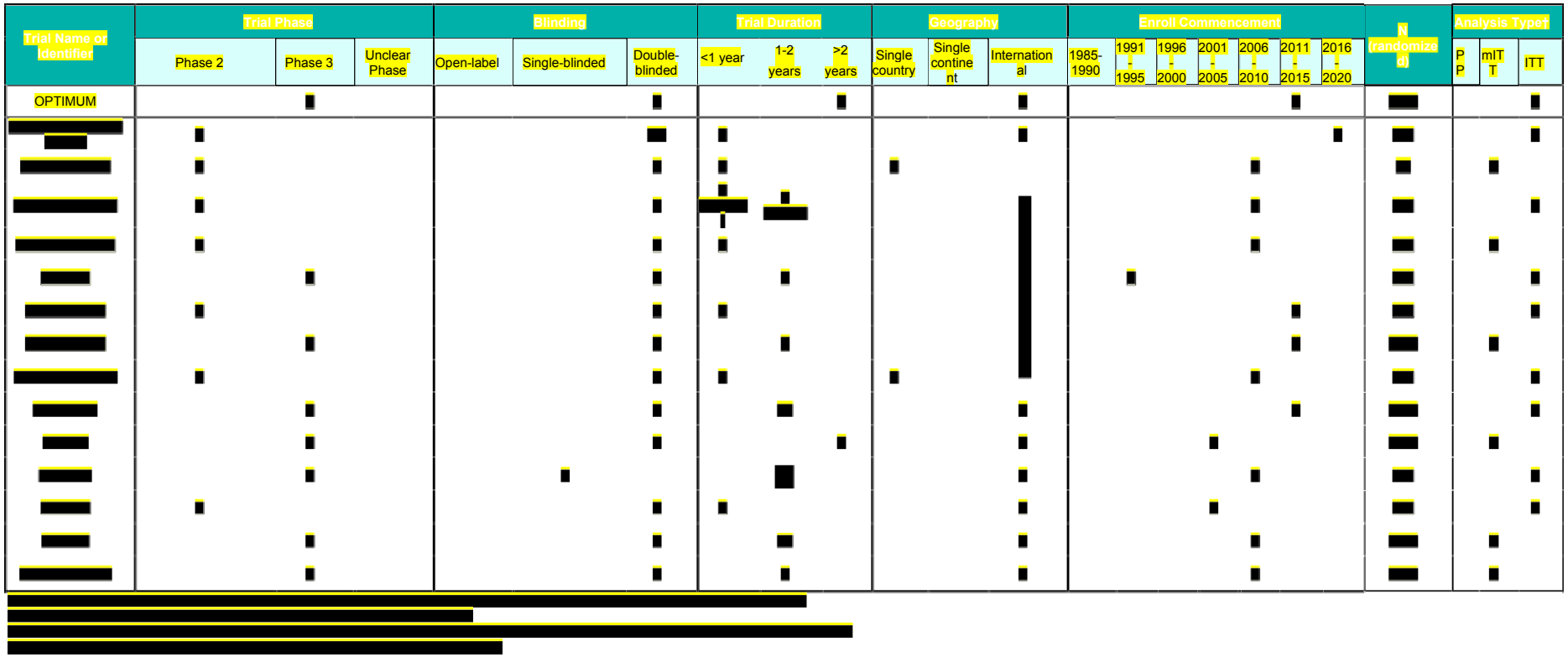
[redacted]

Figure 1: Network Diagram for Main Analysis of ARR

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, ARR = annualized relapse rate; BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

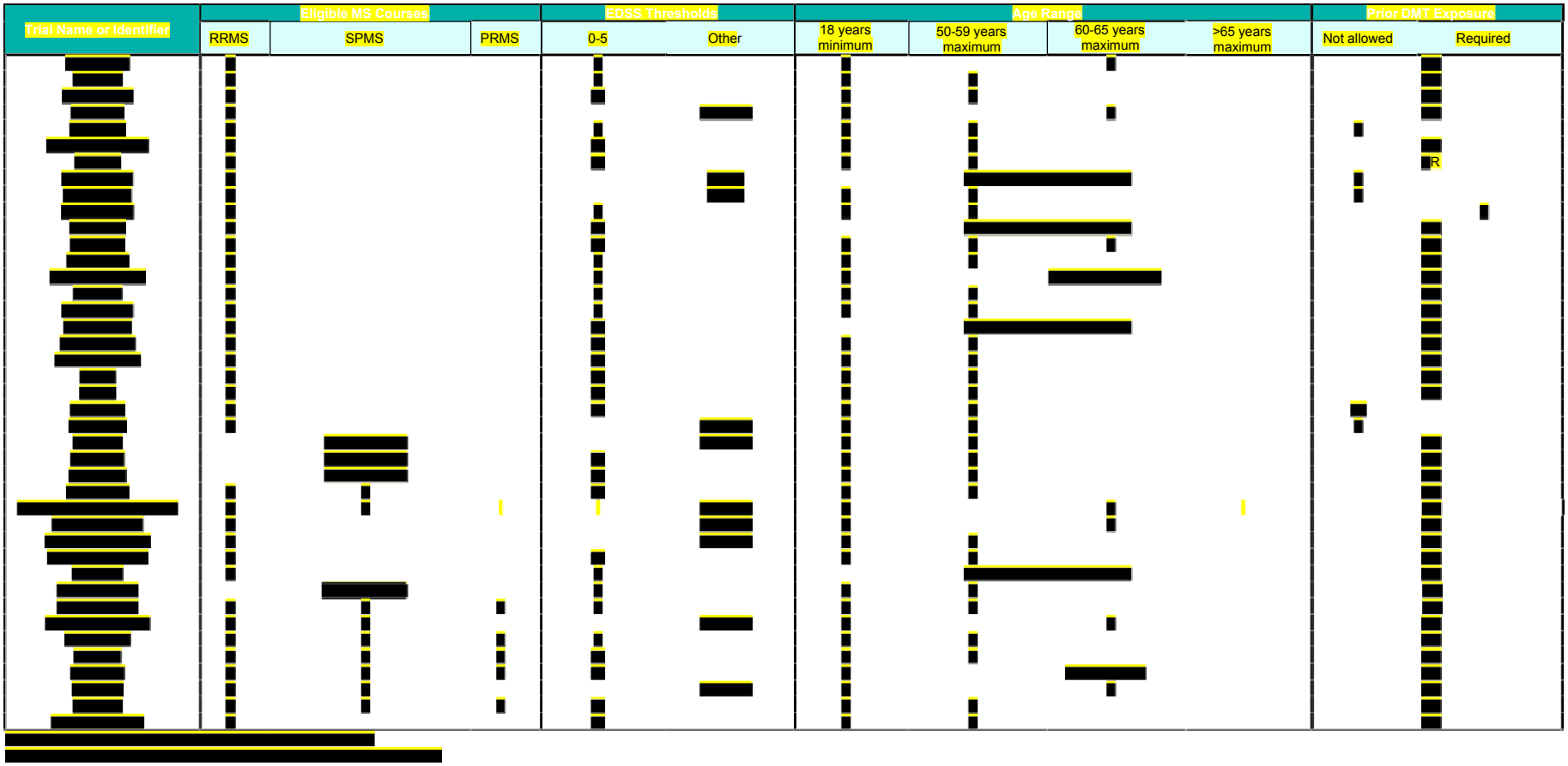
Table 9 Comparison of Key Study Design Details for Studies in the ARR Network





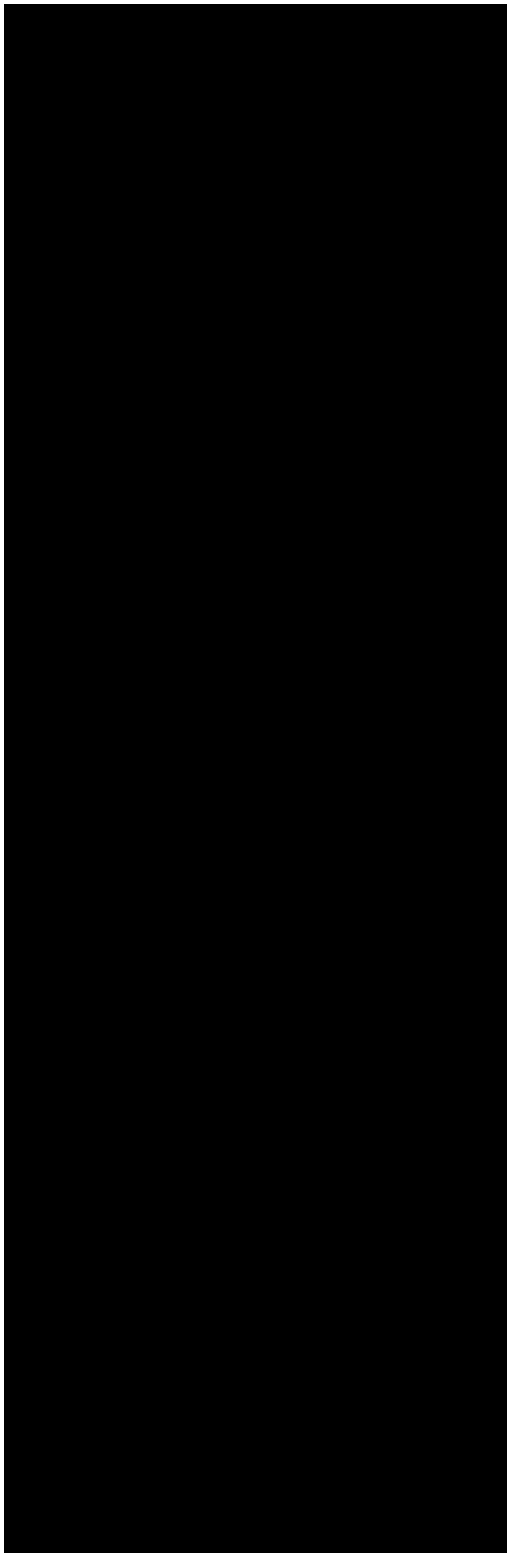
KEY: ARR = annualized relapse rate, ITT = intention-to-treat (randomized patients), mITT = modified intention-to-treat, PP = per protocol.

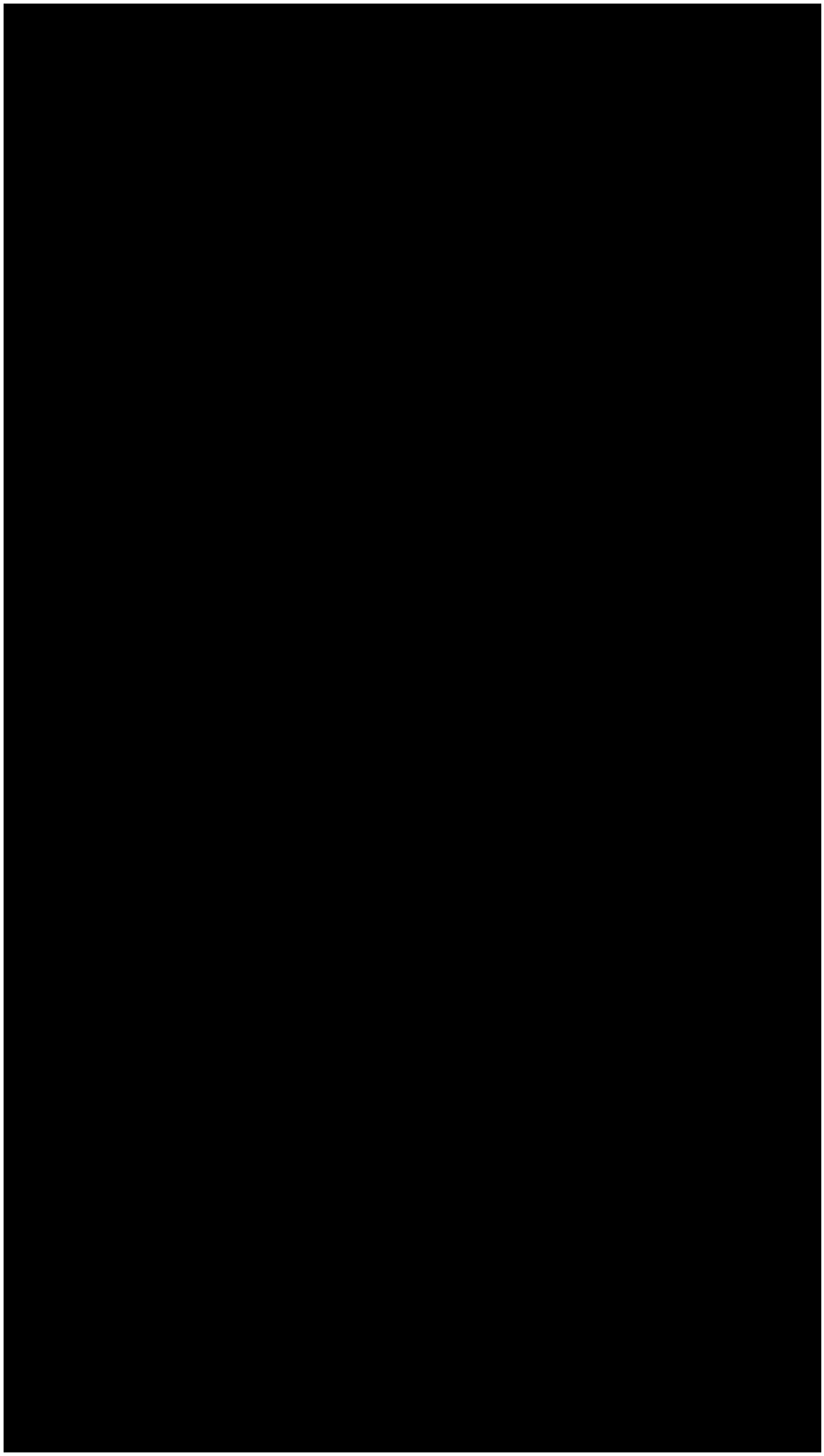
Table 10 Comparison of Key Eligibility Criteria for Studies in the ARR Network

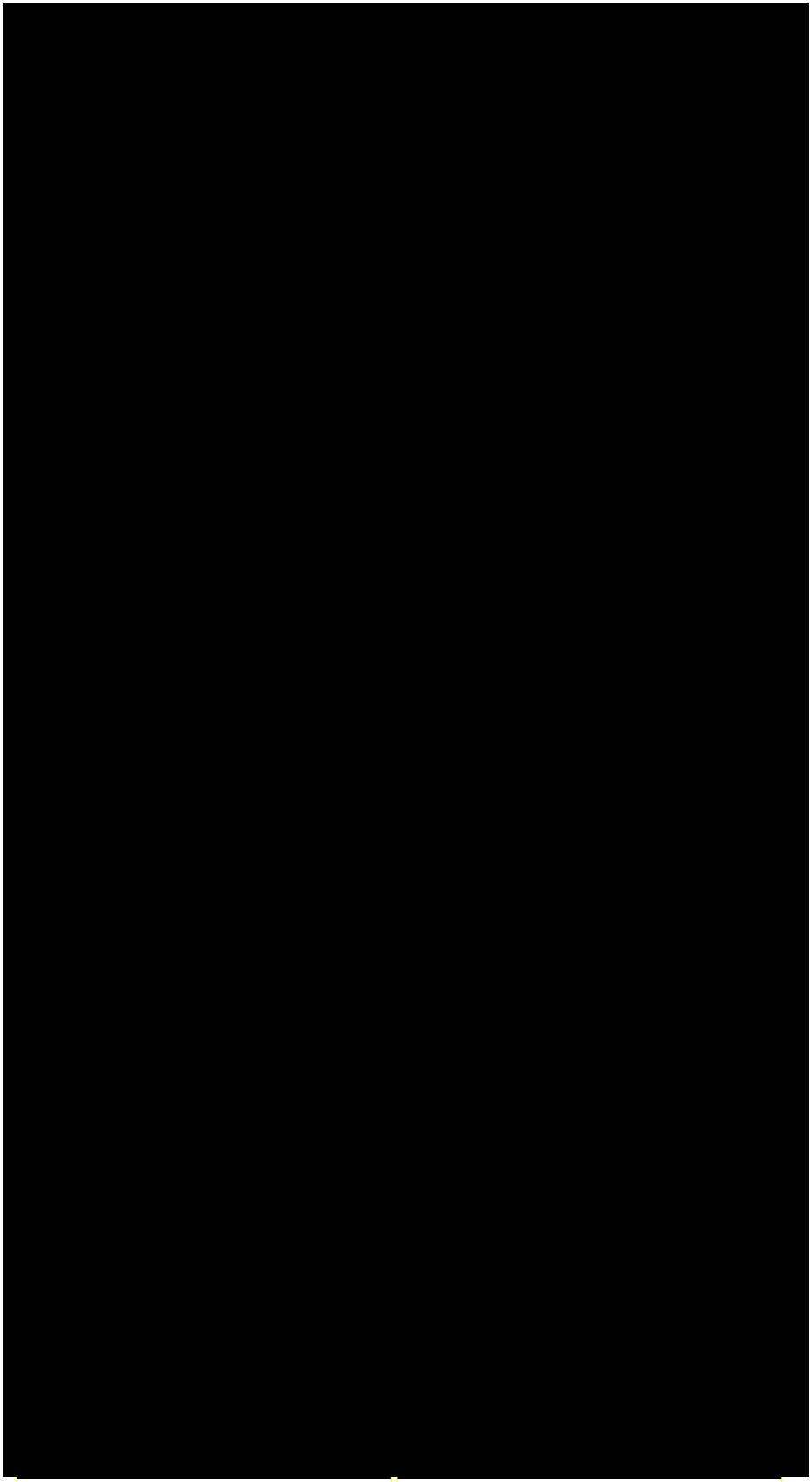


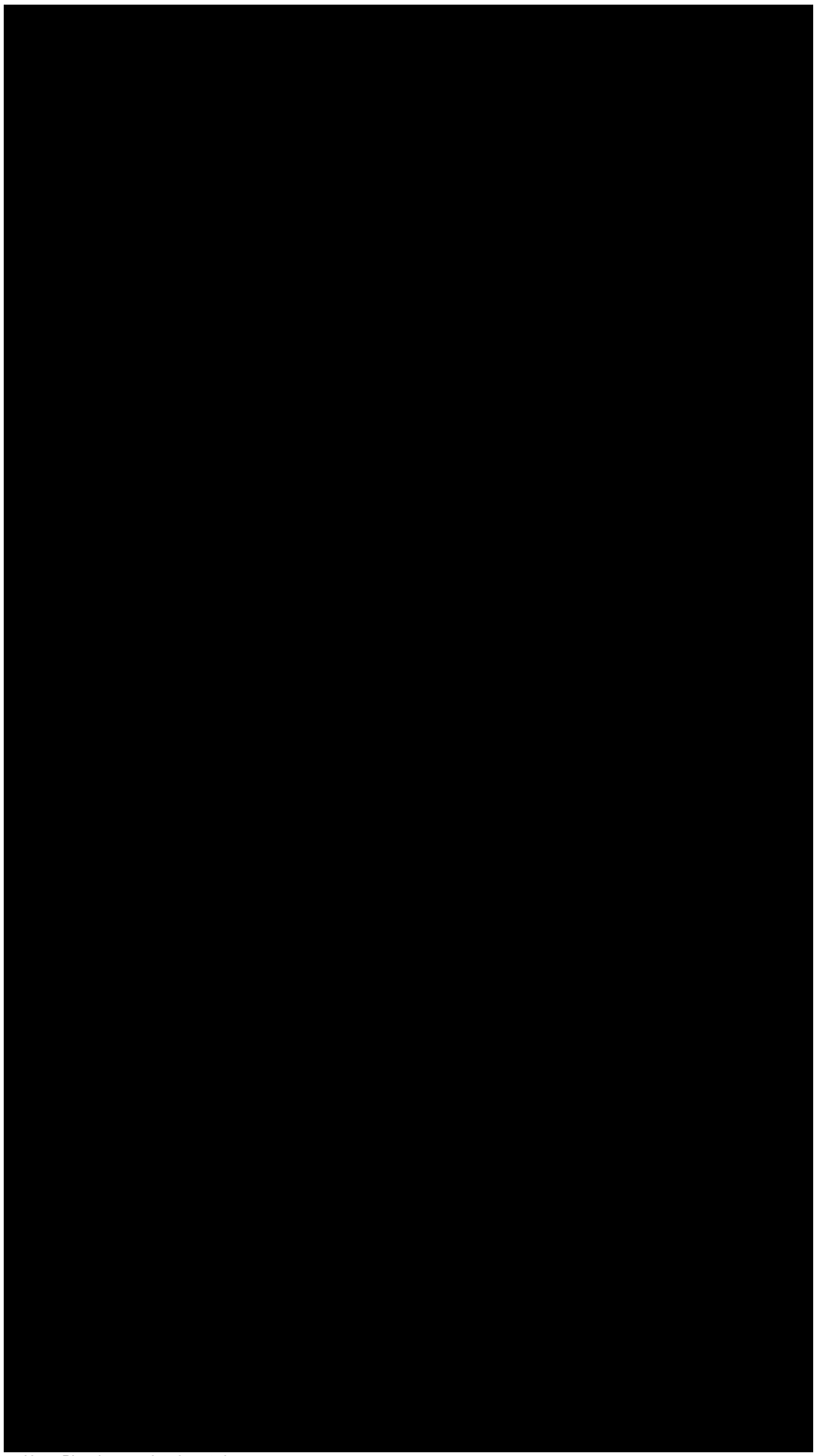
KEY: ARR = annualized relapse rate, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, MS = multiple sclerosis, NR = not reported, PRMS = progressive-relapsing multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary-progressive multiple sclerosis, yrs = yea

Figure 2 Comparison of Patient Baseline Traits for Studies in ARR Network





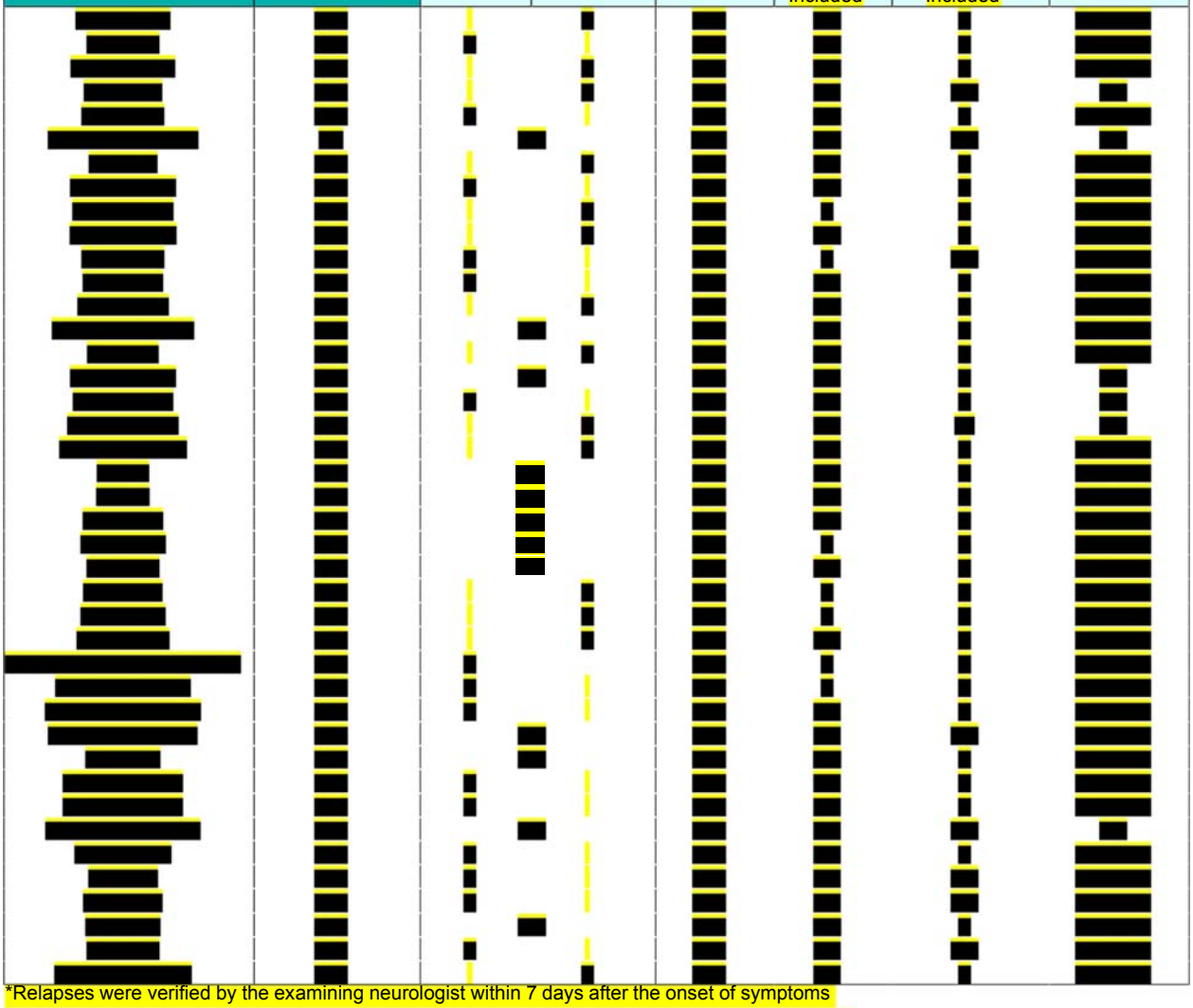




Note: Placebo arm data is not shown.
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, ARR = annualized relapse rate; BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod; PEG = peginterferon; PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, RRMS = relapsing-remitting multiple sclerosis, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Table 11 Comparison of Outcome Definitions and Statistical Analysis Methods for Studies in the ARR Network

Trial Name or Identifier	Definition of ARR Reported?	Regression Type		Relapse Definition			
		Poisson	Negative Binomial	Definition Reported?	EDSS Threshold Included	Neurological Symptoms Included	24 or 48-hour Persistence



*Relapses were verified by the examining neurologist within 7 days after the onset of symptoms
**Main publication indicated that eligible relapses were confirmed by magnetic resonance imaging
KEY: ARR = annualised relapse rate, EDSS = Expanded Disability Status Scale, NR = not reported.

C.1.2.1 Constructing Networks for Subgroup NMAs for ARR

C.1.2.1.1 Subgroups: RRMS patients

Thirty-one trials were incorporated into a network restricted to data for RRMS patients.

Table 12: Trials and Regimens Included in ARR Subgroup Networks

Network Details	RRMS only
Trials incorporated	• [redacted]
Regimens incorporated	1. [redacted] 7. [redacted] 8. [redacted] 9. [redacted]
[redacted]	[redacted]

[redacted]

C.1.2.1.2 Subgroups: Patients with highly active disease

[redacted]

[redacted]

Table 13: Trials and Regimens Included in ARR Subgroup Network – Highly-Active Disease

Trials incorporated	Regimens incorporated	Definition of highly-active selected	Notes	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trials incorporated	Regimens incorporated	Definition of highly-active selected	Notes	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*ITT data incorporated as stated above, given that HA subgroup data was unavailable.
KEY: 4W: =every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, ARR = annualised relapse rate, CLA = cladribine, FIN = fingolimod, IFNB-1a = interferon beta-1a, IM = intramuscular, NAT= natalizumab, OCR = ocrelizumab, PBO = placebo, PON = ponesimod, SC = subcutaneous, TER = teriflunomide, TIW = three times per week, QD = every day.

C.1.3 Feasibility Assessment for NMA of 3-month CDA

[redacted]

[redacted]

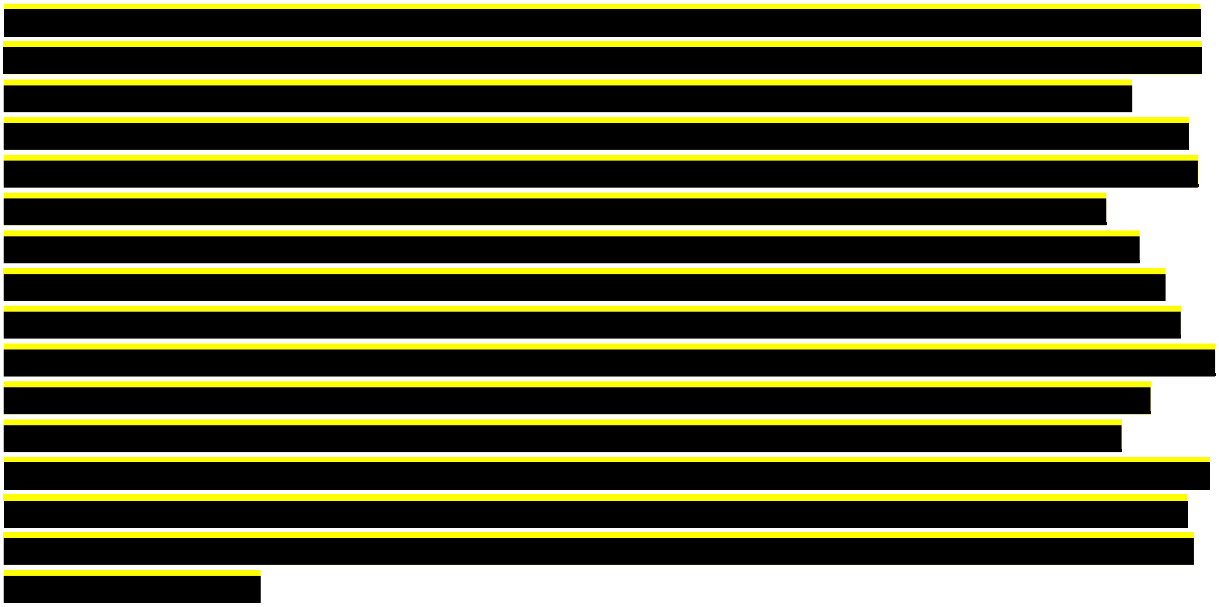
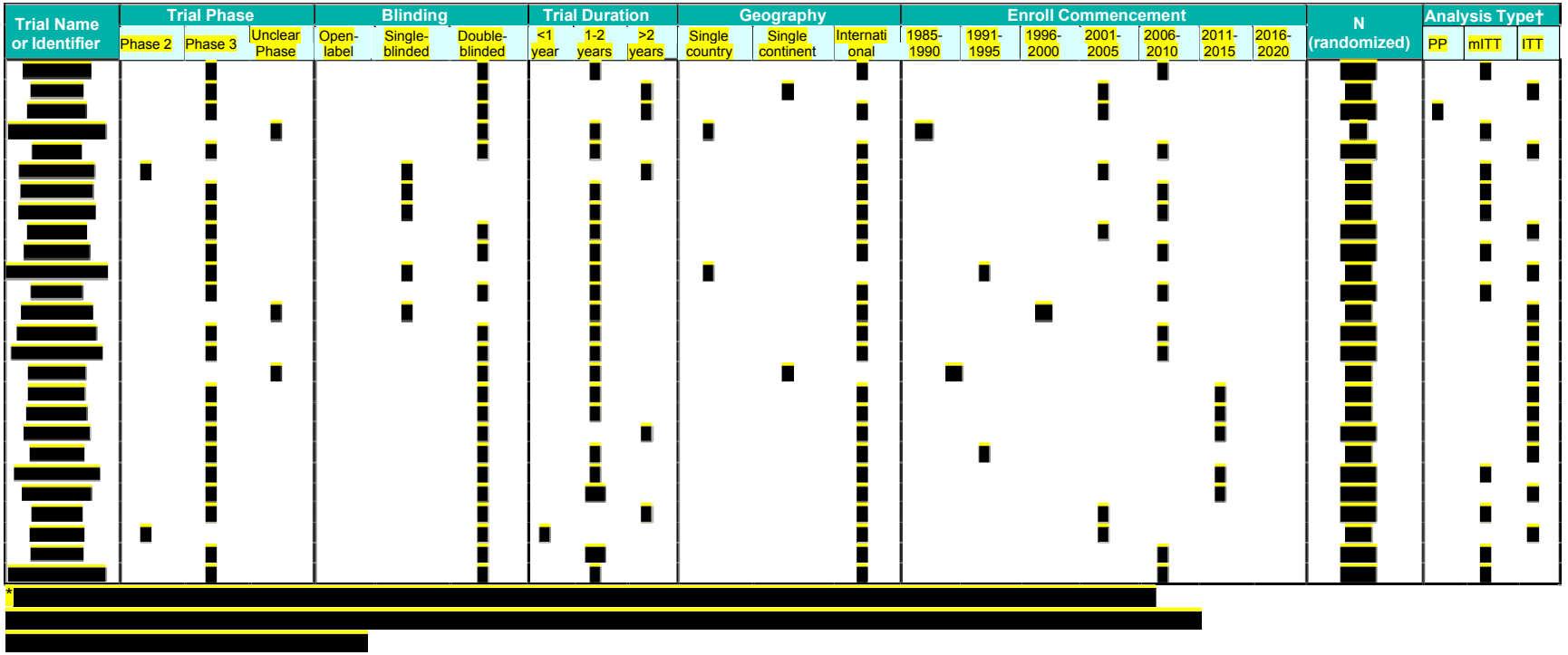


Figure 3 Initial Network Diagram for Main Analysis of 3-month CDA

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability accumulation, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Table 14: Comparison of Key Study Design Details for Studies in the 3-month CDA Network



KEY: CDA= confirmed disability accumulation, ITT = intention-to-treat (randomized patients), mITT = modified intention-to-treat, PP = per protocol.

Table 15: Comparison of Key Eligibility Criteria for Studies in the 3-month CDA Network

Trial Name or Identifier	Eligible MS Courses			EDSS Thresholds		Age Range				Prior DMT Exposure	
	RRMS	SPMS	PRMS	0-5	Other	18 years minimum	50-59 years maximum	60-65 years maximum	>65 years maximum	Not allowed	Required
*											

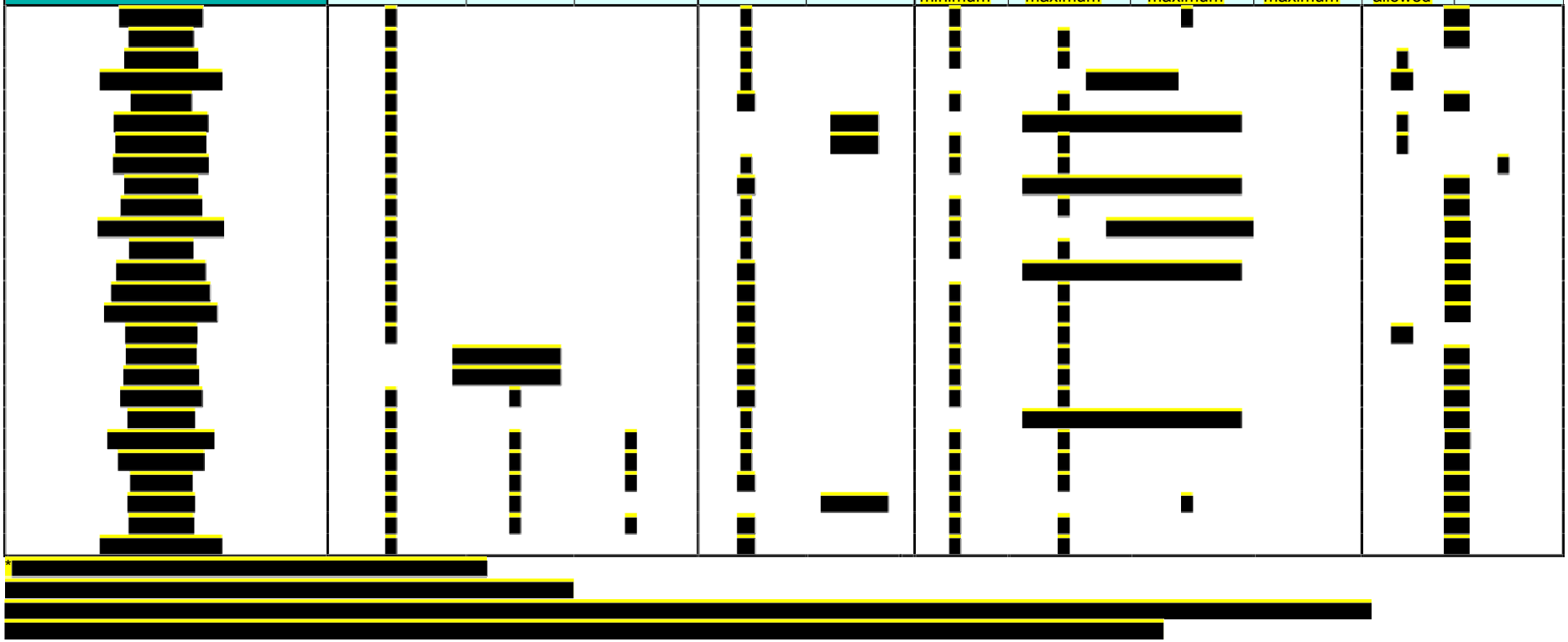
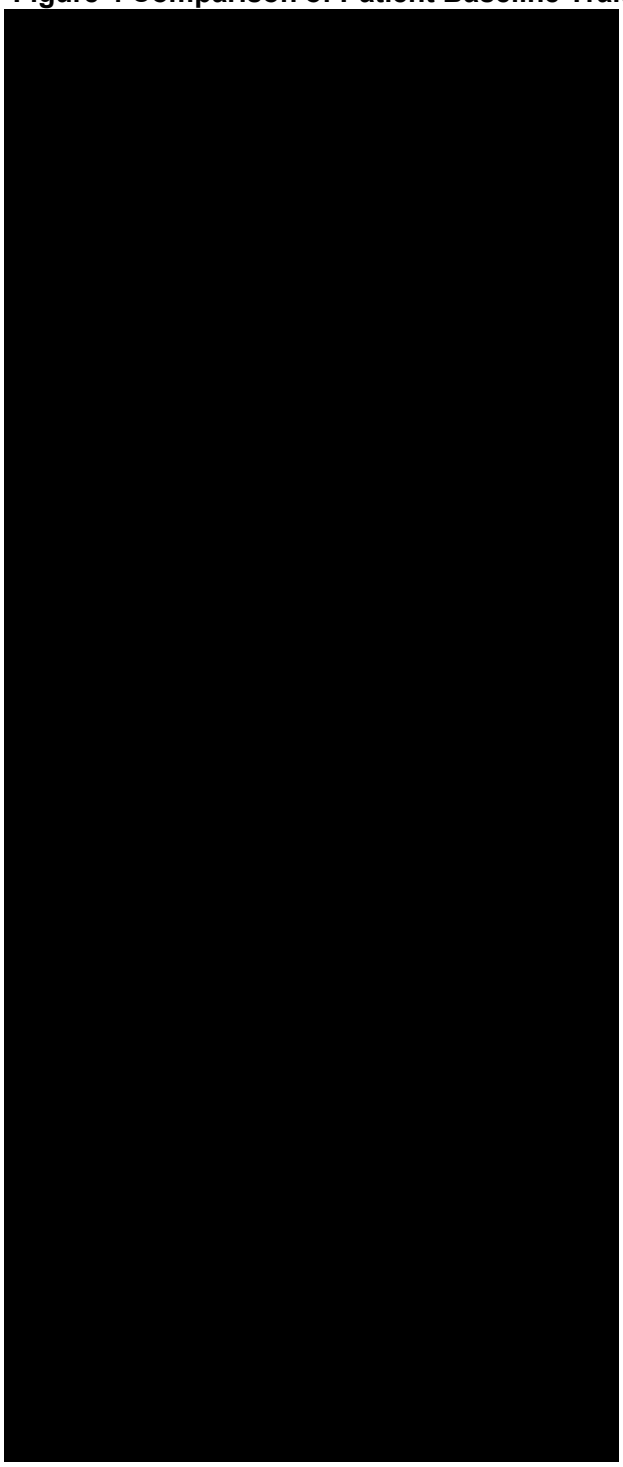
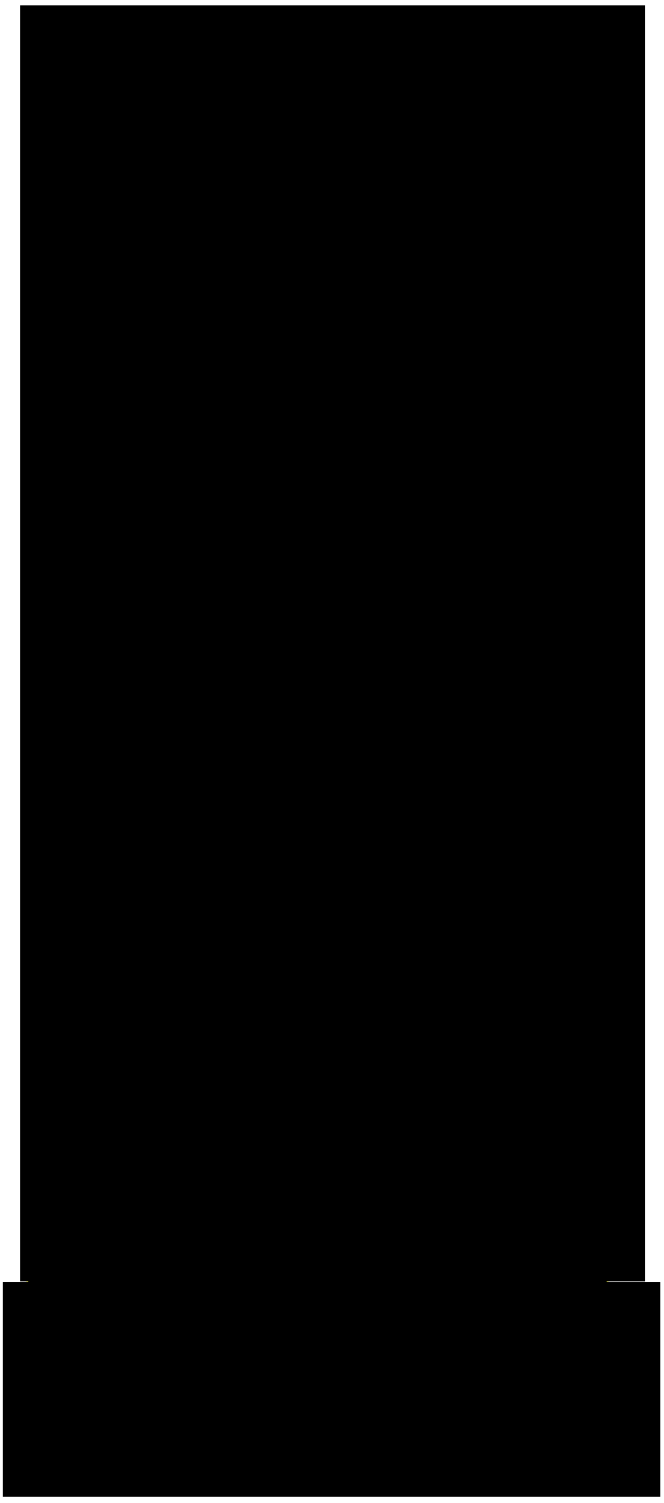
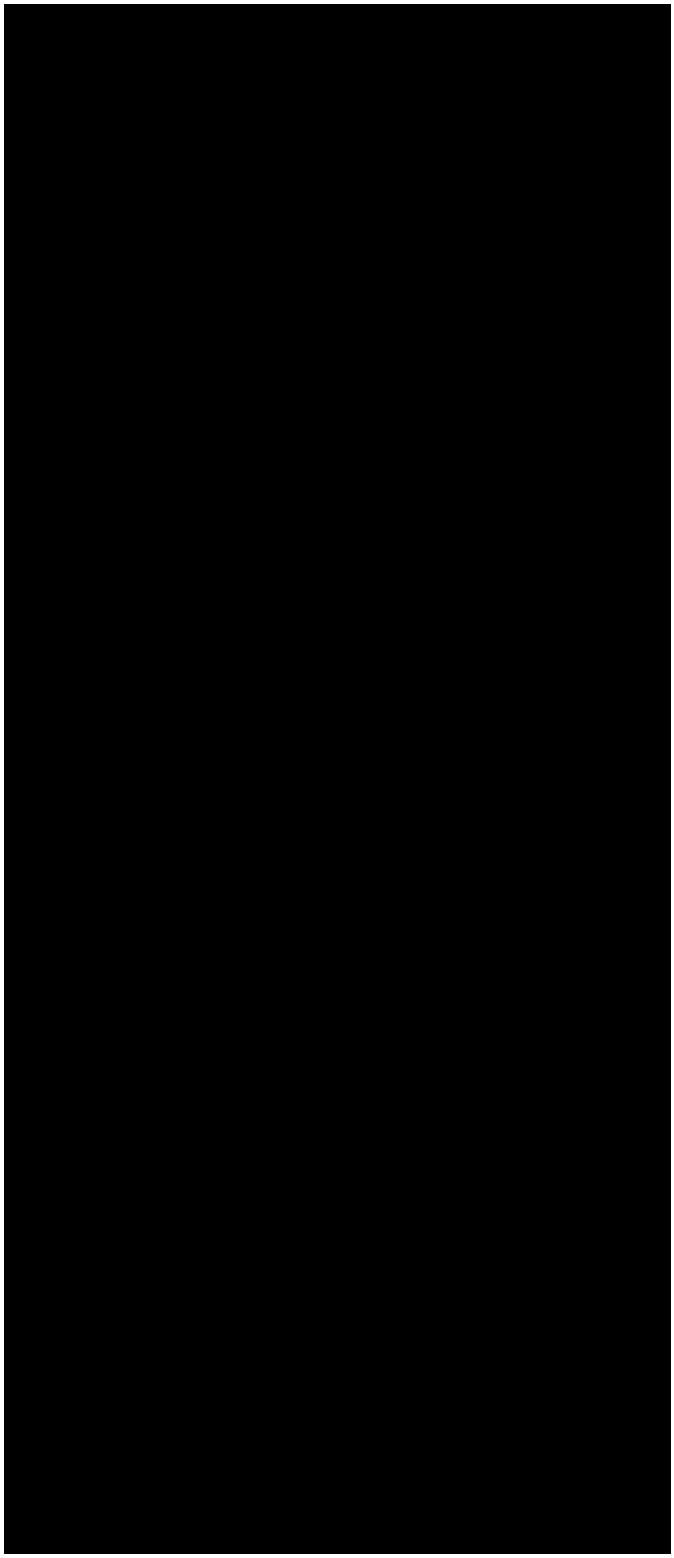
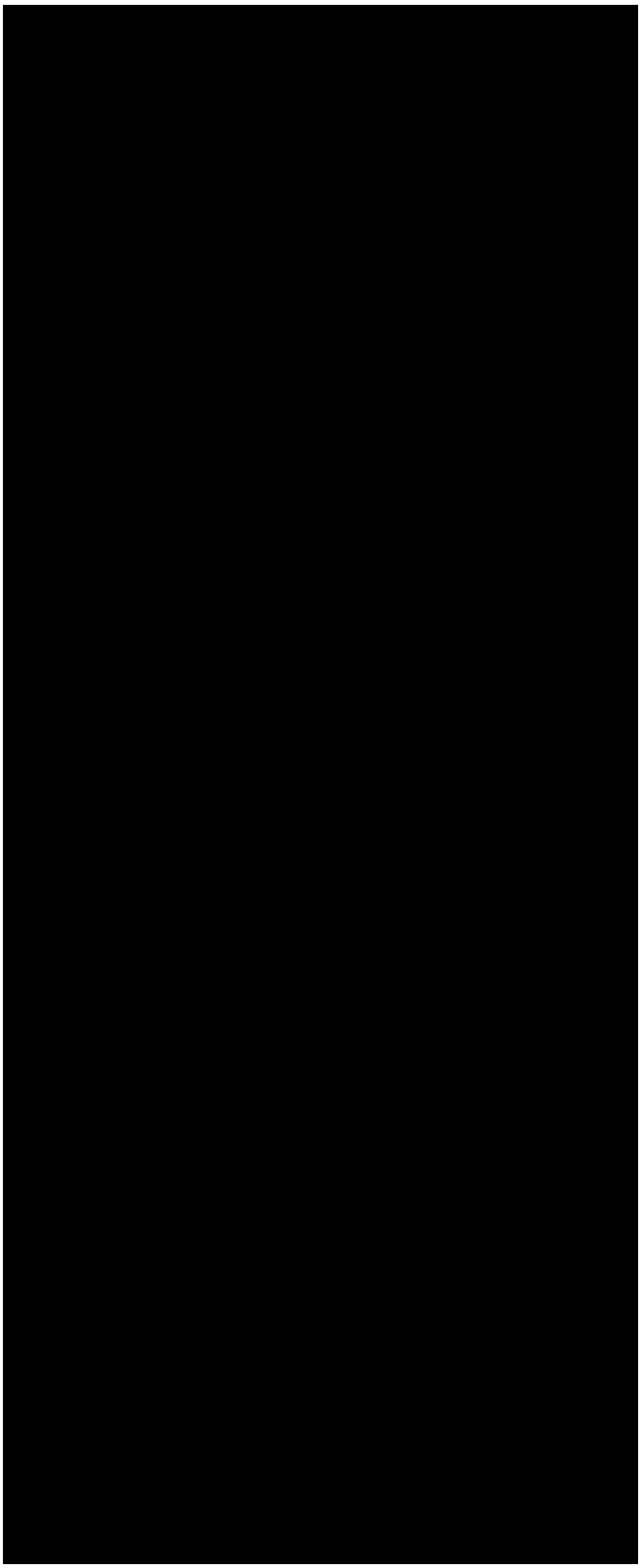


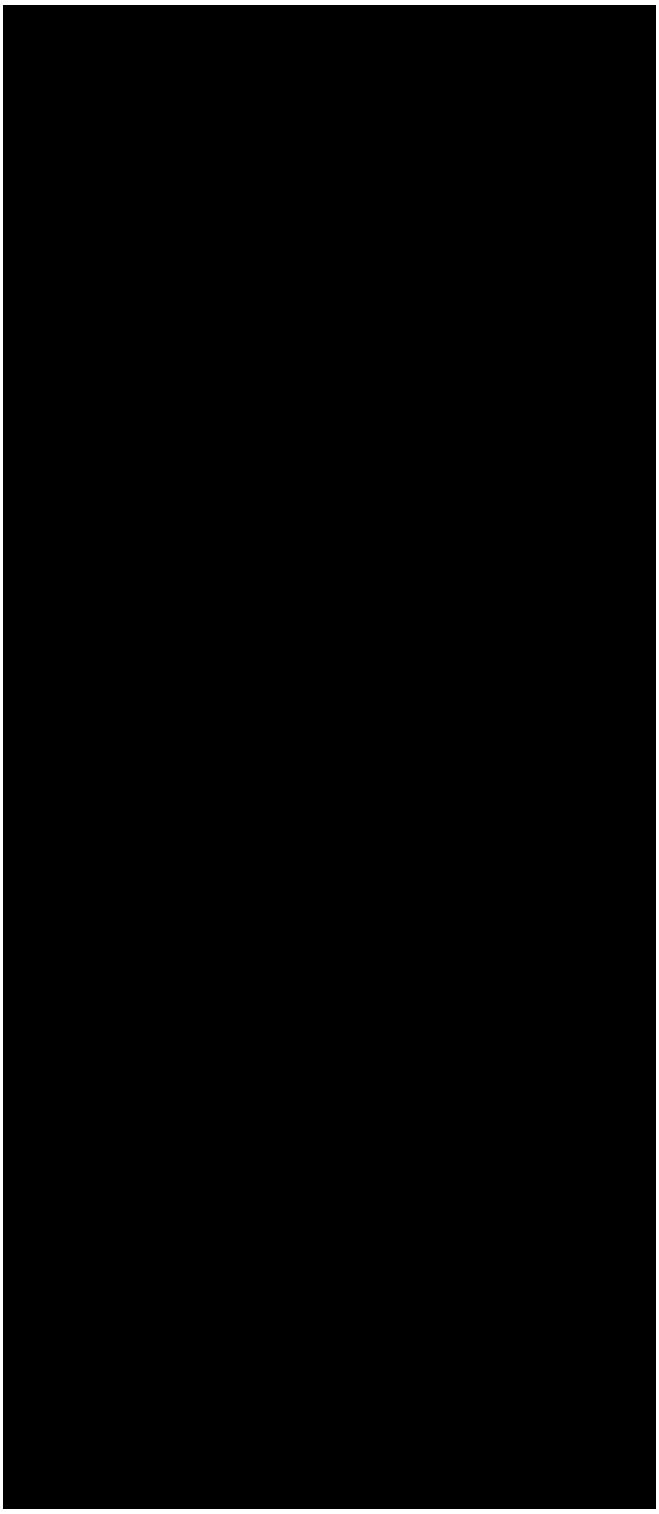
Figure 4 Comparison of Patient Baseline Traits for Studies in 3-month CDA Network

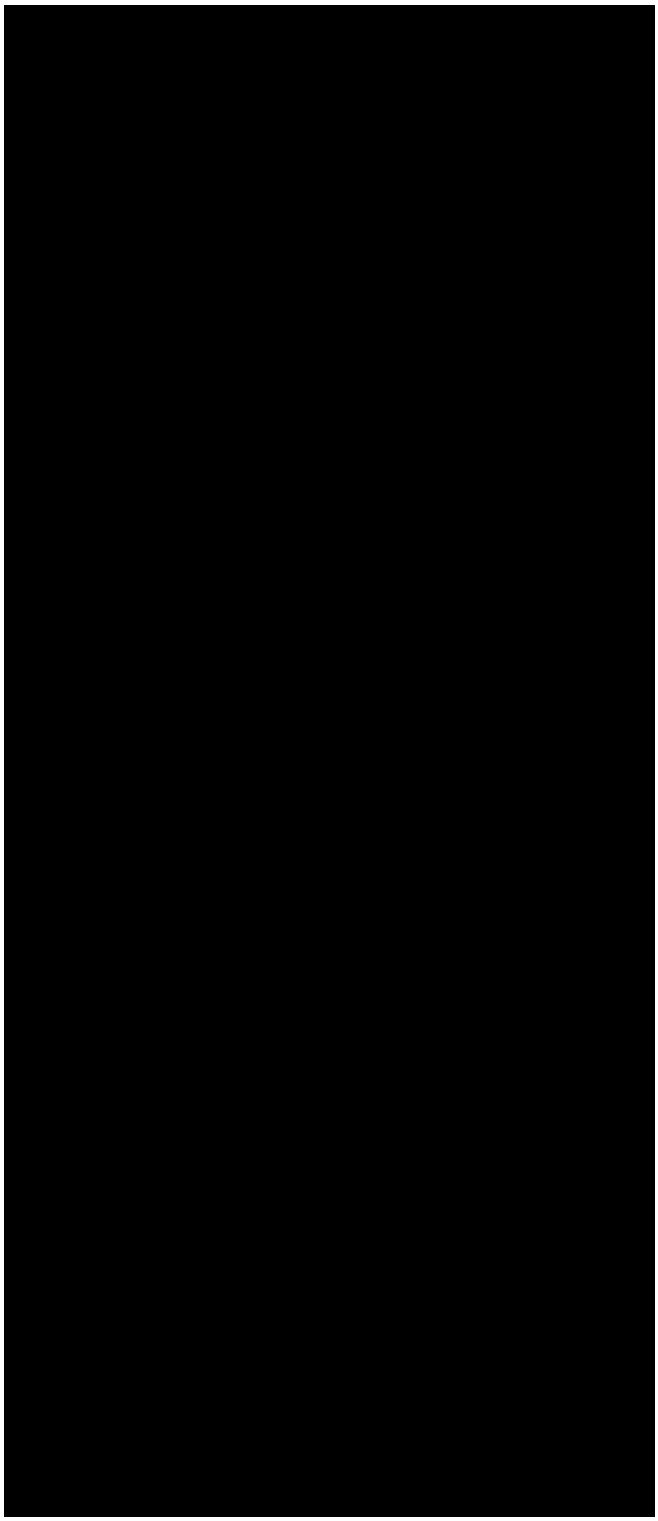


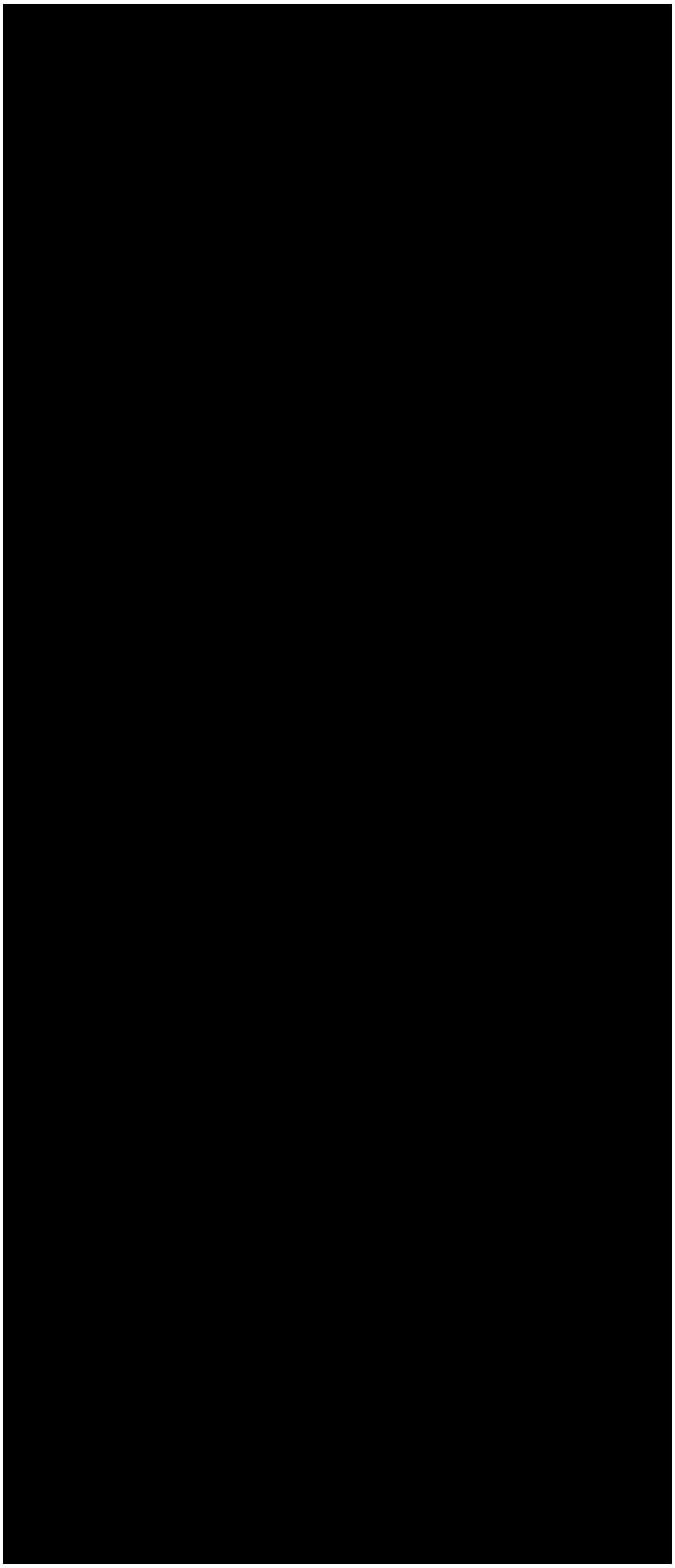






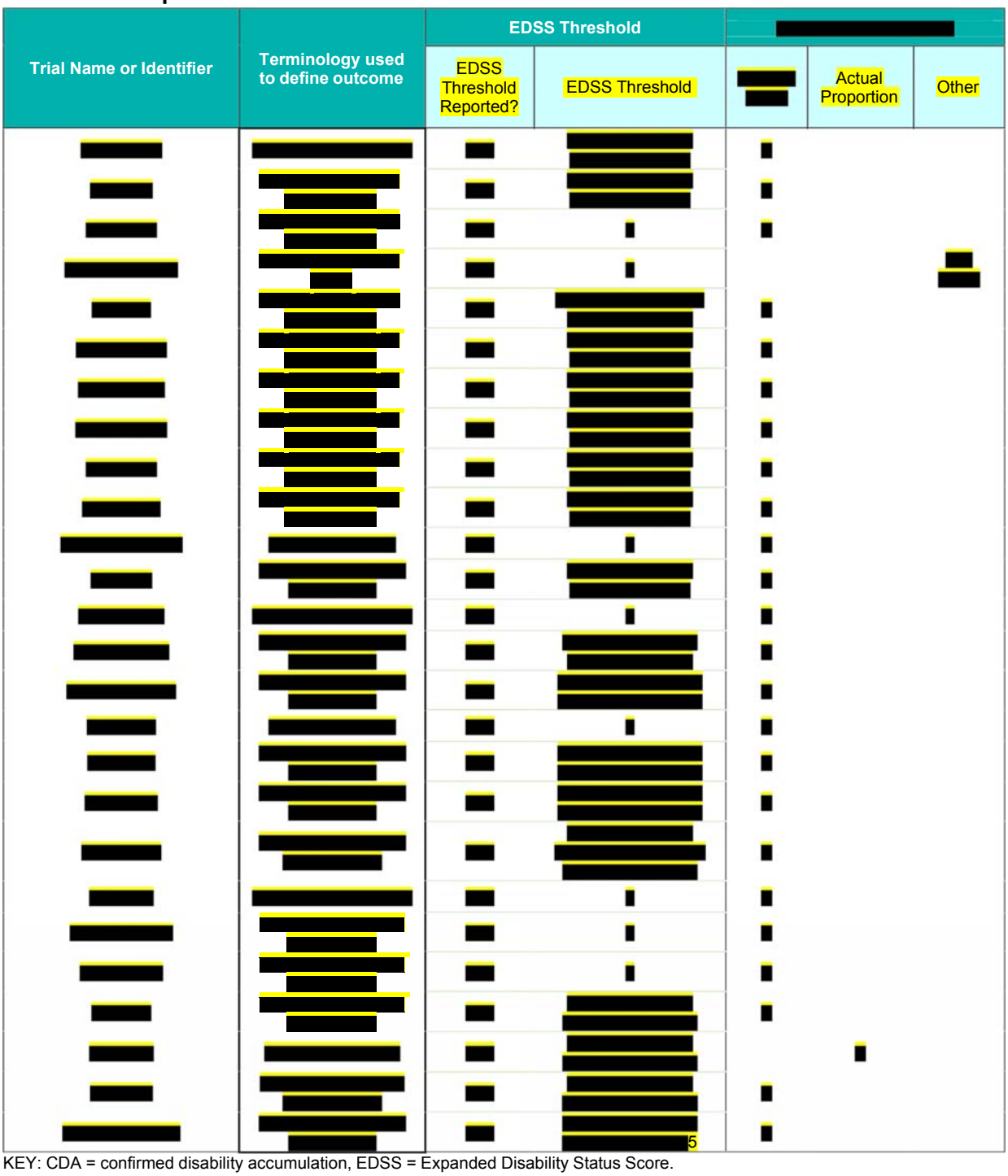






*Median baseline data was used in place of mean baseline data.KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability aaccumulation, CLA = cladribine, DMF = dimethyl fumarate, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod; PEG = peginterferon; PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, RRMS = relapsing-remitting multiple sclerosis, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Table 16: Comparison of Outcome Definitions for Studies in the 3-month CDA Network



KEY: CDA = confirmed disability accumulation, EDSS = Expanded Disability Status Score.

Figure 5 Final Network Diagram for Main Analysis of 3-month CDA Reported as a Hazard Ratio

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability accumulation, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

C.1.3.1 Constructing Networks for Subgroup NMAs for 3-month CDA

C.1.3.1.1 Subgroups: RRMS

Sixteen trials were incorporated into a network restricted to data for RRMS patients (where three of these were inputted together as pooled data) (**Error! Reference source not found.**7).

Table 17: Trials and Regimens Included in 3-month CDA Subgroup Networks

	RRMS only
Trials incorporated	• [redacted] • [redacted]
Regimens incorporated	[redacted]
Regimens of interest that could not be incorporated due to lack of data	[redacted]

*ITT data incorporated per the assumptions stated above.
KEY: CDA = confirmed disability accumulation, DMT = disease modifying therapy, RRMS = relapsing-remitting multiple sclerosis.

C.1.3.1.2 Subgroups: Patients with highly active disease

[redacted]

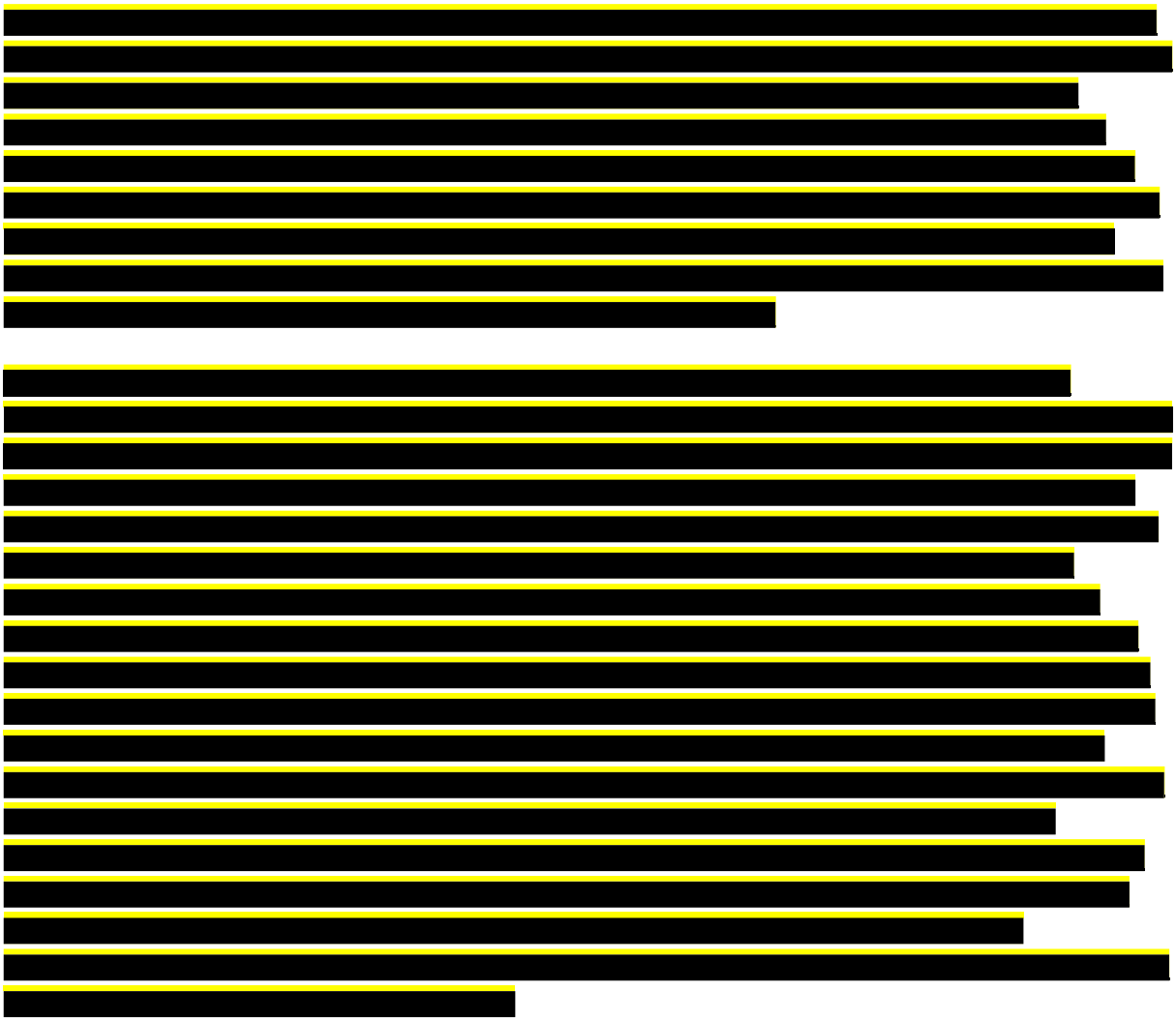


Table 18: Trials and Regimens Included in 3-month CDA Subgroup Network – Highly-Active Disease

Trials incorporated	Regimens incorporated	Definition of highly-active selected	Notes	Source
[redacted]				

Trials incorporated	Regimens incorporated	Definition of highly-active selected	Notes	Source
[redacted]				

*6-month CDA outcome data incorporated as stated above, given that 3-month CDA outcome data was not reported as a hazard ratio.
**ITT data incorporated as stated above, given that HA subgroup data was unavailable.
KEY: 4W: =every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, ARR = annualised relapse rate, CLA = cladribine, FIN = fingolimod, IFNB-1a = interferon beta-1a, IM = intramuscular, NAT= natalizumab, OCR = ocrelizumab, PBO = placebo, PON = ponesimod, SC = subcutaneous, TER = teriflunomide, TIW = three times per week, QD = every day, QW = every week.

C.1.4 Feasibility Assessment for NMA of 6-month CDA

[redacted]

[redacted]

[redacted]

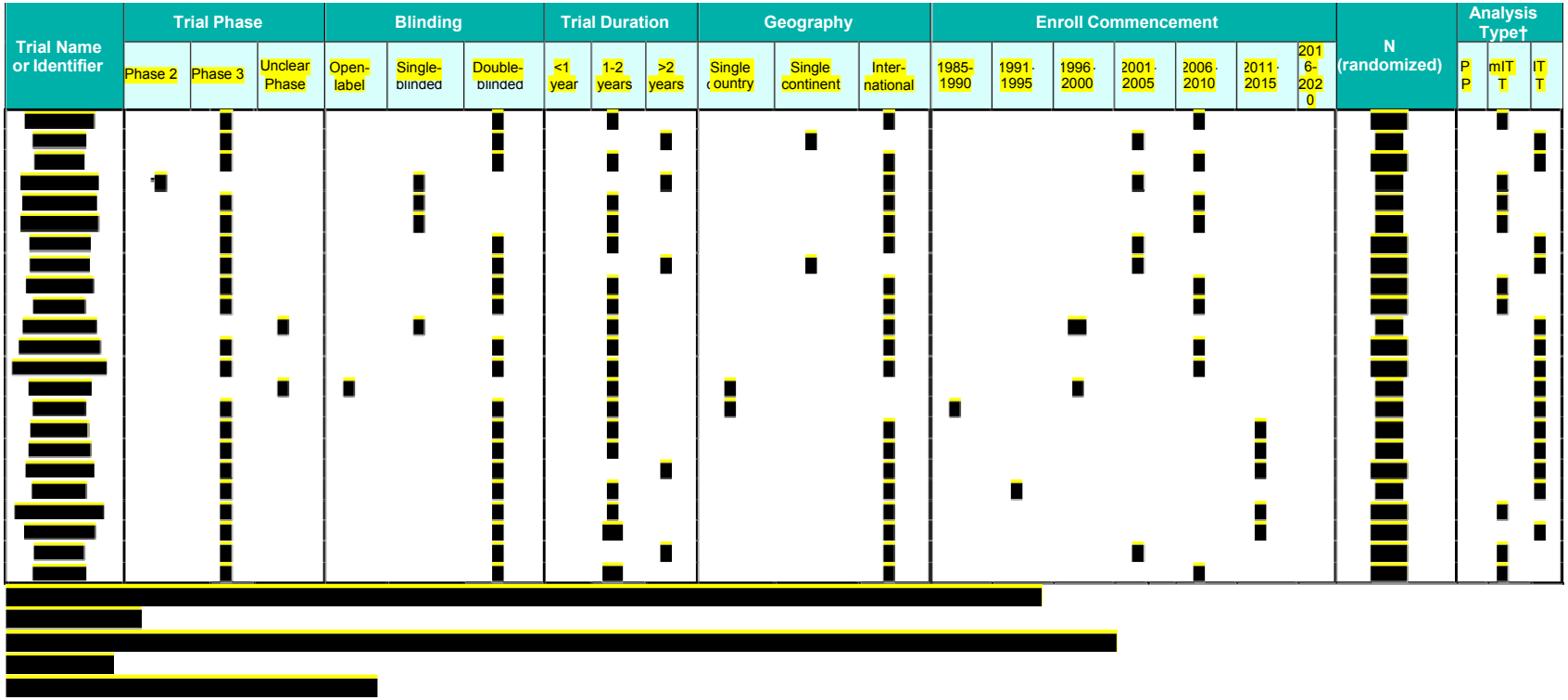
[redacted]

[redacted]

Figure 6 Initial Network Diagram for Main Analysis of 6-month CDA

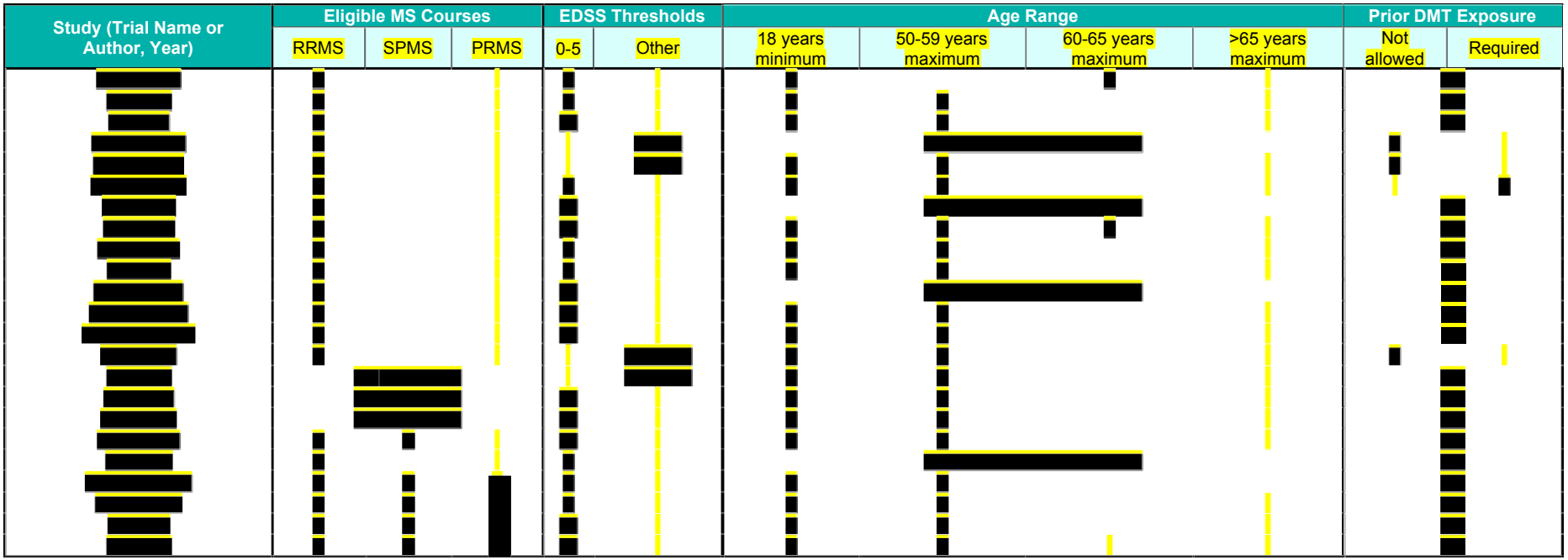
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability accumulation, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Table 19: **Comparison of Key Study Design Details for Studies in the 6-month CDA Network**



KEY: CDA= confirmed disability accumulation, ITT = intention-to-treat (randomized patients), mITT = modified intention-to-treat, PP = per protocol.

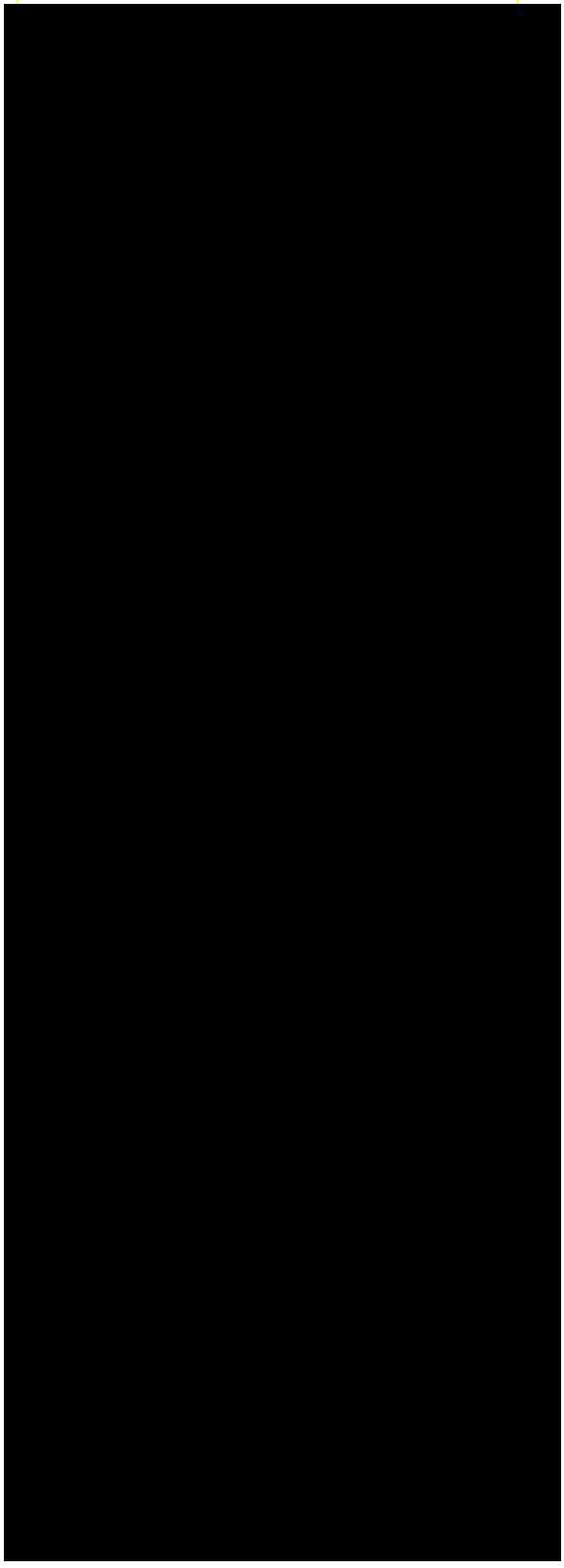
Table 20: **Comparison of Key Eligibility Criteria for Studies in the 6-month CDA Network**

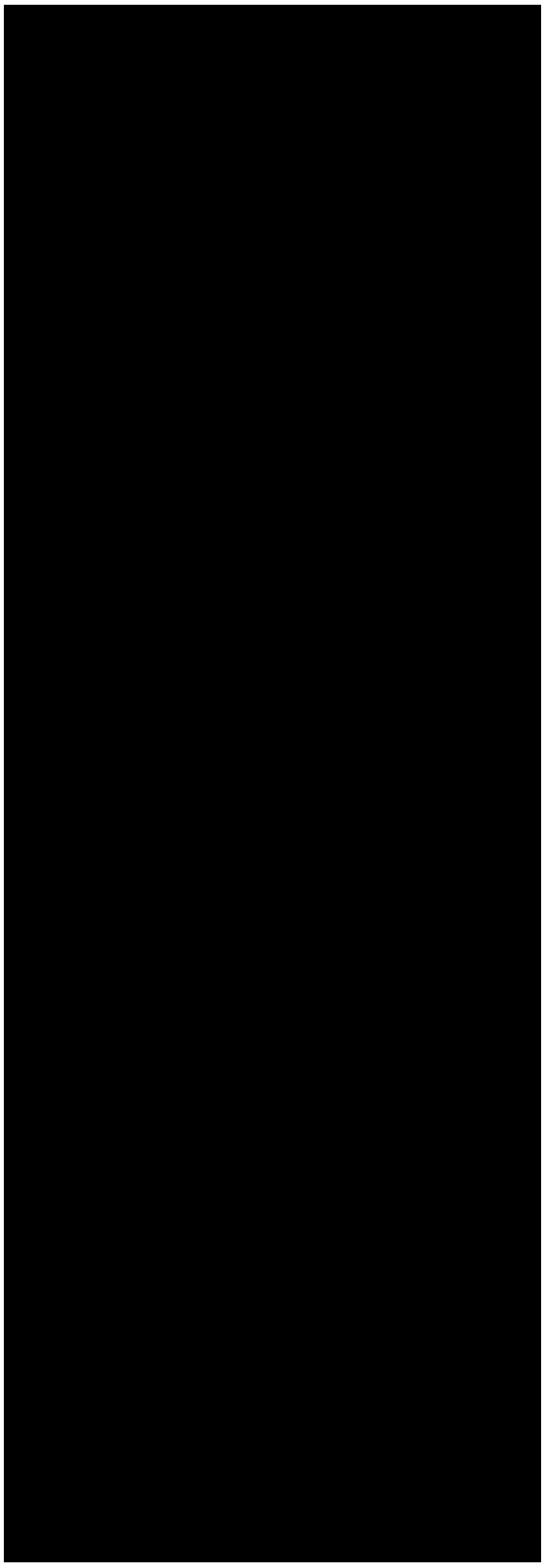


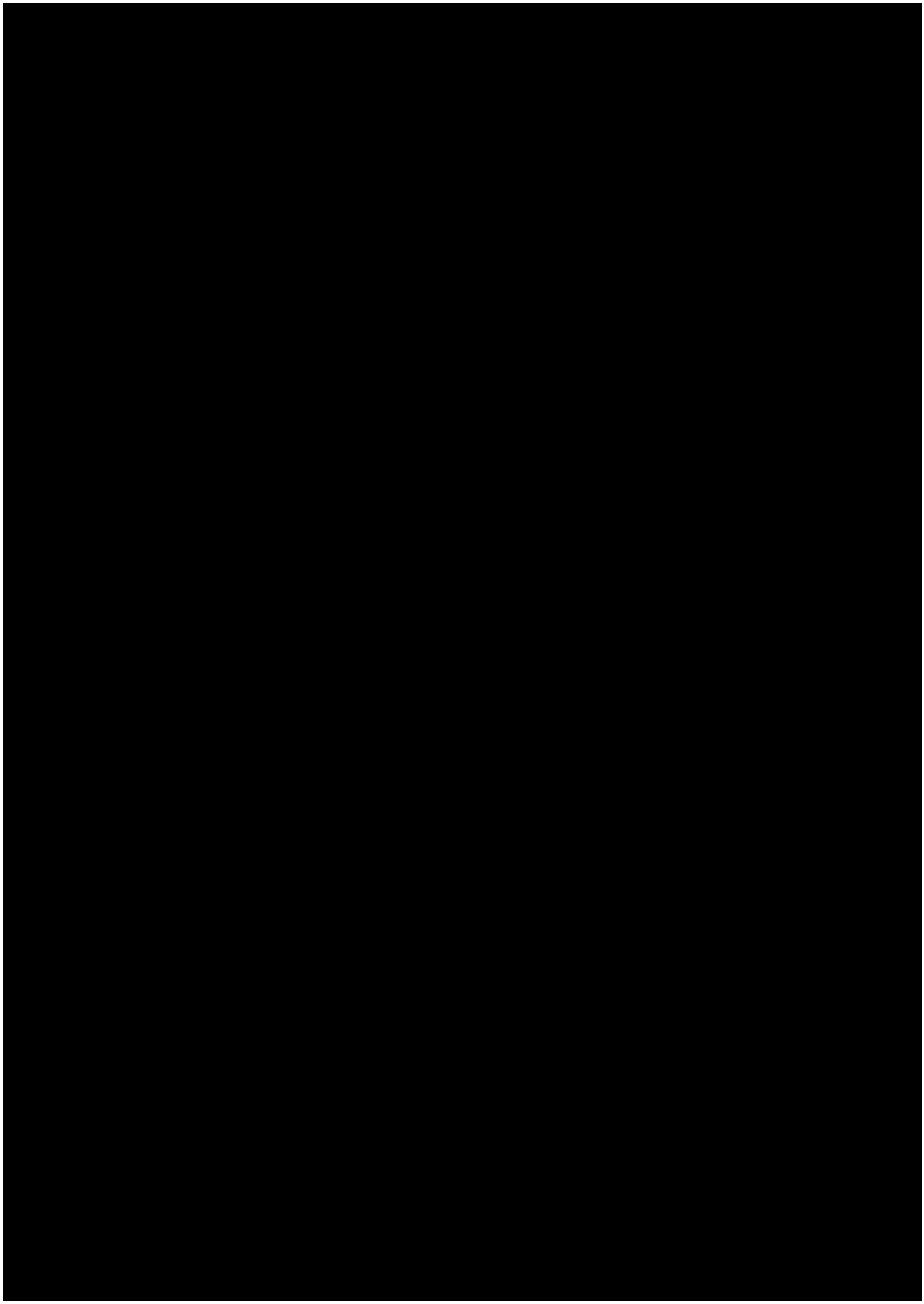
*Patients with EDSS scores ranging from 0 to 5.5 were eligible

KEY: CDA= confirmed disability accumulation, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, MS = multiple sclerosis, NR = not reported, PRMS = progressive-relapsing multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary-progressive multiple sclerosis, yrs = years.

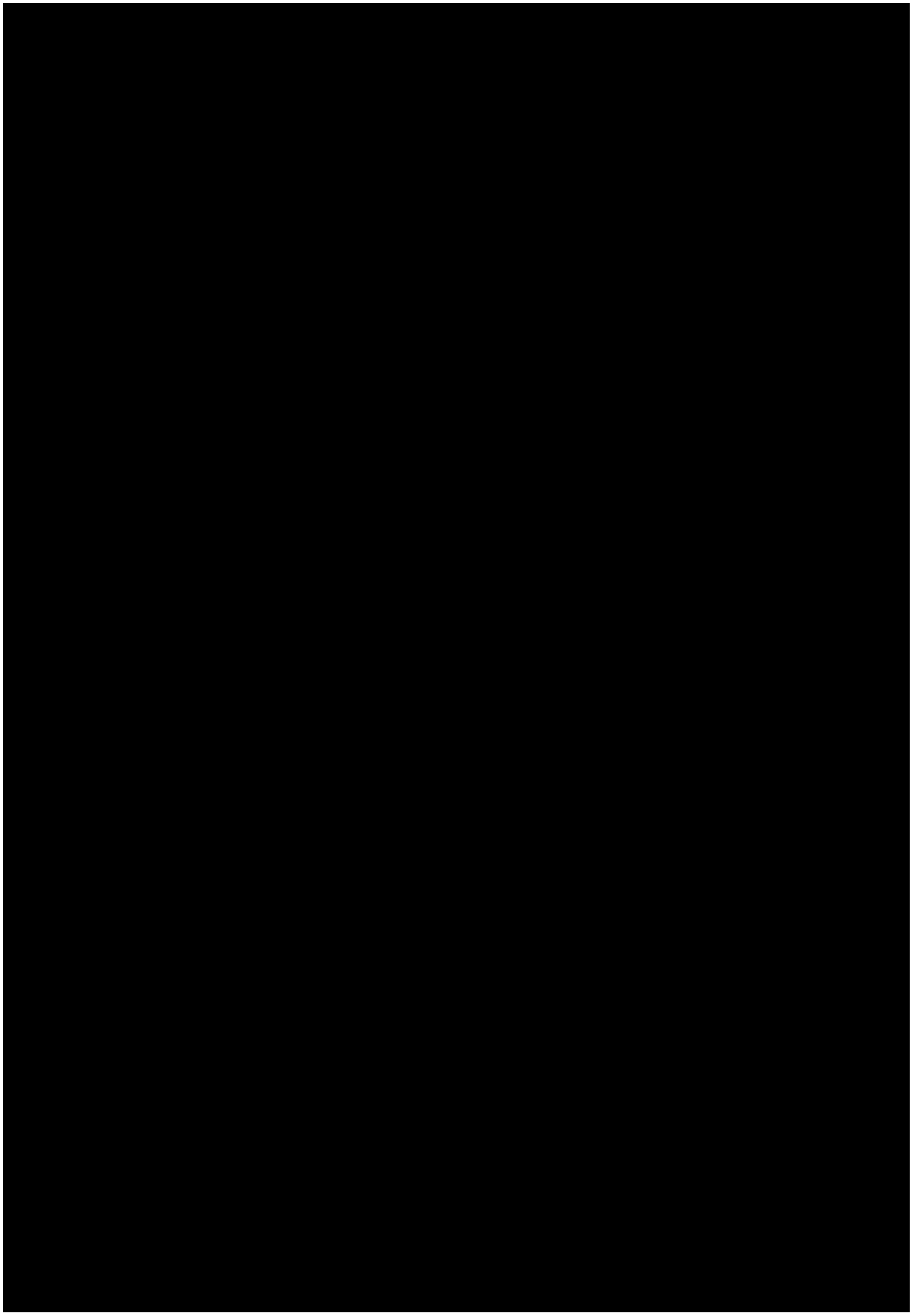
Figure 7 Comparison of Patient Baseline Traits for Studies in 6-month CDA Network

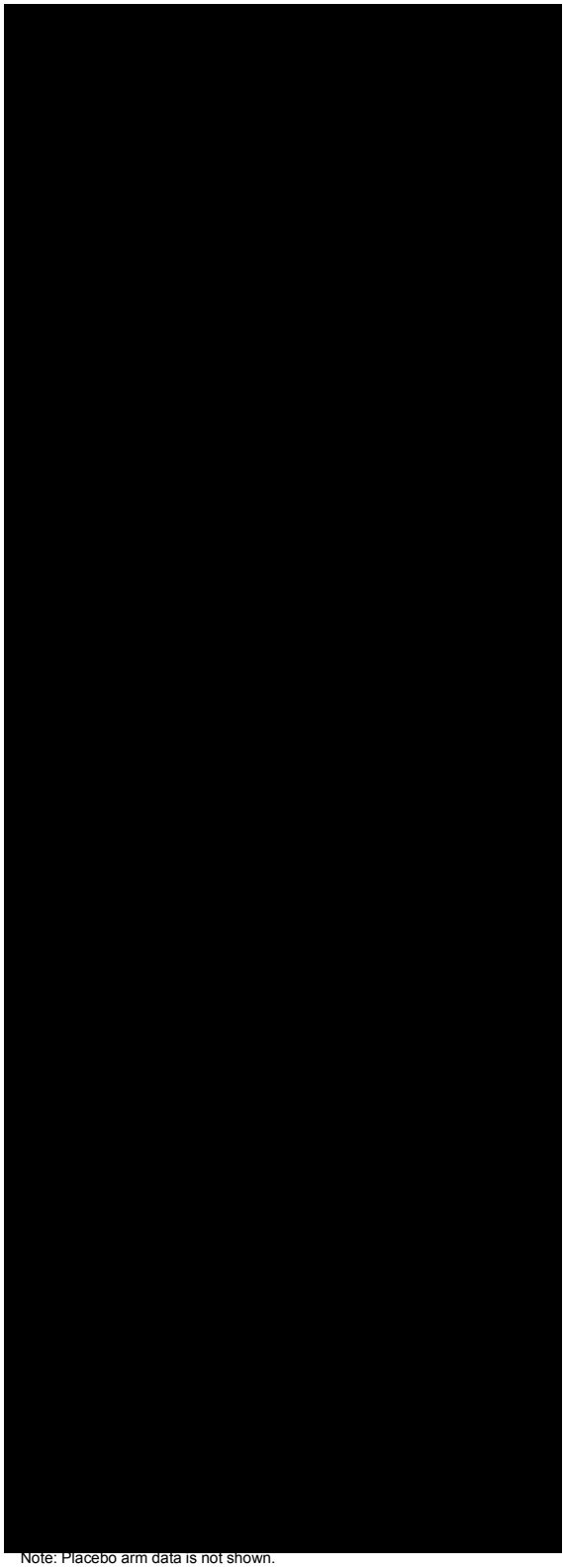






Company evidence submission for ponesimod for relapsing MS [ID1393]





Note: Placebo arm data is not shown.
*Median baseline data was used in place of mean baseline data.KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability aaccumulation, CLA = cladribine, DMF = dimethyl fumarate, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod; PEG = peginterferon; PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, RRMS = relapsing-remitting multiple sclerosis, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

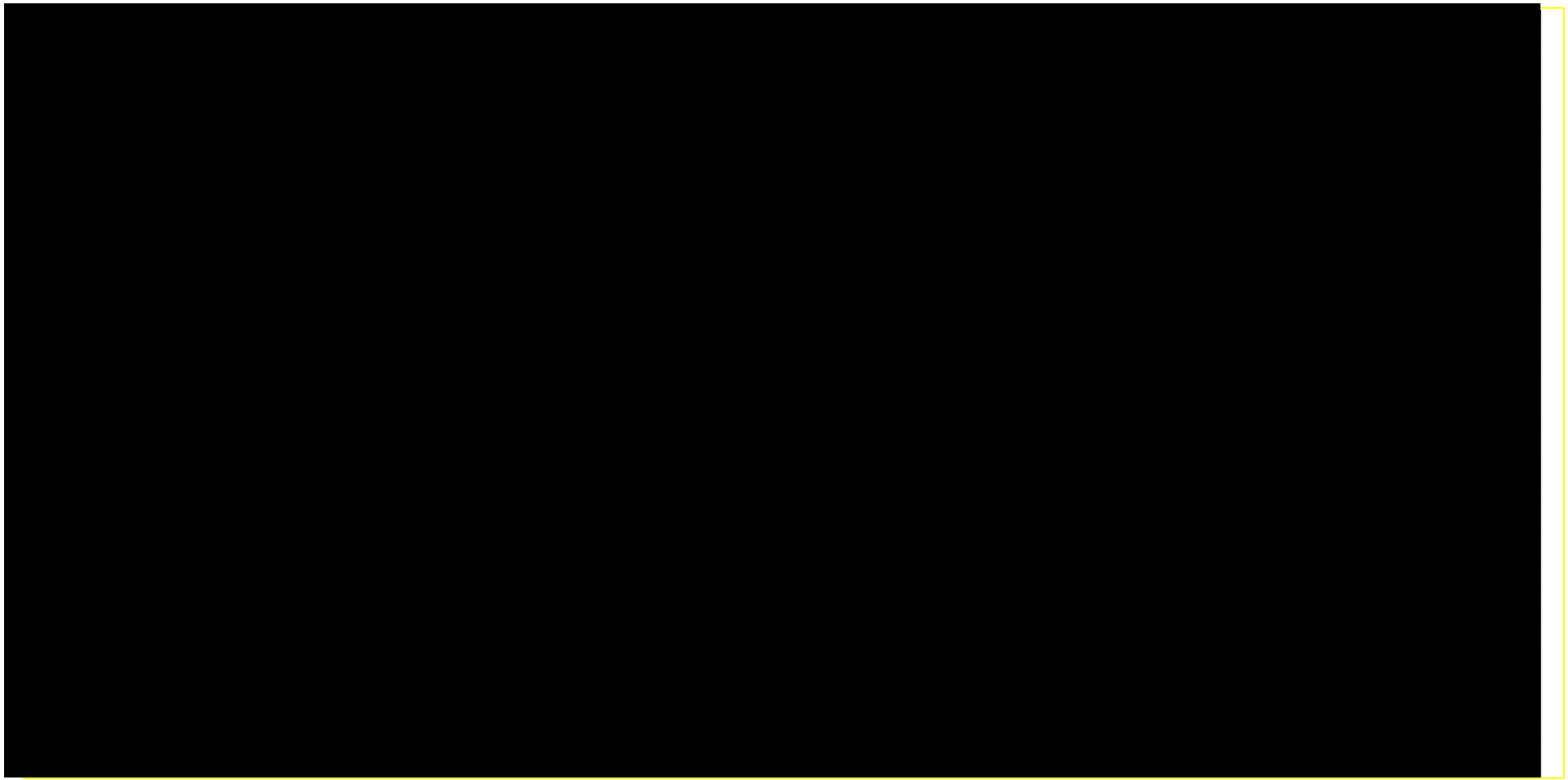
Table 21: Comparison of Outcome Definitions for Studies in the 6-month CDA Network

Trial Name or Identifier	Terminology used to define outcome	EDSS Threshold		Determination Method		
		EDSS Threshold Reported?	EDSS Threshold	Not Reported	Kaplan-Meier	Other

Trial Name or Identifier	Terminology used to define outcome	EDSS Threshold		Determination Method		
		EDSS Threshold Reported?	EDSS Threshold	Not Reported	Kaplan-Meier	Other

KEY: CDA = confirmed disability accumulation, EDSS = Expanded Disability Status Score.

Figure 8 Network Diagram for Main Analysis of 6-month CDA (Reported as a Hazard Ratio)



KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability accumulation, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

C.1.4.1 Constructing Networks for Subgroup NMAs for 6-month CDA

C.1.4.1.1 Subgroups: RRMS

Fourteen trials were incorporated into a network restricted to data for RRMS patients.

Table 22: Trials and Regimens Included in 6-month CDA Subgroup Networks

Network Details	RRMS only
Trials incorporated	• [redacted]
Regimens incorporated	1. [redacted] 10. [redacted]
[redacted]	[redacted]

*ITT data incorporated per the assumptions stated above.
KEY: CDA = confirmed disability accumulation, DMT = disease modifying therapy, ITT = intention-to-treat, RRMS = relapsing-remitting multiple sclerosis.

C.1.4.1.2 Subgroups: Patients with highly active disease

[redacted]

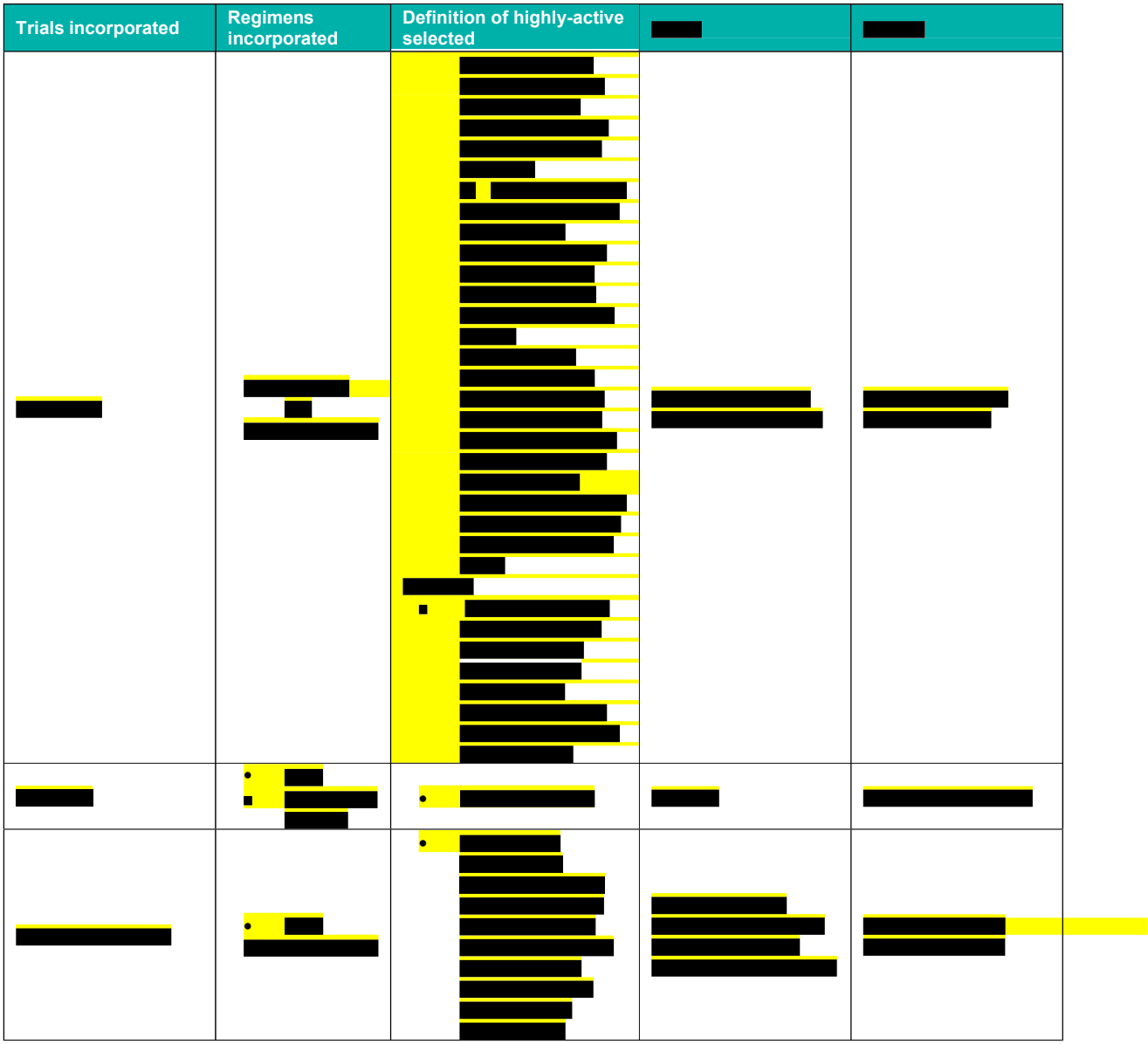
[redacted]

[redacted]

Table 23: Trials and Regimens Included in 6-month CDA Subgroup Network – Highly-Active Disease

Trials incorporated	Regimens incorporated	Definition of highly-active selected	Notes	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trials incorporated	Regimens incorporated	Definition of highly-active selected	Notes	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



*ITT data incorporated as stated above, given that HA subgroup data was unavailable.
KEY: 24W = every 24 weeks, ALE = alemtuzumab, CLA = cladribine, DMD = disease modifying drug, DMT = disease modifying therapy, EMA= European Medicines Agency, EDSS = Expanded Disability Status Scale, Fin = fingolimod, Gd = Gadolinium, HA= highly-active, IFNB-1a = interferon β-1a, ITT = intention-to-treat, MRI = magnetic resonance imaging, MS = multiple sclerosis, NAT = natalizumab, NICE = National institute for Health and Care Excellence, OCR = ocrelizumab, PBO = placebo, PON = ponesimod, QD = everyday, RES = rapidly evolving severe, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

C.1.5 Feasibility Assessment for NMA of All-cause Treatment Discontinuation

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Figure 9 Network Diagram for Main Analysis of All-cause Treatment Discontinuations

KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Table 24 Comparison of Key Study Design Details for Studies in the All-cause Treatment Discontinuations Network

Trial Name or Identifier	Trial Phase			Blinding			Trial Duration			Geography			Enroll Commencement							N (randomized)	Analysis Type†		
	Phase 2	Phase 3	Unclear Phase	Open-label	Single-blinded	Double-blinded	<1 year	1-2 years	>2 years	Single country	Single continent	International	1985 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2010	2011 - 2015	2016 - 2020		PP	mITT	ITT
ADVANCE																							
AFFIRM																							
APEX Part I																							
ASSESS																							
BEYOND																							
Boiko, 2018 (GA)																							
BRAVO																							
CAMMS223																							
CARE-MS I																							
CARE-MS II																							
CLARITY																							
CombiRx																							
CONFIRM																							
COPOLYMER 1																							
DEFINE																							
Eur/Can GA																							
EVIDENCE																							
FREEDOMS																							
FREEDOMS II																							
GALA																							
GATE																							
GLACIER																							
IMPROVE																							

Trial Name or Identifier	Trial Phase			Blinding			Trial Duration			Geography			Enroll Commencement							N (randomized)	Analysis Type†		
	Phase 2	Phase 3	Unclear Phase	Open-label	Single-blinded	Double-blinded	<1 year	1-2 years	>2 years	Single country	Single continent	International	1985 - 1990	1991 - 1995	1996 - 2000	2001 - 2005	2006 - 2010	2011 - 2015	2016 - 2020		PP	mITT	ITT
INCOMIN																							
Mokhber, 2015																							
OPERA I																							
OPERA II																							
OPTIMUM																							
Ph2/Evobrutinib/Montalban																							
Ph2/NAT/Saida																							
Ph2/OCR/Kappos																							
Ph2/PON/Olsson																							
PRISMS																							
RADIANCE A																							
RADIANCE B																							
REFORMS																							
Saida, 2012 Fin																							
SUNBEAM																							
TEMSO																							
TENERE																							
TER-MS																							
TOWER																							
TRANSFORMS																							

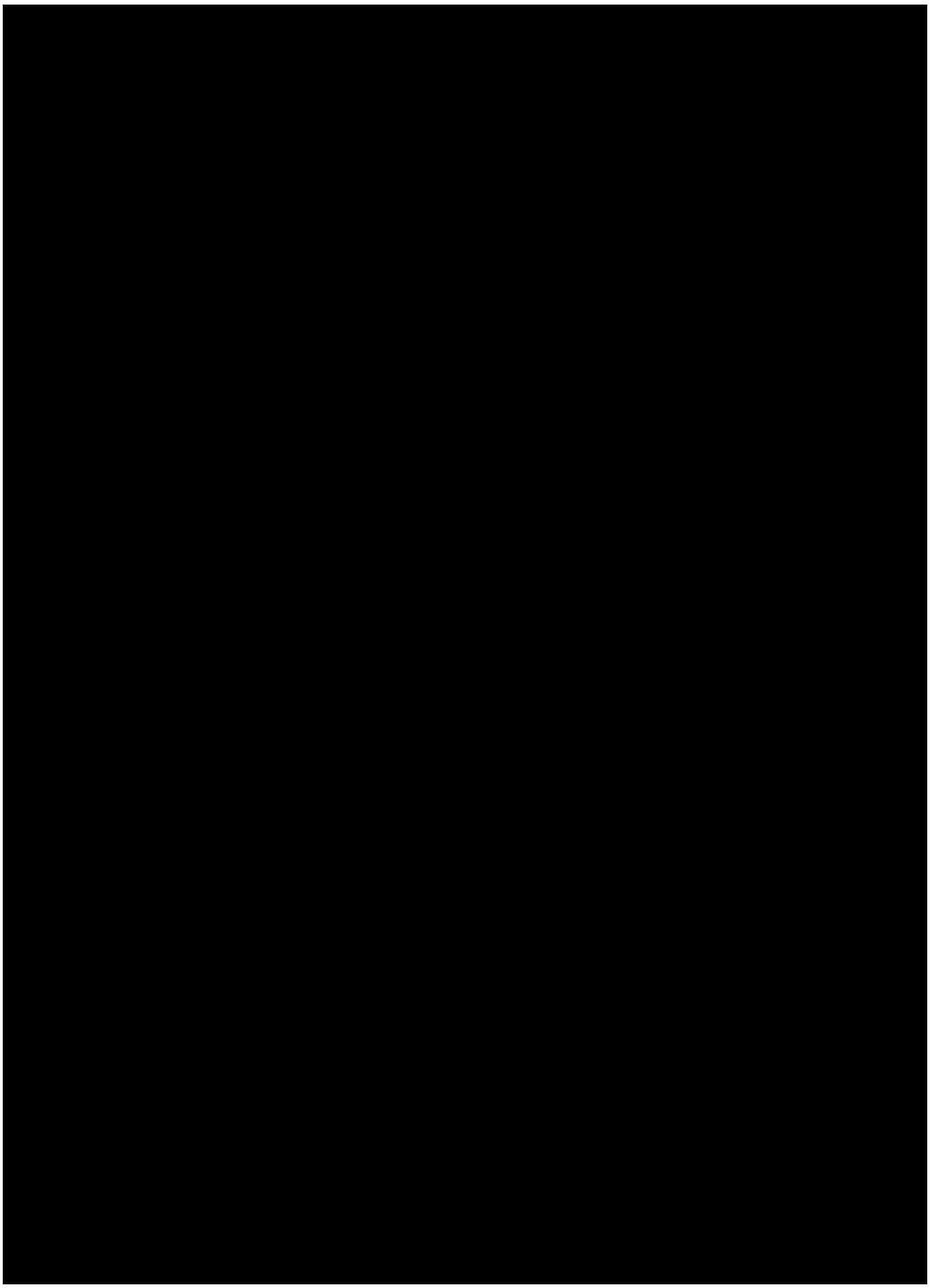
*In some cases, the enrollment commencement date was unclear, and the presented dates were inferred from main study publication date.
**One arm of study received open-label treatment, dimethyl fumarate twice daily.
†Analysis population was determined based on author descriptions of the analyses, rather than the terminology utilized in the main publications.
‡ Studies had variable follow-up. Mean or median treatment duration was considered.
KEY: ARR = annualised relapse rate, ITT = intention-to-treat (randomized patients), mITT = modified intention-to-treat, PP = per protocol.

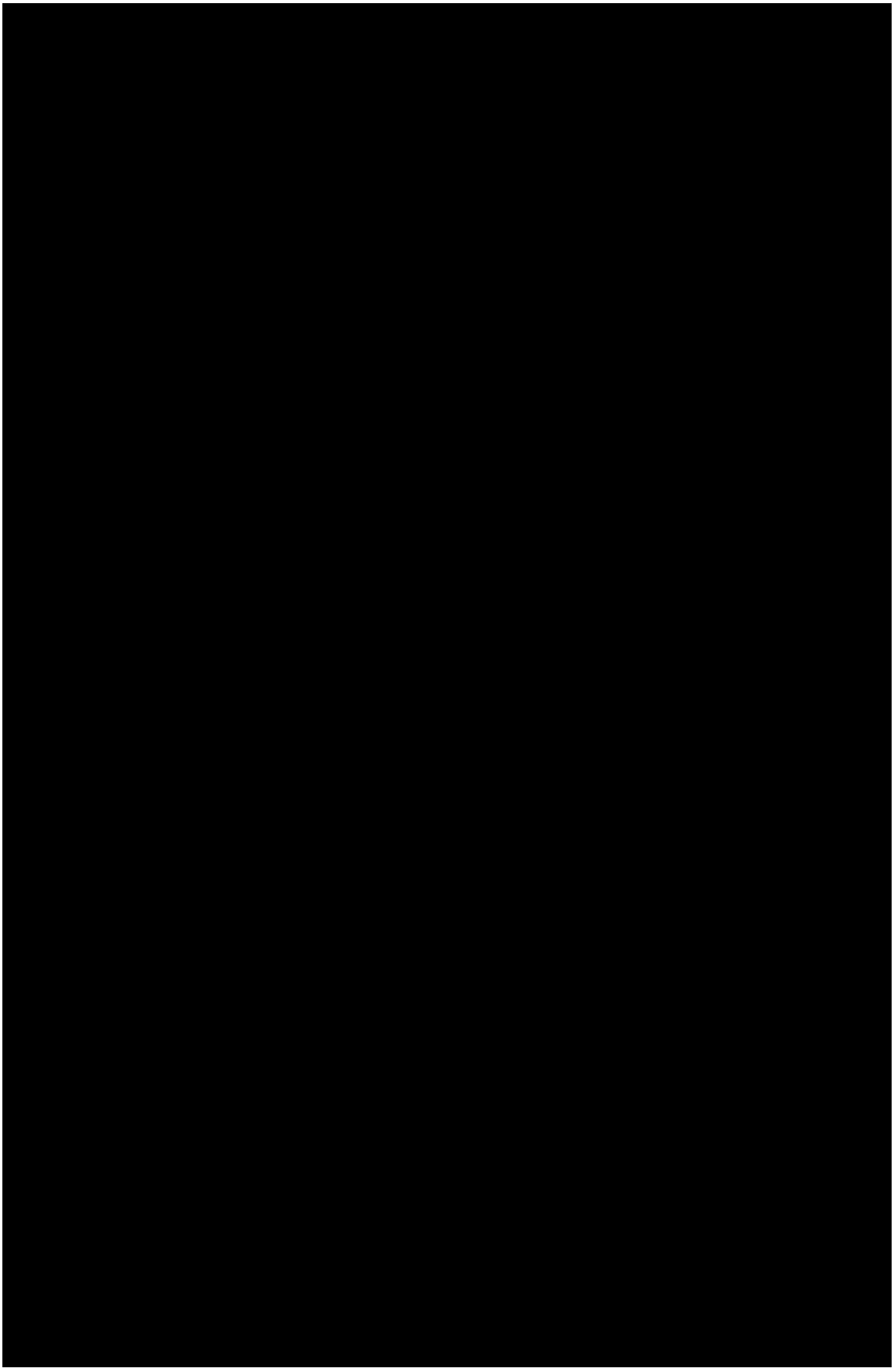
Table 25: Comparison of Key Eligibility Criteria for Studies in the All-cause Treatment Discontinuations Network

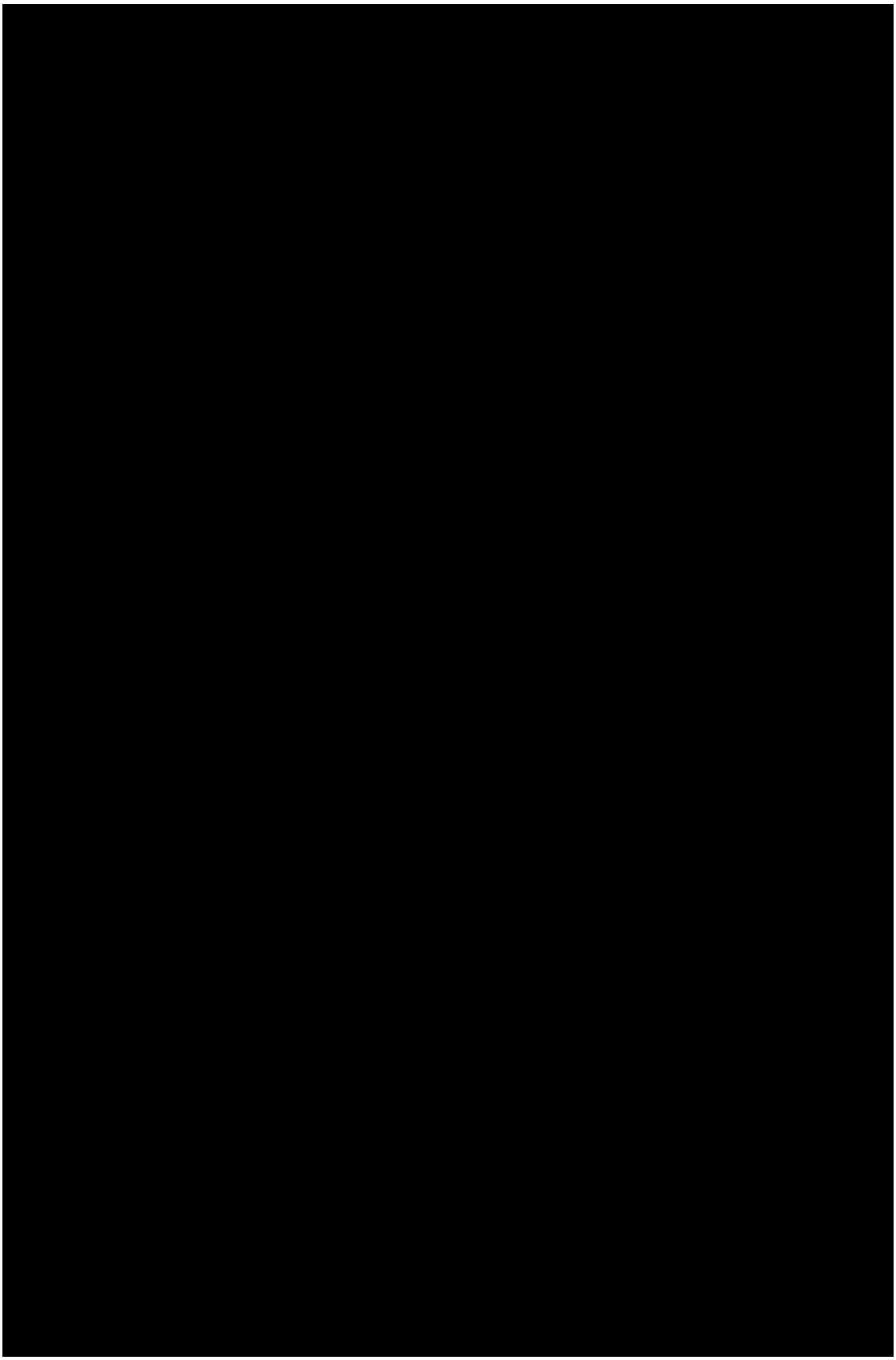
Trial Name or Identifier	Eligible MS Courses			EDSS Range		Age Range				Prior DMT Exposure	
	RRMS	SPMS	PRMS	0-5	Other	18 years minimum	50-59 years maximum	50-65 years maximum	65 years maximum	Not allowed	Required
ADVANCE											
AFFIRM											
APEX Part I											
ASSESS											
BEYOND											
Boiko, 2018 (GA)											
BRAVO											
CAMMS223											
CARE-MS I											
CARE-MS II											
CLARITY											
CombiRx											
CONFIRM											
COPOLYMER 1											
DEFINE											
Eur/Can GA											
EVIDENCE											
FREEDOMS											
FREEDOMS II											
GALA											
GATE											
GLACIER											
IMPROVE											
INCOMIN											
Mokhber, 2015											
OPERA I											
OPERA II											
OPTIMUM											
Ph2/Evobrutinib/Montalban											
Ph2/NAT/Saida											
Ph2/OCR/Kappos											
Ph2/PON/Olsson											
PRISMS											
RADIANCE A											
RADIANCE B											
REFORMS											
Saida, 2012 Fin											
SUNBEAM											
TEMSO											
TENERE											
TER-MS											
TOWER											
TRANSFORMS											

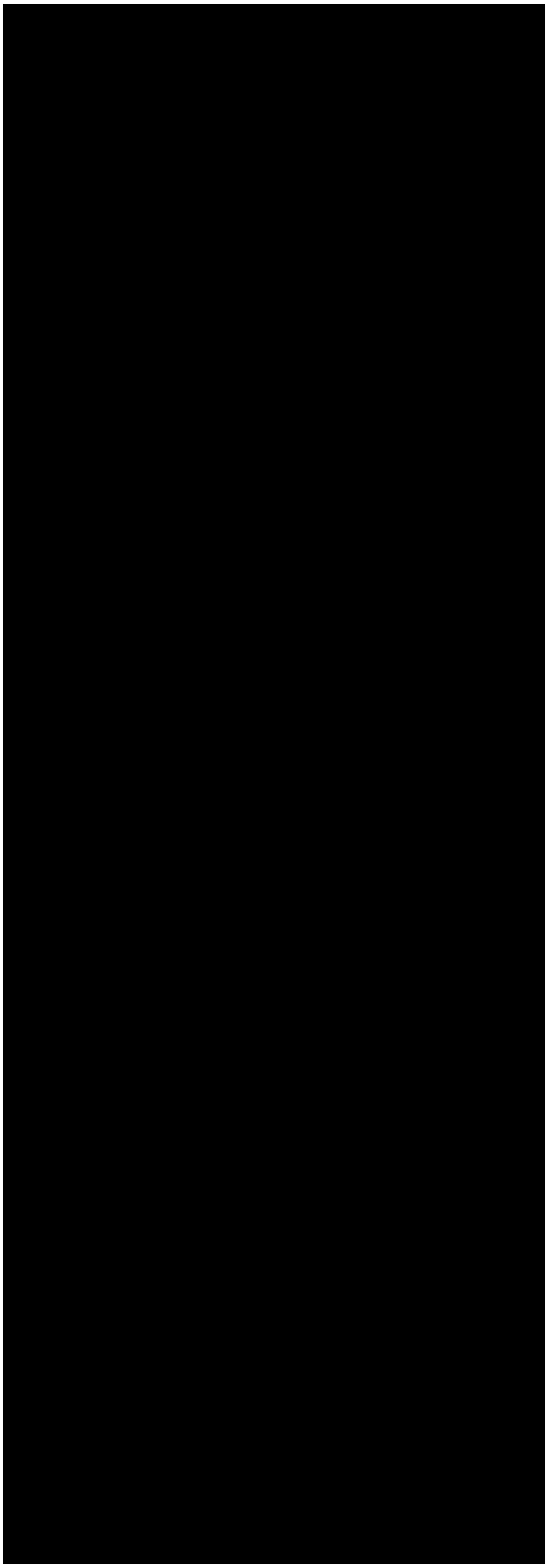
[redacted]

Figure 10 Patient Baseline Traits for Studies in All-cause Treatment Discontinuations





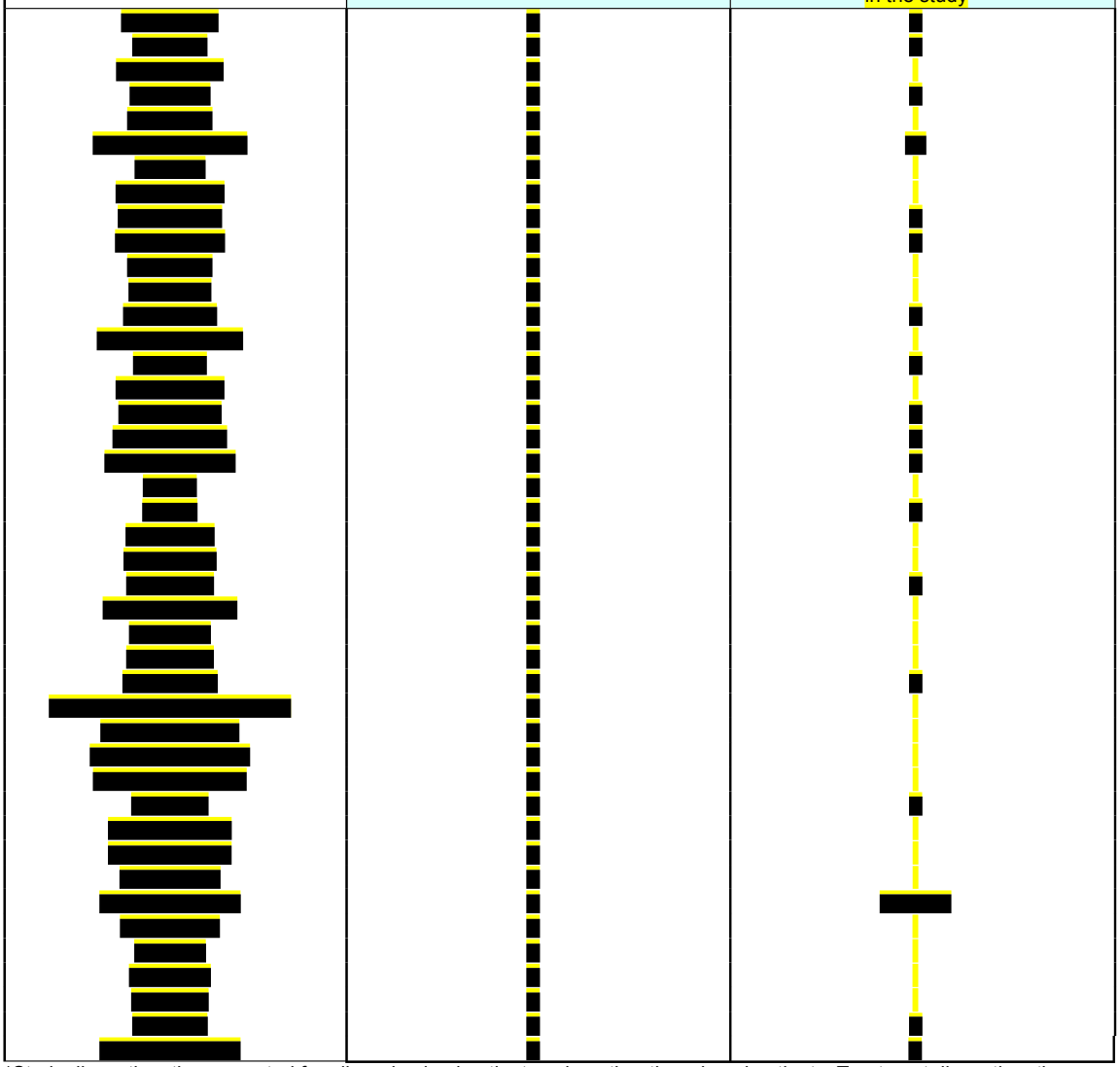




*Median baseline data was used in place of mean baseline data.
KEY: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CDA = confirmed disability aaccumulation, CLA = cladribine, DMF = dimethyl fumarate, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OZA = ozanimod; PEG = peginterferon; PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, RRMS = relapsing-remitting multiple sclerosis, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Table 26: Comparison of Reporting for All-cause Treatment Discontinuations Outcome

Trial Name or Identifier	Reporting of discontinuations	
	Authors reported discontinuations from study	Authors reported proportion of patients who discontinued treatment but remained in the study



*Study discontinuations reported for all randomized patients only, rather than dosed patients. Treatment discontinuations on-study were reported but not considered since it was unclear whether the group was mutually exclusive from study discontinuations.

C1.5.1 Constructing Networks for Subgroup NMAs for All-cause Treatment Discontinuations

Subgroups analyses of RRMS patients was not pursued, as this data was lacking from the OPTIMUM trial.

C.2 Risk of Bias

[redacted]

Appendix D. Updated Network Meta Analyses for Technical Engagement

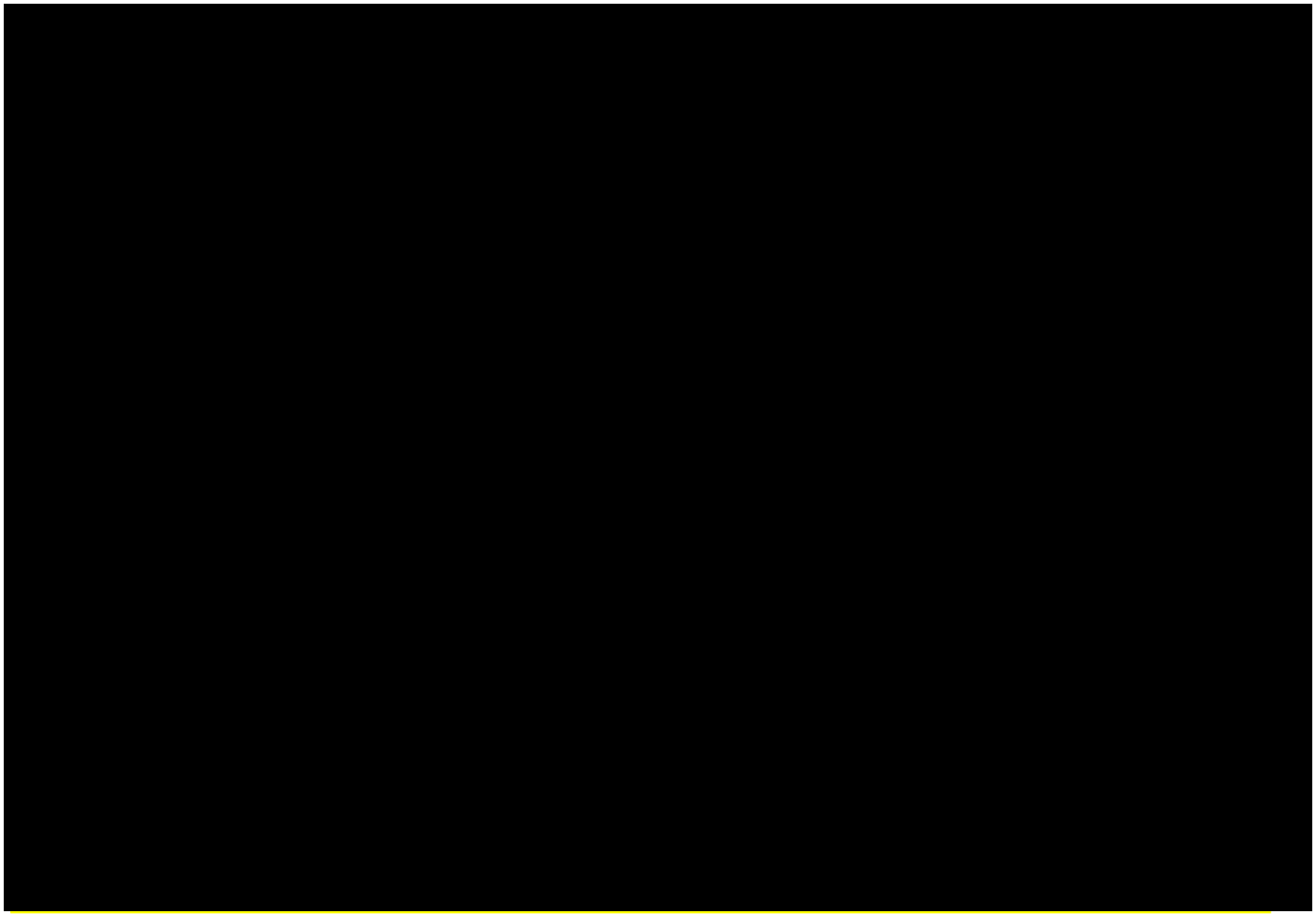
D.1 NMAs Considering Interferons Regimens as a Class Effect

[redacted]

D.1.1 Annualised relapse rate

[redacted]

Figure 11 Evidence network for ARR, considering interferon regimens as a class



acetate, IFN=interferons, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, TER = teriflunomide, TIW = three times per week.

[redacted]

Figure 12 NMA Results for ARR, considering interferon regimens as a class (fixed effects). Effect estimates less than 1 indicate that ponesimod is favoured.

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferons, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide, TIW = three times per week.

Figure 13 NMA Results for ARR, considering interferon regimens as a class (random effects with vague priors). Effect estimates less than 1 indicate that ponesimod is favoured.

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, ARR = annualised relapse rate, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferons, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide, TIW = three times per week.

D.1.2 3-month CDA

The EVIDENCE trial was excluded due to evaluating only interferon regimens. Overall, as shown in **Error! Reference source not found.**, 24 trials (with 13 treatment regimens) have been included in this analysis, of which 12 were anchored to the interferon node.

Figure 14 Evidence network for 3-month CDA, considering interferon regimens as a class

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN=interferons, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, TER = teriflunomide.

[redacted]

Figure 15 NMA Results for 3-month CDA, considering interferon regimens as a class (fixed effects). Effect estimates less than 1 indicate that ponesimod is favoured.


[redacted]

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide.

Figure 16 NMA Results for 3-month CDA, considering interferon regimens as a class (random effects with vague priors).

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide.

D.1.3 6-month CDA

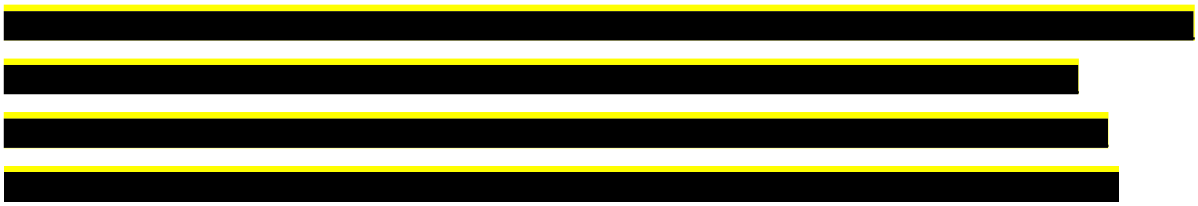


Figure 17 Evidence network for 6-month CDA, considering interferon regimens as a class

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN=interferons, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, TER = teriflunomide

[redacted]

Figure 18 NMA Results for 6-month CDA, considering interferon regimens as a class (fixed effects).


[redacted]

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide.

Figure 19 NMA Results for 6-month CDA, considering interferon regimens as a class (random effects with vague priors). Effect estimates less than 1 indicate that ponesimod is favoured.

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide.

D.1.4 All-cause treatment discontinuations

[redacted]

Figure 20 Evidence network for all cause treatment discontinuations, considering interferon regimens as a class

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN=interferon, kg = kilogram, mg = milligram, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, TER = teriflunomide, TIW = three times per week.

[redacted]

Figure 21 NMA Results for all-cause treatment discontinuations, considering interferon regimens as a class (fixed effects).

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide, TIW = three times per week.

Figure 22 NMA Results for all-cause treatment discontinuations, considering interferon regimens as a class (random effects with vague priors)

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Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFN = interferon, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, RR = rate ratio, TER = teriflunomide, TIW = three times per week.

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D.2 NMAs Excluding ADVANCE and INCOMIN

[redacted]

[redacted]

[redacted]

[redacted]

D.2.1 Annualised relapse rate

[redacted]

Figure 23 Evidence network for ARR, excluding ADVANCE and INCOMIN

dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC=subcutaneous, TER = teriflunomide, TIW = three times per week.

Figure 24 NMA results for ARR, excluding ADVANCE and INCOMIN (fixed effects).

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, kg = kilogram, mg = milligram. NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, QOD = every other day, QW = weekly, RR = rate ratio, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

D.2.2 3-month CDA

[redacted]

Figure 25 Evidence network for 3-month CDA, excluding ADVANCE

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, , IFNB-1b = interferon β-1b, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC=subcutaneous, TER = teriflunomide, TIW = three times per week.

Figure 26: NMA results for 3-month CDA, excluding ADVANCE (fixed effects).

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, HR = hazard ratio, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram. NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

D.2.3 6-month CDA

[redacted]

Figure 27 Evidence network for 6-month CDA, excluding ADVANCE

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Figure 28 NMA results for 6-month CDA, excluding ADVANCE (fixed effects)

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Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, HR = hazard ratio, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram. NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

D.2.4 All-cause treatment discontinuations

Figure 29 Evidence network for all-cause discontinuations, excluding ADVANCE and INCOMIN

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer

OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous TER = teriflunomide, TIW = three times per week.

Figure 30 NMA results for all-cause treatment discontinuations, excluding ADVANCE and INCOMIN (random effects with vague priors).

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Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, CrI = credible interval, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, kg = kilogram, mg = milligram. NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, OR = odds ratio, PBO = placebo, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

D.3 Subgroup NMAs for patients with highly active disease: considering the definition used by NICE/NHSE

[redacted]

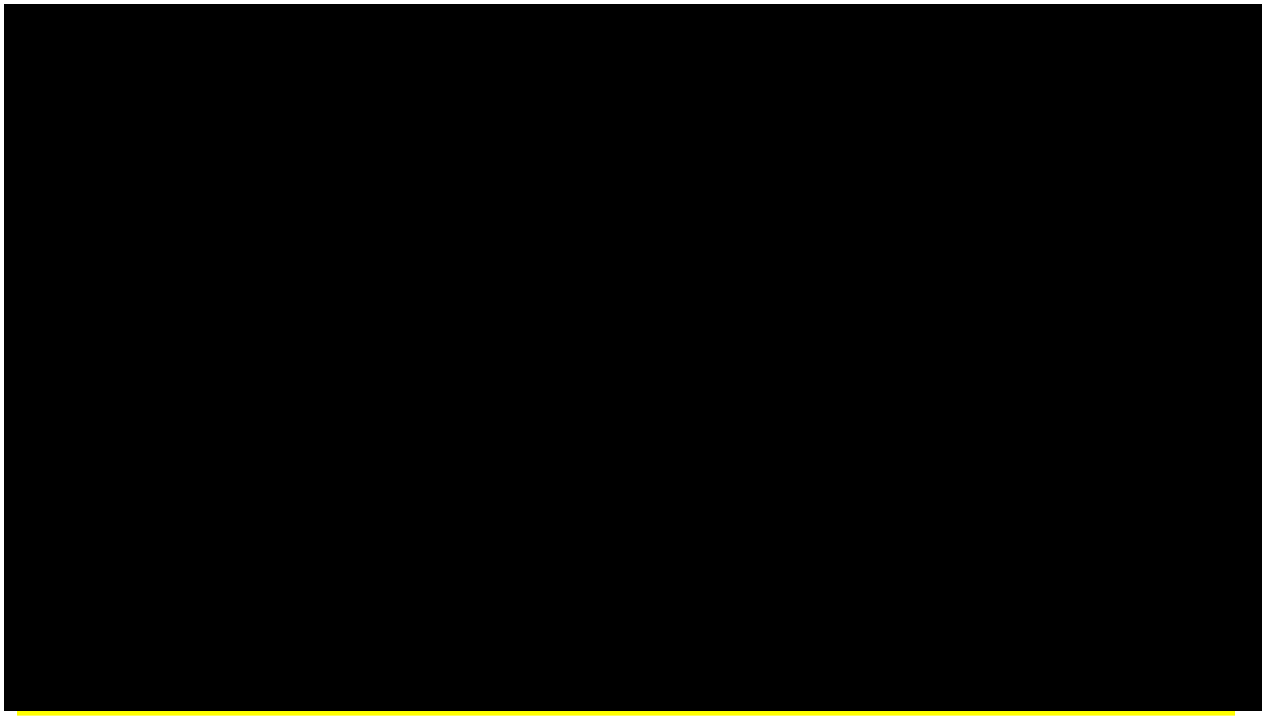
D.3.1 Annualised relapse rate

[redacted]

Figure 31 Network diagram for ARR: Highly active disease subgroup including ofatumumab, ozanimod and natalizumab

on β-1a, IM = intramuscular, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Figure 32 Results for highly active subgroup NMA of ARR, considering definition used by NICE (fixed effects).



Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, CLA = cladribine, CrI = credible interval, FIN = fingolimod, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, RR = rate ratio, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

D.3.2 3-month CDA

[redacted]

Figure 33 Network diagram for 3-month CDA: Highly active disease subgroup including ofatumumab, ozanimod and natalizumab

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, CLA = cladribine, FIN = fingolimod, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Figure 34 Results for highly active subgroup NMA of 3-month CDA, considering definition used by NICE.

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, CLA = cladribine, CrI = credible interval, FIN = fingolimod, HR = hazard ratio, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

D.3.3 6-month CDA

[redacted]

Figure 35 Network diagram for 6-month CDA: Highly active disease subgroup including ofatumumab, ozanimod and natalizumab

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, CLA = cladribine, FIN = fingolimod, IFNB-1a = interferon β-1a, IM = intramuscular, NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week

Figure 36 Results for highly active subgroup NMA of 6-month CDA, considering definition used by NICE

Abbreviations: 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, , CrI = credible interval, FIN = fingolimod, HR = hazard ratio, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Appendix E. Safety Evidence, Adverse Events and Serious Adverse Events

E.1 NMAs of Safety in a Reduced Network of S1P1 Drug Trials

[redacted]

[redacted]

E.1.1 All-cause treatment discontinuations

[redacted]

Figure 37 Evidence network for all-cause treatment discontinuations, S1P1 network

Abbreviations: FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, TER = teriflunomide.

Figure 38 NMA Results for all-cause treatment discontinuations, S1P1 network (fixed effects). Effect estimates less than 1 indicate that ponesimod is favoured.

Abbreviations: CrI interval = credible interval, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OR = odds ratio, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, TER = teriflunomide.

Figure 39 NMA Results for all-cause treatment discontinuations, S1P1 network (random effects with vague priors). Effect estimates less than 1 indicate that ponesimod is favoured.

Abbreviations: CrI = credible interval, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OR = Odds ratio, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, TER = teriflunomide

E.1.2 Adverse Events

[redacted]

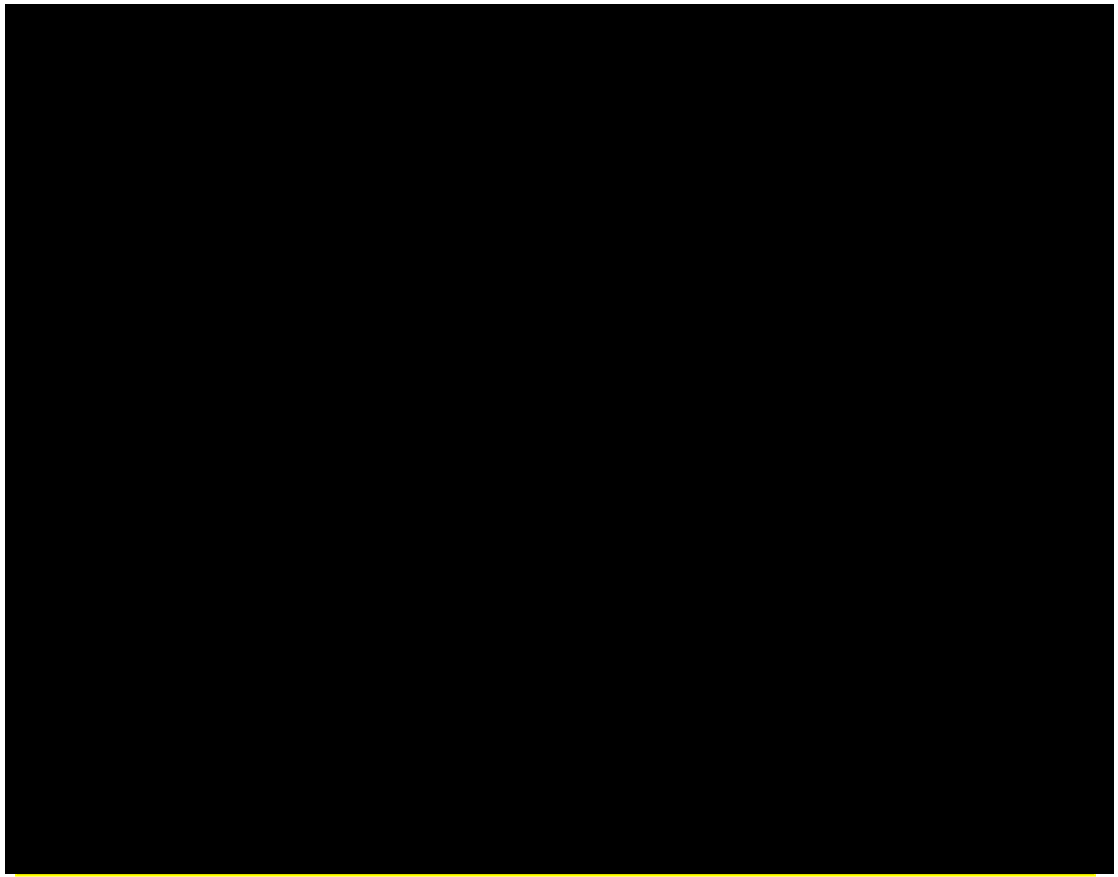
Figure 40 Evidence network for adverse events, S1P1 network

Abbreviations: FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, TER = teriflunomide.

Figure 41 NMA Results for adverse events, S1P1 network (fixed effects).

Abbreviations: CrI = credible interval, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OR = Odds ratio, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, TER = teriflunomide.

Figure 42 NMA Results for adverse events, S1P1 network (random effects with vague priors).



Abbreviations: CrI = credible interval, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OR = Odds ratio, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, TER = teriflunomide.

E.1.3 Serious Adverse Events

[redacted]

Figure 43 Evidence network for serious adverse events, S1P1 network

Abbreviations: FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OZA = ozanimod, PBO = placebo, PON = ponesimod, QD = every day, QW = weekly, TER = teriflunomide.

Figure 44 NMA Results for serious adverse events, S1P1 network (fixed effects).

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Abbreviations: CrI = credible interval, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OR = Odds ratio, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, TER = teriflunomide.

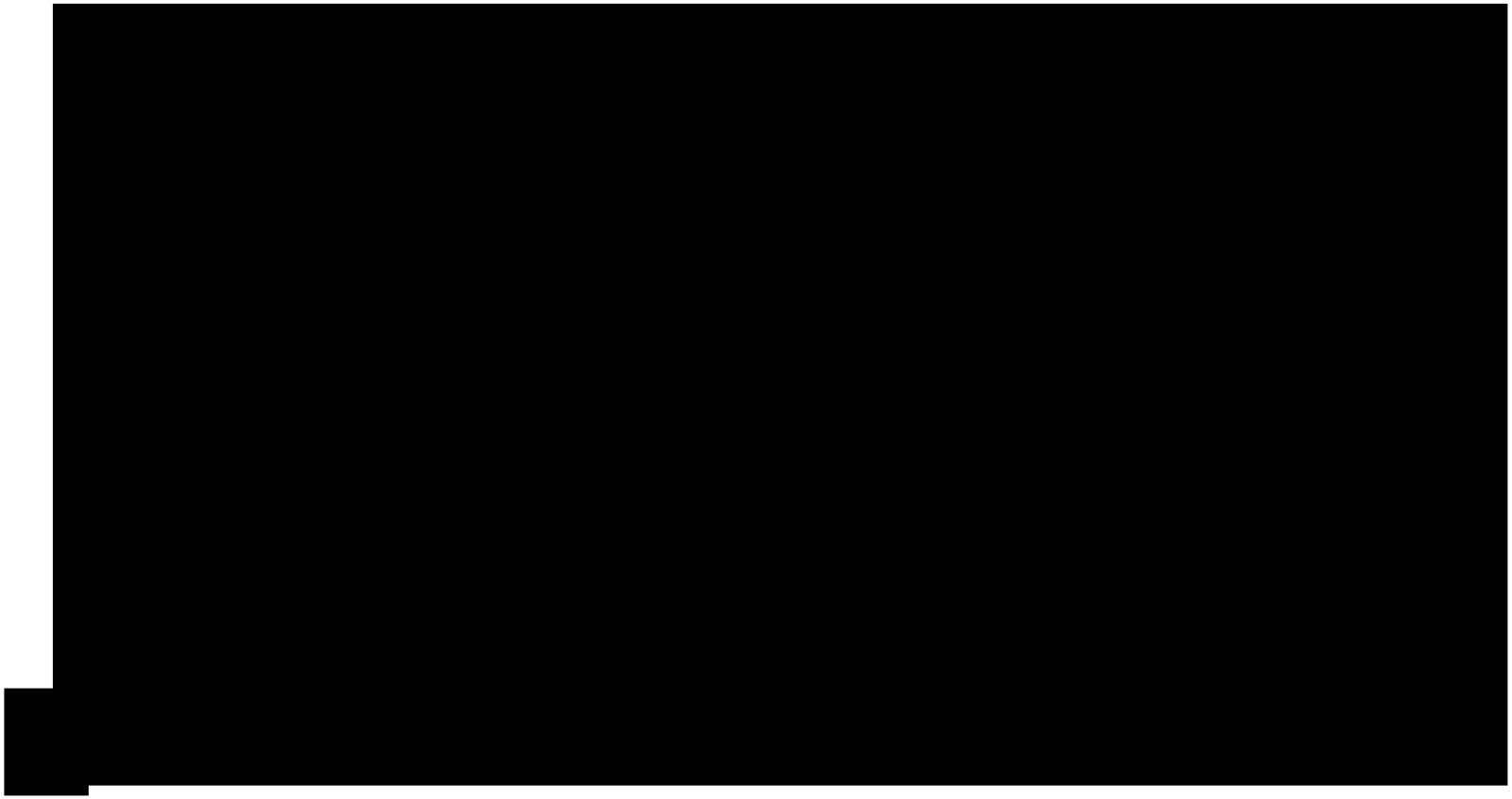
.

Figure 45 NMA Results for serious adverse events, S1P1 network (random effects with vague priors).

Abbreviations: CrI = credible interval, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, OR = Odds ratio, OZA = ozanimod, PBO = placebo, QD = every day, QW = weekly, TER = teriflunomide.

E.2 NMAs of Safety in a Network of DMTs with Class-Based Interferons

Figure 46 NMA Results for all-cause treatment discontinuations, S1P1 network (fixed effects).



E.3 Two-dimensional plots exploring the relative safety and efficacy of ponesimod versus other regimens

E.3.1 Adverse Events

[redacted]

Figure 47 Full network analyses of ARR and adverse events (fixed effects): Effect estimates for ponesimod versus treatments

Abbreviations: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, kg = kilogram, mg = milligram. NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

E.3.2 Serious Adverse Events

[redacted]

[redacted]

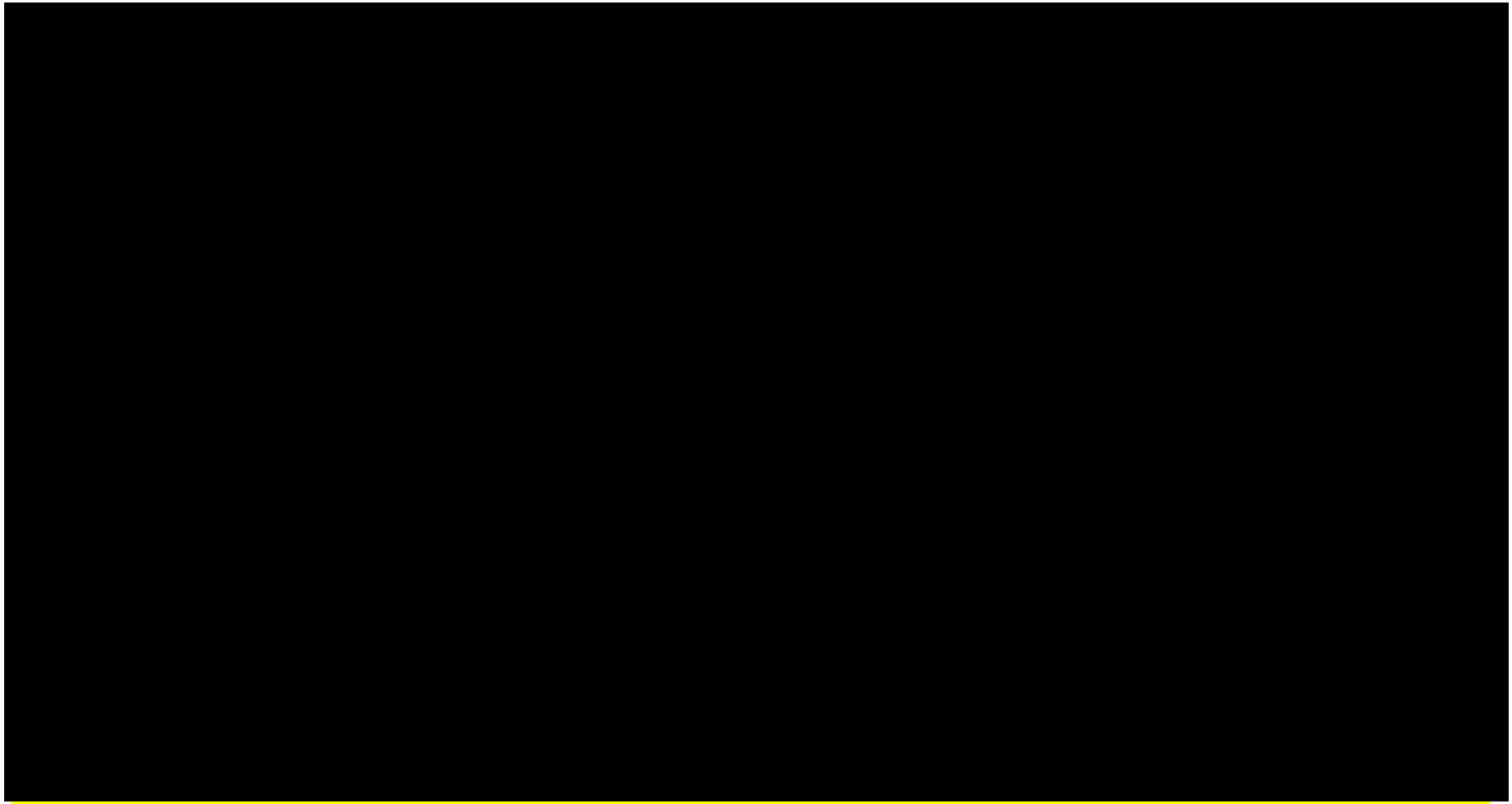
Figure 48 Full network analyses of ARR and serious adverse events (fixed effects): Effect estimates for ponesimod versus treatments.

Abbreviations: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IFNB-1b = interferon β-1b, IM = intramuscular, kg = kilogram, mg = milligram. NAT = natalizumab, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, QD = every day, QOD = every other day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Appendix F. No Evidence of Disease Activity (NEDA-3)

F.1 NMA of NEDA-3 outcomes

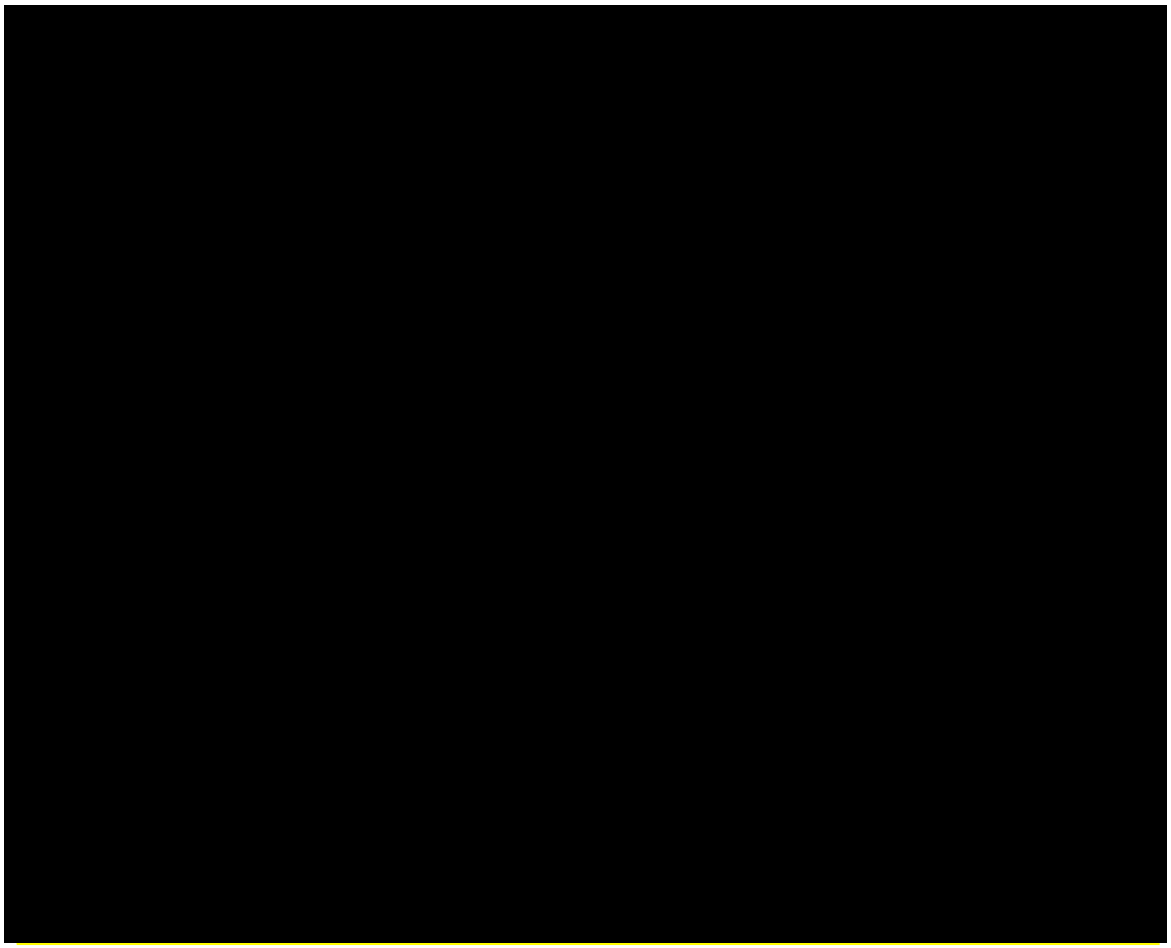
Figure 49 Evidence network for NEDA-3 outcome



Abbreviations: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, NAT = natalizumab, NEDA = no evidence of disease activity, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, PON = ponesimod, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

[redacted]

Figure 50 NMA of NEDA-3: Fixed Effects. Effect estimates greater than 1 indicate that ponesimod is favoured.


[redacted]

Abbreviations: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, NAT = natalizumab, NEDA = no evidence of disease activity, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

[redacted]

Figure 51: NMA of NEDA-3: Random Effects with Vague Priors. Effect estimates greater than 1 indicate that ponesimod is favoured.

Abbreviations: 2W = every 2 weeks, 4W = every 4 weeks, 24W = every 24 weeks, ALE = alemtuzumab, BID = twice daily, CLA = cladribine, DMF = dimethyl fumarate, FIN = fingolimod, GA = glatiramer acetate, IFNB-1a = interferon β-1a, IM = intramuscular, NAT = natalizumab, NEDA = no evidence of disease activity, OCR = ocrelizumab, OFA = ofatumumab, OZA = ozanimod, PBO = placebo, PEG = peginterferon, QD = every day, QW = weekly, SC = subcutaneous, TER = teriflunomide, TIW = three times per week.

Appendix G. Updated Economic Model Results

G.1 New Base Case Model Results

Following discussion with the ERG at technical engagement, two new sets of NMAs were conducted to address the uncertainty resulting from heterogeneity in the interferon beta (IFN-B) evidence base. In the first set, data for NICE-recommended interferons (including PegIFN-B) were pooled to average out overestimation of any treatment effects across trials (IFN-B class NMAs). This will now be the new base case for the ITT population in the economic model. In the second set, the NMAs were re-run, excluding any IFN-B trials that were deemed as outliers to align with the evidence base reviewed in the ofatumumab appraisal (TA699).

The results of these NMAs were used to inform treatment effects in the economic models, which were updated to use the ERG's preferred assumptions for the base case:

1. 6-month CDA is used to model disease progression

2. 25% of SPMS patients assumed to receive siponimod and 75% receive best supportive care (BSC)

Results based on IFN Class

Updated values for treatment effects on ARR are described in Table 27, while those for disease progression based on 3-month and 6-month CDA are presented in Table 28 (ITT population) and Table 29 (highly active subgroup). Updated inputs for annual treatment discontinuation rates are presented in Table 30.

To obtain the adverse event rates for the interferon class, the person-months for individual trials were estimated by multiplying the trial sample size by the trial duration. The rate of each adverse event was then estimated as the average of the rates reported in each trial, weighted by the person-months of each trial. For the interferon class comparator specifically, the rate of each adverse event was estimated as the average of the rates reported in each interferon trial, weighted by the person-months of each trial.

Table 27Treatment Effects on Annual Relapse Rates

Treatment	Rate Ratio for Relapse Rate (vs. Natural History) for the ITT Population[a]		Rate Ratio for Relapse Rate (vs. Natural History) for the Highly Active Subgroup[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on relapse rates for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

Table 28Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the ITT Population

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]

Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] 6-month data assumed to be equal to 3-month data due to lack of data availability.

Table 29Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the Highly active RRMS Subgroup

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

RRMS = relapsing-remitting multiple sclerosis; OWSA = one-way sensitivity analysis.

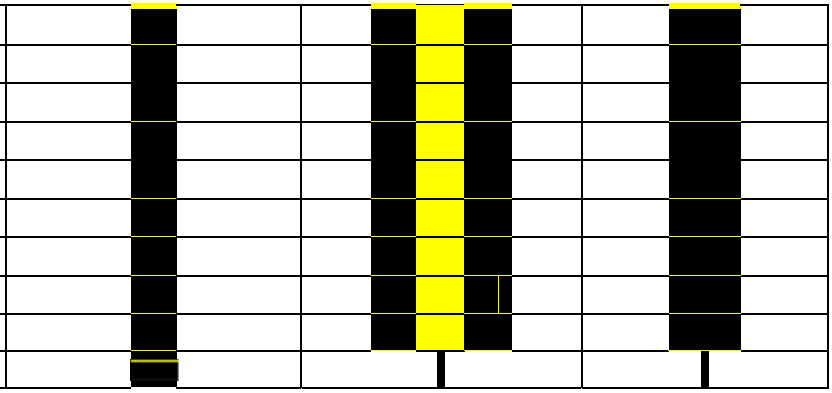
[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] Data are assumed to be equal those for interferon beta-1a 44 mcg due to lack of data availability.

Table 30 Annual Treatment discontinuation Rates

Treatment	Odds Ratio: Ponesimod vs. Treatment[a]		Annual Discontinuation Rate[b]
	Value	Range	
Ponesimod	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]

Interferon beta-1a 22 mcg	
Ocrelizumab	
Ofatumumab	
Ozanimod	
Teriflunomide	
Alemtuzumab	
Cladribine	
Fingolimod	
Natalizumab[e]	
Best supportive care[e]	

NA = not applicable; NMA = network meta-analysis; OWSA = one-way sensitivity analysis.

[a] Odds ratios for ponesimod versus treatment for annual risk of discontinuation for all treatments except best supportive care and ponesimod were varied in the OWSA and in the probabilistic sensitivity analysis (the latter utilizing a lognormal distribution); ranges were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in NMA.

[b] Annual discontinuation rates for all treatments were calculated from the annual discontinuation rate of ponesimod times a relative risk of discontinuation for each treatment versus ponesimod, where the relative risk was calculated from the odds ratios.

[c] Annual discontinuation rate of ponesimod was varied in the OWSA and in the probabilistic sensitivity analysis (the latter using a beta distribution); the range was set to the bounds of the 95% confidence interval from the sampled distribution; that confidence interval was estimated assuming a sample size of 580, the sum of the clinical trial population sizes used for estimating the discontinuation rate of ponesimod in the NMA.

[d] For alemtuzumab and cladribine, this rate is applied only in years 1 to 5. They are both taken for two years and assumed to have no all-cause discontinuation after year 5.

[e] Considered in the model only as a post-discontinuation treatment.

Acquisition costs for the interferon class were calculated as a weighted average of individual treatments using market share data and calculated as £8,879.37 (Table 31). Standard administration costs for injectable treatments were applied for the treatment class (£165.00) as per the model submitted with the original CS. Monitoring costs included unit costs of all tests common to individual interferons. As a result, the overall monitoring cost excluded an annual thyroid function test which is recommended in patients receiving Rebif. Since monitoring costs are not a key driver of the cost effectiveness results, we excluded thyroid function test from the overall monitoring costs since this was expected to impact approximately a minority of patients receiving an MS DMT.

Table 31 Calculation of acquisition costs for IFN class

Treatment	Market Share as a proportion of		List price	Weighted cost
	All DMTs	IFNs		
Interferon beta-1a 30 mcg	[redacted]	[redacted]	£8,531.20	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	£10,608.03	[redacted]
Interferon beta-1b 250 mcg	[redacted]	[redacted]	£7,263.97	[redacted]
Peginterferon beta-1a 250 mcg	[redacted]	[redacted]	£8,531.20	[redacted]
Average cost of interferon	[redacted]	-	-	[redacted]

Table 32 Updated CEM results for the ITT population (IFN class)

	PON	TER	DMF	GA	IFN class	OCR	OFA	OZA
Economic Outcomes								
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health Outcomes								
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, ponesimod vs. comparator (£ per QALY)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CEM = cost-effectiveness model; DMF = dimethyl fumarate; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; ITT = intent-to-treat; NA = not applicable; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PEG = peginterferon beta 1a; PON=ponesimod; QALY = quality-adjusted life-year; TER = teriflunomide

[a] Number of relapses outcomes are undiscounted.

Table 33 Updated CEM results for the highly active subgroup

	PON	OCR	OFA	OZA	ALE	CLA	FIN
Economic outcomes							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related (pre-discontinuation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost-effectiveness							
ICER, ponesimod vs. comparator (£ per QALY)							

ALE = alemtuzumab; CEM = cost-effectiveness model; CLA = cladribine; FIN = fingolimod; ICER = incremental cost-effectiveness ratio; NA = not applicable; PON = ponesimod; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

[a] Number of relapses outcomes are undiscounted.

Table 34 Scenario analyses: ITT population

	PON	TER	DMF	GA	IFN class	OCR	OFA	OZA
Base case: 6mCDA, 25% Siponimod, 50 yr time horizon								
Total costs								
Total QALY								
ICER								
Scenario 1: 3mCDA								
Total costs								
Total QALY								
ICER								
Scenario 2: 15% Siponimod								
Total costs								
Total QALY								

ICER	[redacted]							
Scenario 3: 40% Siponimod								
Total costs	[redacted]							
Total QALY	[redacted]							
ICER	[redacted]							
Scenario 4: 5-year time horizon								
Total costs	[redacted]							
Total QALY	[redacted]							
ICER	[redacted]							
Scenario 5: 10-year time horizon								
Total costs	[redacted]							
Total QALY	[redacted]							
ICER	[redacted]							
Scenario 6: 15-year time horizon								
Total costs	[redacted]							
Total QALY	[redacted]							
ICER	[redacted]							

[redacted]

[redacted]

Table 35 Scenario analysis: Highly active population

	PON	OCR	OFA	OZA	ALE	CLA	FIN
Base case: 6mCDA, 25% Siponimod, 50 yr time horizon)							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: 3mCDA							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: 15% Siponimod							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: 40% Siponimod							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: 5-year time horizon							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: 10-year time horizon							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: 15-year time horizon							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

G.2 Probabilistic Sensitivity Analysis Model Results for Interferon Class-Based Model

Table 36 PSA results (mean) compared with deterministic results (ITT population) for INF class-based model

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 52 Cost-effectiveness scatter plot (ITT population) for INF class-based model

Figure 53 Cost-effectiveness acceptability curve (ITT population) for INF class-based model

Table 37 PSA results (mean) compared with deterministic results (highly active) for INF class-based model

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]									
Ocrelizumab 600mg IV	[redacted]								Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]								Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]								Dominates	Dominates
Alemtuzumab 12mg IV	[redacted]								Less Effective and Less Costly	Dominated
Cladribine 3.5mg/kg PO	[redacted]								Dominated	Dominated
Fingolimod 0.5mg PO	[redacted]								Dominates	Dominates

Figure 54 Cost-effectiveness scatter plot (highly active) for INF class-based model

Figure 55 Cost-effectiveness acceptability curve (highly active) for INF class-based model

G.3 Results based on IFN trials excluding INCOMIN and ADVANCE

Updated values for treatment effects on ARR are described in Table 38, while those for disease progression based on 3-month and 6-month CDA are presented in Table 39 (ITT population) and Table 40 (highly active subgroup). Updated inputs for annual treatment discontinuation rates are presented in Table 41.

Table 38 Treatment Effects on Annual Relapse Rates

Treatment	Rate Ratio for Relapse Rate (vs. Natural History) for the ITT Population[a]		Rate Ratio for Relapse Rate (vs. Natural History) for the Highly Active Subgroup[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 mcg	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab[b]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care[b]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on relapse rates for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

Table 39 Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the ITT Population

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]

Glatiramer acetate	[redacted]		[redacted]		[redacted]		[redacted]	
Interferon beta-1a 22 mcg	[redacted]		[redacted]		[redacted]		[redacted]	
Interferon beta-1a 30 mcg	[redacted]		[redacted]		[redacted]		[redacted]	
Interferon beta-1a 44 mcg	[redacted]		[redacted]		[redacted]		[redacted]	
Ocrelizumab	[redacted]		[redacted]		[redacted]		[redacted]	
Ofatumumab	[redacted]		[redacted]		[redacted]		[redacted]	
Ozanimod	[redacted]		[redacted]		[redacted]		[redacted]	
Teriflunomide	[redacted]		[redacted]		[redacted]		[redacted]	
Alemtuzumab	[redacted]		[redacted]		[redacted]		[redacted]	
Cladribine	[redacted]		[redacted]		[redacted]		[redacted]	
Fingolimod	[redacted]		[redacted]		[redacted]		[redacted]	
Natalizumab[b]	[redacted]		[redacted]		[redacted]		[redacted]	
Best supportive care[b]	[redacted]		[redacted]		[redacted]		[redacted]	

ITT = intent-to-treat; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] 6-month data assumed to be equal to 3-month data due to lack of data availability.

Table 40 Treatment Effects on Disease Progression, Based on 3- and 6-Month Effects Data for the Highly active RRMS Subgroup

Treatment	Relative Risk on Disease Progression (vs. Natural History)			
	Based on 3-Month Data[a]		Based on 6-Month Data[a]	
	Value	Range	Value	Range
Ponesimod	[redacted]		[redacted]	
Dimethyl fumarate	[redacted]		[redacted]	
Glatiramer acetate	[redacted]		[redacted]	
Interferon beta-1a 22 mcg[c]	[redacted]		[redacted]	
Interferon beta-1a 30 mcg	[redacted]		[redacted]	
Interferon beta-1a 44 mcg	[redacted]		[redacted]	
Ocrelizumab	[redacted]		[redacted]	
Ofatumumab	[redacted]		[redacted]	
Ozanimod	[redacted]		[redacted]	
Teriflunomide	[redacted]		[redacted]	
Alemtuzumab	[redacted]		[redacted]	
Cladribine	[redacted]		[redacted]	
Fingolimod	[redacted]		[redacted]	
Natalizumab[b]	[redacted]		[redacted]	
Best supportive care[b]	[redacted]		[redacted]	

RRMS = relapsing-remitting multiple sclerosis; OWSA = one-way sensitivity analysis.

[a] Treatment effects on disease progression for all treatments except best supportive care were varied in the OWSA and in the probabilistic sensitivity analysis; ranges for both were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in the network meta-analysis.

[b] Considered in the model only as a post-discontinuation treatment.

[c] Data are assumed to be equal those for interferon beta-1a 44 mcg due to lack of data availability.

Table 41 Annual Treatment discontinuation Rates

Treatment	Odds Ratio: Ponesimod vs. Treatment[a]		Annual Discontinuation Rate[b]
	Value	Range	
Ponesimod	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	
Glatiramer acetate	[redacted]	[redacted]	
Interferon beta-1a 22 mcg	[redacted]	[redacted]	
Interferon beta-1a 30 mcg	[redacted]	[redacted]	
Interferon beta-1a 44 mcg	[redacted]	[redacted]	
Ocrelizumab	[redacted]	[redacted]	
Ofatumumab	[redacted]	[redacted]	
Ozanimod	[redacted]	[redacted]	
Teriflunomide	[redacted]	[redacted]	
Alemtuzumab	[redacted]	[redacted]	
Cladribine	[redacted]	[redacted]	
Fingolimod	[redacted]	[redacted]	
Natalizumab[e]	[redacted]	[redacted]	
Best supportive care[e]	[redacted]	[redacted]	

NA = not applicable; NMA = network meta-analysis; OWSA = one-way sensitivity analysis.

[a] Odds ratios for ponesimod versus treatment for annual risk of discontinuation for all treatments except best supportive care and ponesimod were varied in the OWSA and in the probabilistic sensitivity analysis (the latter utilizing a lognormal distribution); ranges were set to the bounds of the 95% confidence intervals from the sampled distributions; those confidence intervals were estimated from the standard errors, which were calculated from the 95% credible intervals calculated in NMA.

[b] Annual discontinuation rates for all treatments were calculated from the annual discontinuation rate of ponesimod times a relative risk of discontinuation for each treatment versus ponesimod, where the relative risk was calculated from the odds ratios.

[c] Annual discontinuation rate of ponesimod was varied in the OWSA and in the probabilistic sensitivity analysis (the latter using a beta distribution); the range was set to the bounds of the 95% confidence interval from the sampled distribution; that confidence interval was estimated assuming a sample size of 580, the sum of the clinical trial population sizes used for estimating the discontinuation rate of ponesimod in the NMA.

[d] For alemtuzumab and cladribine, this rate is applied only in years 1 to 5. They are both taken for two years and assumed to have no all-cause discontinuation after year 5.

[e] Considered in the model only as a post-discontinuation treatment.

Table 42 Updated CEM results for the ITT population

	PON	TER	DMF	GA	IFNB -1a 22 mg	IFNB-1a 30 mg	IFNB-1a 44 mg	OCR	OFA	OZA
Economic outcomes										
Total costs	[redacted]									
Treatment-related	[redacted]									
Disease management	[redacted]									
Relapse	[redacted]									
Incremental costs, ponesimod vs. comparator	[redacted]									[redacted]5
Health outcomes										
QALYs	[redacted]									
Patients	[redacted]									
Caregivers[a]	[redacted]									
Incremental QALYs, ponesimod vs. comparator	[redacted]									
Life-years	[redacted]									
Time on treatment	[redacted]									
Number of relapses	[redacted]									

Cost-effectiveness										
ICER, ponesimod vs. comparator	[redacted]	Dominates	Dominates	Dominates	[redacted]	Dominates	Dominates	Less costly and less effective	Less costly and less effective	[redacted]

CEM = cost-effectiveness model; DMF = dimethyl fumarate; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; ITT = intent-to-treat; NA = not applicable; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; PEG = peginterferon beta 1a; PON=ponesimod; QALY = quality-adjusted life-year; TER = teriflunomide

[a] Number of relapses outcomes are undiscounted.

Results of the base-case incremental cost-effectiveness analysis for the highly active population

Table 43 Updated CEM results for the highly active subgroup

	PON	OCR	OFA	OZA	ALE	CLA	FIN
Economic outcomes							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs, ponesimod vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness							
ICER, ponesimod vs. comparator (£ per QALY)	NA	[redacted] Less costly and less effective	[redacted] Less costly and less effective	[redacted] Dominates	[redacted] Less costly and less effective	[redacted] Dominated	[redacted] Dominates

ALE = alemtuzumab; CEM = cost-effectiveness model; CLA = cladribine; FIN = fingolimod; ICER = incremental cost-effectiveness ratio; NA = not applicable; PON = ponesimod; OCR = ocrelizumab; OFA = ofatumumab; OZA = ozanimod; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis.

[a] Number of relapses outcomes are undiscounted.

G.4 Probabilistic Sensitivity Analysis Model Results excluding INCOMIN and ADVANCE

Table 44 PSA results (mean) compared with deterministic results (ITT population) excluding ADVANCE and INCOMIN

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Interferon beta-1a 22mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30mcg IM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Interferon beta-1a 44mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 56 Cost-effectiveness scatter plot (ITT population) excluding ADVANCE and INCOMIN

Figure 57 Cost-effectiveness acceptability curve (ITT population) excluding ADVANCE and INCOMIN

Table 45 PSA results (mean) compared with deterministic results (highly active) excluding ADVANCE and INCOMIN

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 58 Cost-effectiveness scatter plot (highly active) excluding ADVANCE and INCOMIN

Figure 59 Cost-effectiveness acceptability curve (highly active) for INF class-based model

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

Information on completing this form:

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

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

Please return this form by **5pm** on **Friday 16th July 2021.**

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Completing this form

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

Important information on completing this expert statement

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

NICE National Institute for Health and Care Excellence

PART 1 – Treating a patient with relapsing multiple sclerosis and current treatment options	
About you	
1. Your name	**Eli Silber**
2. Name of organisation	**Kings College Hospital**
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 relapsing multiple sclerosis? ☐ a specialist in the clinical evidence base for relapsing multiple sclerosis 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** 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 I did not write it
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**My trials unit at Kings College Hospital did commercial trials sponsored by a number of pharmaceutical companies, but not ponesimod. I have received consulting fees and support to attend meetings from a number of pharmaceutical companies. To the best of my knowledge I have not received fees/ support from the manufacturers of this drug.**
The aim of treatment for relapsing multiple sclerosis	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	In relapsing disease to reduce relapses and thereby reduce long term disability.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	At least a 30% reduction in relapse rate compared to placebo. At least equivalence and preferably superiority in efficacy, with better safety and/ or tolerability compared to a standard platform therapy.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in relapsing multiple sclerosis	The SIP inhibitors have proven to be of value as disease modifying therapies in MS. There are current limitations: 1. Fingolimod has a narrow NICE approval in relapsing remitting MS (RR MS) and requires cardiac monitoring (with a hospital admission) for first dose. 2. Siponimod is the first DMT approved in secondary progressive MS but is not available for relapsing remitting MS. 3. Ozanimod is licensed, but not NICE approved in RR MS.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	See NHE- England guidelines. There are a range of therapies available in RR MS. Therapy is decided with patients according to guidelines based on 1. The number and severity of relapses. 2. The presence or not of new or enhancing MRI lesions 3. Response to therapy thus far.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	See NHS England guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes, treatment decisions are in multidisciplinary teams. In general whilst there may be differences in patters of prescribing between individual clinicians and centres there is broad consensus as to treatment options.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	This would add a potentially useful oral therapy to the existing range of treatments. It is likely to slot into existing therapy pathways as a potentially valuable therapeutic option.
12. 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?	This may reduce the number of patients requiring intravenous therapies to manage their MS. This may haveresource implications, particularly in the current pandemic with limited hospital resources.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist MS disease modifying therapy clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil in addition.
13. Do you expect the technology to provide clinically meaningful	It provides a different therapeutic option for some patients receiving disease modifying therapies.

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No, there are other drugs that have at least the same if not superior effect on relapses and the development of disability.
• Do you expect the technology to increase health-related quality of life more than current care?	No, there are other drugs that have at least the same if not superior effect on relapses and the development of disability.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	It provides another effective oral MS disease modifying therapy that may be easier and more convenient.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, see NHS England guidance
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	It is another SIP inhibitor drug. There may be particular advantages and a broader spectrum of eligible patients.

improve the way that current need is met?	
• 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?	Not significantly
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is a need for haematological monitoring as with other disease modifying therapies.
Sources of evidence	
20. 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?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Relapse rate Disability progression MRI activity Adverse effects.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MRI is shown to be a good predictor of clinical relapses and disability. In this study the primary endpoints were clinical and MRI only secondary.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance [TA706]?	
23. How do data on real-world experience compare with the trial data?	Likely to be similar
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to my knowledge
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. Is it appropriate for the population for ponesimod to be limited to those with active or highly active relapsing-remitting multiple sclerosis (RRMS)? The	I think that this is reasonable. RES patients are likely to be offered more potent therapies such as one of the monoclonal drugs.

rapidly evolving severe RRMS subgroup is not currently considered in the submission due to a limited evidence base.	
26. Is natalizumab [excluded from company submission] considered to be established clinical practice in the NHS for treating relapsing multiple sclerosis?	Yes, but also anti CD-20 (ocriluzimab and now ofatumimab) are thought to have approximately equal efficacy.
27. Are IFN-beta and other DMTs used outside their MAs [excluded from company submission] considered to be established clinical practice in the NHS for treating relapsing multiple sclerosis?	I assume that this means used outside their Marketing Authorisation? In general the interferon drugs and copaxone are less likely to be initiated compared to previous use and less used that other newer therapies.

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PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population [see ERG report section 2.3]	
Uncertainty in the clinical efficacy of ponesimod and its comparators [see ERG report sections 3.3, 3.4 and 3.5]	
Insufficient comparative evidence for the safety of ponesimod [see	

ERG report sections 3.4.1, 3.5.3 and 3.5.4]	
Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model [see ERG report sections 1.5 and 6.1.1.1]	
Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC [see ERG report section 1.5 and 6.1.1.2]	
Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
28. In up to 5 sentences, please summarise the key messages of your statement:	

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-
-
-
-
-

Thank you for your time.

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

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

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Clinical expert statement & technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

Information on completing this form:

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

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

Please return this form by **5pm** on **Friday 16th July 2021.**

NICE National Institute for Health and Care Excellence

Completing this form

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

Important information on completing this expert statement

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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PART 1 – Treating a patient with relapsing multiple sclerosis and current treatment options	
About you	
1. Your name	**Neil Robertson**
2. Name of organisation	**Cardiff University**
3. Job title or position	**Professor of Neurology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with relapsing multiple sclerosis? ☐ a specialist in the clinical evidence base for relapsing multiple sclerosis or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it **X** 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. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for relapsing multiple sclerosis	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent or reduce MS relapses and slow accumulation of fixed disability
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Reduction in relapses by >30% vs placebo, more to difficult to enumerate against active control in this case teriflunomide prob>20% CDA 24 weeks > 20%

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in relapsing multiple sclerosis	Yes; the main issue is that the higher efficacy treatments are generally associated with a higher risk of adverse event and tend to be infusions or other more complex administration (ie BMT). There is a need for a safe highly effective oral medication to be available first line
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Active RMS is currently treated with DMTs
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHSE/ABN guidelines
• 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.)	These are complex and often contested guidelines with variation on definitions or active, highly active, REMS etc. Some variation exists across the home nations for example Fingolimod (another S1P inhibitor) is available first line in Wales for very active disease. In addition, the obligate use of Bluteq can lead to some clinicians forcing criteria to allow selected treatments in patents who physicians feel have poor prognostic factors but may not fit strictly into guidelines. Furthermore, recent Covid issues have allowed a more relaxed interpretation
• What impact would the technology have on the current pathway of care?	If allowed as a first line indication for active disease this technology would allow early access for patients to more effective oral DMT

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology would be absorbed into current practice and clinical infrastructure and could reduce workload in some instances and generally no requirement for inpatient monitoring, unlike existing S1P inhibitors
• How does healthcare resource use differ between the technology and current care?	As above, may reduce resource requirements in some instances but otherwise similar
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics and MS centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional infrastructure investment Some training required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes there are some clinically meaningful benefits compared with current platform DMTs
• Do you expect the technology to increase	There is not current evidence to support this, and as longevity of MS is approx. 34+ yrs it may be difficult to generate this evidence in a timely fashion

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as patients are increasingly started on more efficacious first line DMTs at an early stage of disease there is some evidence that disability and some measures of QoL are improving
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As with many DMTs they are likely to be less effective in older patients or in those lacking evidence of inflammatory disease activity
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or	Generally easier, as no obligate requirement to admit for first dose observation in the majority of patients. No requirement for concomitant treatments. There may be issues with lower humoral response to Covid vaccinations for ponesimod and other S1P inhibitors that may require additional counselling and/or booster extended interval vaccination

ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting will be based on documentation of inflammatory disease activity which is routinely used in clinical practice and requires no change Stopping is more complex and controversial. Current general guidelines suggest stopping DMT for RMS at EDSS 6.5 and or onset of SPMS but in practice this may be difficult and concept of stopping one S1Pi to put on another ie Siponimod appears flawed
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	No; but represents a refinement of an existing drug class and short washout which will be useful in patients considering families etc

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes if approved for first line treatment in active disease
• Does the use of the technology address any particular unmet need of the patient population?	Yes; early more effective oral DMT
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Generally safe with limited and predictable AE profile
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	The use of teriflunomide is popular in P111 trials for new DMTs, and whilst it may reflect common practice in the USA and selected parts of Europe, use of Teriflunomide in the UK is very limited and a more contemporary comparator would have been DMF
• If not, how could the results be extrapolated to the UK setting?	Via network analysis as performed

• What, in your view, are the most important outcomes, and were they measured in the trials?	Annualised relapse rate, SAD 24 weeks and MRI endpoints Yes all were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Use of MRI endpoints to predict longer-term outcomes is well establised
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance [TA706]?	
23. How do data on real-world experience compare with the trial data?	Reasonable comparison given the selected recruitment criteria and represent an important and significant patient sub-population
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Age
24b. Consider whether these issues are different from issues with current care and why.	No different to current care issues
Topic-specific questions	
25. Is it appropriate for the population for ponesimod to be limited to those with active or highly active relapsing-remitting multiple sclerosis (RRMS)? The	Yes

rapidly evolving severe RRMS subgroup is not currently considered in the submission due to a limited evidence base.	
26. Is natalizumab [excluded from company submission] considered to be established clinical practice in the NHS for treating relapsing multiple sclerosis?	Yes, but only in HA/REMS so would not be a fair comparator for active RMS
27. Are IFN-beta and other DMTs used outside their MAs [excluded from company submission] considered to be established clinical practice in the NHS for treating relapsing multiple sclerosis?	No

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PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population [see ERG report section 2.3]	Agree this is an issue and requires a population-based, long-term study of REMS to act as baseline data for comparison; I am not aware of any such data at present
Uncertainty in the clinical efficacy of ponesimod and its comparators [see ERG report sections 3.3, 3.4 and 3.5]	The indication requested for ponesimod seems to be active MS, therefore Tysabri, Alemtuzumab, Cladribine do not seem appropriate comparators Fingolimod in some areas of the UK would be considered a fair comparator
Insufficient comparative evidence for the safety of ponesimod [see	Common in period following P111, but likely to be class effects and more data from P1V should become available. No particular concerns here

ERG report sections 3.4.1, 3.5.3 and 3.5.4]	
Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model [see ERG report sections 1.5 and 6.1.1.1]	Most clinicians prefer the 24 week CDA model
Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC [see ERG report section 1.5 and 6.1.1.2]	The number of PwMS who convert to SPMS that receive an alternative DMT ie Siponimod is difficult to be accurate on but some will certainly receive DMTs
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages
28. In up to 5 sentences, please summarise the key messages of your statement:

- A useful addition of a moderately effective more specific S1Pi to the DMT repertoire for active RMS
- Low burden of management and monitoring
- Low and predictable frequency of adverse events but vaccination response to S1Pi may limit use in periods of high transmission
- Convenient oral administration
- Less convincing disability data

Thank you for your time.

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

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Your privacy

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

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

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

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Patient expert statement and technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

About this Form

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

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

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

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

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

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

Please return this form by **5pm** on **Friday 16th July 2021.**

Completing this form

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

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

Important information on completing this expert statement

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

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

5. How did you gather the information included in your statement? (please tick all that apply) I am drawing from personal experience, and I took part in the expert zoom conferance	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with relapsing multiple sclerosis? If you are a carer (for someone with relapsing multiple sclerosis) please share your experience of caring for them.	I Have been diagnosed with MS since 2007, I had symptoms since 2006. I have RRMS and mostly sensory symptoms, fatigue and some cognition issues. I am on DMT treatment, Tecfidera since 2016. I have been relapse free since
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for relapsing multiple sclerosis on the NHS?	On the whole I am positive about it. I think for myself there has been a lot of good options. However, for people with a more progressive for of MS there hasn't been. I also think a lot of neuros are not always up to date with the "treat early" approach as I still hear of a lot of PWMS been told that they are "too well" for treatment. Some treatments like HSCT seems to be more of potluck and it differs a lot from centre to cenrte if they will be a "fan" of that particular treatment. This approach can

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	be very confusing for people with MS. I think PWMS have very different opinions as our condition can be so varied. But in general I think there is a lot of frustration for people with progressive MS and lack of treatment.
8. If there are disadvantages for patients of **current NHS treatments** for relapsing multiple sclerosis (for example how ponesimod is given or taken, side effects of treatment etc) please describe these	Not sure if I understand the question correct, but having to take time off to go to hospital for treatments can be disruptive and even expensive. I take tablets so that is easy enough. I get flushing from them at times, and I have to take 6 monthly bloodtests to check my white blood cell count is ok. I think a lot of people are put off by potential side effects and having to inject themselves. But once it is part of your life it isn't so bad.
Advantages of this treatment	
9a. If there are advantages of ponesimod over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does ponesimod help to overcome/address any of the listed disadvantages of current treatment that you	aAfter listening to the talk we had before, I would say that the pregnancy angle would be an advantage. B But obvs things like bigger chance of no relapses and delay in progression would be the biggest advantages for me. C. As it is not taken in hospital then it addresses that concern. The part in the spec that says "Ponesimod provides a new treatment option, with significantly greater reduction in the frequency of relapses compared with teriflunomide (30.5% reduction), while having a favourable tolerability profile and high treatment persistence demonstrated up to 9 years of follow-up." Makes it sound like a good option. The Ms Trust website also stated with regards to the trial Those on ponesimod experienced a 30% reduction in relapse rate, 56% reduction in active lesions, and a statistically significant improvement in fatigue symptoms compared to Aubagio. Which was an interesting thing about fatigue I thought as that is a big thing for quality of life

have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of ponesimod over current treatments on the NHS please describe these? For example, are there any risks with ponesimod? If you are concerned about any potential side affects you have heard about, please describe them, and explain why.	I guess some of the side effects listed where things I had not seen before: "the most frequent side effects included nasopharyngitis, headache, chest infections and Patient organisation submission Ponesimod for treating relapsing multiple sclerosis [ID1393] 10 of 12 an increase in liver enzymes measured in the blood. Seizures and macular oedema occurred more frequently in those taking ponesimod" Seizure being a rather scary one I think.
Patient population	
11. Are there any groups of patients who might benefit more from ponesimod or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity, or cognitive impairments) that affect the suitability of different treatments	I don't think I can really guess on that topic. It feels like it would be a good alternative to the treatment that I am on, so probably would think of people that are on the same level as myself first. I guess one tricky thing with having cogfog issues is to actually remembering taking your pills. I do forget at times. Would things like macular oedema as a side effect be a risk for people who often struggle with Optic neuris. But I am only guessing here as I am no medical expert.

Equality	
12. Are there any potential equality issues that should be taken into account when considering relapsing multiple sclerosis and ponesimod? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	I think a lot of medication seem to be based on men and women might be an after though, with MS more women than men get the condition so things like pregnancy, hormones, cycles and menopause are often ignored will effect how you are feeling. I felt better MS wise during my pregnancies for example. I feel worse when I have my period (due to the body temp going up). Perhaps when making drugs hormones should be considered more. Its good to see that more drugs are now allowed to take through pregnancy and breastfeeding. Because these are huge dealbreakers when it come to picking medication. I am sure that race issues, and also age issues happens in MS a lot. With people thinking it is a white person's condition and you get it in your 30's. So people that fall outside of that window can struggle getting their diagnoses. Not sure how that part would translate into taking ponesimod however.

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No, I think that is mostly all from me. I welcome a bigger choice of drugs and things woth less side effects and easier to take to be on the market.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Are the comparators (the current treatment available in the NHS) in the company	aWell I understand it works similarly to Gilenya and it was also compared to Aubagio and Tecfidera in trials. So those would be my guesses. C easy to take, reduction in relapse rates, less side effects. I am not sure about anything lacking. If it is a safe option then a lot of good things have come across.

submission used in the NHS for treating the condition? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition? 14c. What are the main benefits of this treatment for patients? If there are several benefits, please list them in order of importance. Are there any benefits of this treatment that have not been captured? 14d. What are the benefits of this treatment for carers?	D well as it is a pill that makes it easier for a carer.
15. Are there any important issues that have been missed in the ERG report?	

PART 3 -Key messages

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

- Is it safe for people with MS
- ease of taking the medication
- more choice within pregnancy and breastfeeding on DMTs
- reducing relapses
- bigger quality of life

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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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

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

Information on completing this expert statement

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

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

3. Job title or position	**Medicines 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):
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	☐ yes

here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Current treatment of the condition in the NHS	
8. 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/
9. 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 acetate whereas others use dimethyl fumarate the latter being the most widely used first line treatment currently.

experience is from outside England.)	
10. What impact would the technology have on the current pathway of care?	Ponesimod 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 although it does have a complex loading regimen over the first 14 days. My be better tolerated than dimethyl fumarate.
The use of the technology	
11. 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.
12. 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 ponesimod 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.)	Ponesimod is expected to require a similar level of infrastructure to be in place as fingolimod, due to the similar pharmacology of these two agents. Like fingolimod (which is used as a 2nd line agent for RRMS) it will require a day-case appointment for cardiac monitoring when treatment is initiated.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Not known
13. 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	

14a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any
14b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
15. What is the impact of the interim access to some treatments during the COVID-19 pandemic? Do you anticipate any long-term changes to the treatment pathway based on these current arrangements?	There have been some adjustments to access criteria for 3 of the current DMTs including requiring fewer relapses in a given time period or waiving the requirement for an MRI scan. As this is a new medicine it will depend on the final NICE recommendation to determine whether additional allowances will be made for COVID. Like fingolimod there may be a reduced response to vaccine that might need consideration.

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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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

About this Form

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

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

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

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

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

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

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 16th July 2021.**

Completing this form

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

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

Important information on completing this expert statement

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

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

5. How did you gather the information included in your statement? (please tick all that apply)	☐ **X** I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with relapsing multiple sclerosis? If you are a carer (for someone with relapsing multiple sclerosis) please share your experience of caring for them.	I have lived with relapsing Multiple sclerosis for over 20 years. I experience sever fatigue, muscle spasms, balance issues, pain, numbness, loss of sensation and have had episodes of optic neuritis. In addition, I have bladder and bowel issues which can make me reluctant to go out or stay overnight with friends. My MS restricts my life and makes me cautious to venture into crowded areas. My symptoms are mainly invisible so I have to deal with a lack of understanding from people when I try to explain my problems with everyday life.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for relapsing multiple sclerosis on the NHS?	Treatments have advanced greatly since my diagnosis, when the first beta inteferons were just being introduced to the market, and they have the potential to prevent or at least slow down disability and progression of the disease; however, they are not available to everyone who would benefit from them. I believe my views are broadly representative of other people I am aware of,

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for relapsing multiple sclerosis (for example how ponesimod is given or taken, side effects of treatment etc) please describe these	Disadvantages of current treatments include the mode of delivery e.g. the regular injections of the beta inteferons or glatiramer acetate and the infusions of Ocrelizumab and Alemtuzumab. Side effects of injections include the pitting of skin at the injection sites, which is unsightly and upsetting. There is also the potential for dangerous side effects of some treatments e.g. PML.
Advantages of this treatment	
9a. If there are advantages of ponesimod over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others?	Ponesimod has been shown to reduce the number of relapses, and more importantly slow the advance of disability in relapsing MS. This has a huge impact on quality of life, by enable pwMS to continue working for longer and remain fully independent for longer.
9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	The value of slowing disability progression cannot be underestimated. The many invisible, apparently minor, symptoms have a cumulative load of psychological, emotional, and physical wear that saps even more energy from an already diminished supply. Anything that can delay this is a blessing.
9c. Does ponesimod help to overcome/address any of the listed disadvantages of current treatment that you	As a tablet, ponesimod has none of the inconvenience, stress, or unsightly side effects of other treatments.

have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of ponesimod over current treatments on the NHS please describe these? For example, are there any risks with ponesimod? If you are concerned about any potential side affects you have heard about, please describe them, and explain why.	All medications have side effects. As far as I am aware, Side effect of Ponesimod are milder than those of other treatments currently available.
Patient population	
11. Are there any groups of patients who might benefit more from ponesimod or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity, or cognitive impairments) that affect the suitability of different treatments	As a tablet, there should be no problems in administration of the treatment.

Equality	
12. Are there any potential equality issues that should be taken into account when considering relapsing multiple sclerosis and ponesimod? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	**I am unaware of any equality issues. The only potential issue I can think of is for people whose religion may prevent them taking medications.**

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Are the comparators (the current treatment available in the NHS) in the company	

submission used in the NHS for treating the condition? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition? 14c. What are the main benefits of this treatment for patients? If there are several benefits, please list them in order of importance. Are there any benefits of this treatment that have not been captured? 14d. What are the benefits of this treatment for carers?	
15. Are there any important issues that have been missed in the ERG report?	

PART 3 -Key messages

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

- It is vitally important to provide treatments that not only reduce relapses but also slow disability in MS.
- Slowing disability will save the NHS money as well as improving the health and quality of life of patients with MS.
- Ponesimod has been shown to both reduce the number of relapses and slow disability progression in MS.
- As a tablet, Ponesimod is much easier to administer than many currently available therapies and likely to be more acceptable to pwMS.
-

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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NICE National Institute for Health and Care Excellence

Technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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

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

Deadline for comments **5:00pm, Friday 16 July 2021**

Thank you for your time.

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

Notes on completing this form

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

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

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

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

About you

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

NICE National Institute for Health and Care Excellence

Key issues for engagement

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

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	No	Insufficient data in the OPTIMUM clinical trial to support the use of Ponesimod in RES RRMS population.
Key issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	Yes	Analysis of Phase 2 and OPTIMUM Phase 3 study support superiority of Ponesimod against appropriate comparator (Teriflunomide) in active RRMS and modelled analysis demonstrates likely equivalence to a current therapy (Fingolimod) used in Highly Active RRMS.
Key issue 3: Insufficient comparative evidence for the safety of ponesimod	Yes	Phase 2 and 3 Clinical Trials and extension studies are reassuring showing acceptable safety for this category of therapy. The technology is similar to an existing therapy (Fingolimod) which has a well characterised and acceptable safety profile and the safety data collected on Ponesimod looks to be similar to Fingolimod.
Key issue 4: Uncertainty surrounding use of 3 month CDA as the primary measure of disease progression in the economic model	No	Uncertainty remains on this issue as we would usually view the 6-month measure to be more robust in terms of representing disability worsening than a 3 month measure of disability change. It should be recognised that there is uncertainty over both measures and how they translate to disability worsening in day-to-day clinical practice given the short timescale of clinical trials in general and the relatively

		small number of people in either arm of the studies who worsen regarding their EDSS over the time period of usual Phase 3 study.
Key issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	Yes	We agree with the view expressed by clinicians to the ERG that some people converting to SPMS will now receive Siponimod rather than simply BSC. It is difficult to be certain what is an accurate percentage figure to assign to BSC and Siponimod as it has only very recently become available. The modelling of 25% will go on siponimod in the ERG report is a plausible figure. It should also be noted that as clinicians we are increasingly recognising people with MS who display a SPMS phenotype but then subsequently follow a more recognisable RRMS pattern and hence may move from BSC or Siponimod back to a RRMS disease modifying therapy again.

Additional issues

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

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

Additional issue 1: Clinical outcomes – Fatigue (FSIQ-RMS)	Section 3.2.4 p59	**No**	The OPTIMUM trial shows benefit on the FSIQ-RMS measure of fatigue (a clinically significant symptom to people with MS) associated with Ponesimod in comparison to the teriflunomide arm. Although this a new scale, there is no consensus on the measurement of fatigue in MS, the reported improvement in this symptom which people experienced potentially is clinically significant as other studies have shown correlation between fatigue severity and mental health, cognition, quality of life, social relationships and employment. This may offer additional benefit to people on the therapy which may not well characterised by other outcome measures (relapse rate, 3 month CDA and MRI).
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

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

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

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

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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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**

NICE National Institute for Health and Care Excellence

Key issues for engagement

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

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	**NO**	It is highly unlikely that ponesimod would be considered as a treatment option for the rapidly evolving severe subgroup, unless due to tolerability or compatibility with personal circumstances. For this group, natalizumab would be recommended; other highly effective disease modifying treatments such as ocrelizumab and ofatumumab would also be considered. We would expect ponesimod to be offered as a first line treatment for people with active RRMS, and as a second line treatment for patients who continue to relapse despite treatment (otherwise described as highly active despite treatment) or are unable to tolerate other treatments.
Key issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	**NO**	We recognise the uncertainty inherent in comparing clinical trials which span 30 years of research against the background of an evolving treatment landscape. We note the ERG's conclusion that the methodology used in the company submission is consistent with previous appraisals and in the absence of more direct head-to-head trials, this will continue to be a key issue in future appraisals.
Key issue 3: Insufficient comparative evidence for the safety of ponesimod	**NO**	Limited evidence of adverse events will have also been an issue in previous appraisals; a two-year clinical trial is unlikely to identify rare serious adverse

		events and does not give sufficient data to permit a direct comparison to fingolimod. We would agree with the ERG's conclusion that long-term real-world evidence in larger groups of people will give a more informed insight into the safety of ponesimod.
Key issue 4: Uncertainty surrounding use of 3 month CDA as the primary measure of disease progression in the economic model	**NO**	6-month CDA has been established as the preferred measure of long-term disability in previous appraisals. The documents provided for the technical engagement are heavily redacted, so it is impossible for us to comment on the ERG's scenario analysis. However, we wish to draw attention to the fact that a review of NICE FADs has confirmed that most of the disease modifying treatments have been shown to significantly reduce disability progression compared to placebo but not compared to active comparator. We would also like to highlight recent research which has investigated therapeutic lag for disease modifying drugs[1]. Using data from international registries, researchers were able to show a delay in effectiveness of 7 to 16 months for a reduction in disability progression. This makes it difficult to demonstrate a treatment effect within a 24-month clinical trial.
Key issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	**NO**	Without data on NHS England prescribing levels of siponimod, it is impossible to say which of these two scenarios most closely matches current clinical practice. Again, the documents provided for technical engagement are heavily redacted so it is impossible for us to comment on the impact of assuming 25% of people receive siponimod after concerting to SPMS.

[1] Roos I, et al. Delay from treatment start to full effect of immunotherapies for multiple sclerosis. Brain. 2020 Sep 1;143(9):2742-2756.

Additional issues

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

NICE National Institute for Health and Care Excellence

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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.	

Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	No	Biogen understands that the definition for Highly Active (HA) and Rapidly Evolving Severe (RES) RRMS outlined in England are based on the clinical criteria for treatment eligibility. While the presentation for these sub populations may be similar, Biogen agree with the ERG that the definition used for clinical criteria compared with presentation by disease severity are not the same. There is a paucity of evidence for the subpopulations in this NMA, which has limited the analysis of comparative efficacy. Nevertheless, the highly active RRMS subgroup data from the company's trial should be used in subgroup analysis for the subgroup NMA, without people with RES due to the uncertainty on comparable relative treatment effect in the different subgroups. Biogen have concerns that there is insufficient data available in the current submission to accurately estimate the comparative efficacy of ponesimod in the RES population. Additionally, further analysis must be provided for comparison versus all relevant comparators, including natalizumab.
Key issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	No	While Biogen do not have access to the full methods and results from the NMA, Biogen agrees with the ERG on the approach to estimate the treatment effect for ponesimod and relevant comparators. Multiple sclerosis is a heterogeneous

		condition, and it is well recognised that there are significant challenges and limitations in estimating the treatment effect through a network meta-analysis. Biogen have concerns about the definition used to define the population included in the data presented for highly active subgroup analysis, as the dataset includes rapidly evolving severe patients. The disease presentation of these subgroups will be likely to affect treatment response, and further evidence on the therapeutic benefit in the subgroups would inform the positioning of ponesimod in the treatment pathway. This would ordinarily have been identified in the NMA feasibility assessment.
Key issue 3: Insufficient comparative evidence for the safety of ponesimod	Yes	Transparency of the adverse event profile selection should be clearly documented, it is not clear in the submission the nature of the selection criteria for inclusion of adverse events into the economic model. Fingolimod received an article 20 restriction (EMA, 2012), published following the NICE appraisal earlier that year (NICE, 2012). The higher discontinuation rate in ponesimod observed in the naïve comparison undertaken by the ERG on AE rates reported for ponesimod and fingolimod are of a concern given the risk of serious adverse events associated with S1P modulators. Further investigation should be undertaken to understand and establish the safety profile of ponesimod. Along with the advice from the clinical advisors to the ERG, Biogen agree with the ERG that further evidence would inform its positioning in the treatment pathway and identification to the most relevant comparators for cost-effectiveness analysis. In the absence of longer-term data, in the model it would be reasonable to estimate that monitoring of ponesimod should match that of fingolimod (as they are in the same therapeutic class). In the absence of the relevant data in the NICE appraisal of fingolimod and with the latest available evidence on the cardiovascular

		risks, a full review of the fingolimod evidence should be considered and incorporated into the safety data. "Fingolimod For The Treatment Of Highly Active Relapsing–Remitting Multiple Sclerosis | Guidance | NICE". *Nice.Org.Uk*, 2012, https://www.nice.org.uk/guidance/ta254. Accessed 7 July 2021. *Assessment Report For GILENYA Review Under Article 20 Of Regulation (EC) No 726/2004 INN: Fingolimod Procedure Number: EMEA/H/C/2202/A-20/008*. European Medicines Agency, London, 2012, pp. 39-42, https://www.ema.europa.eu/en/documents/variation-report/gilenya-h-c-2202-a20-0008-epar-assessment-report-article-20_en.pdf. Accessed 7 July 2021.
Key issue 4: Uncertainty surrounding use of 3 month CDA as the primary measure of disease progression in the economic model	No	Biogen agrees that 3 month CDA as the primary measure of disease progression in the economic model would give a more informative perspective for assessing the cost-effectiveness of ponesimod due to the broader network that enables comparison to the majority of relevant comparators. While 6 month CDA can be more indicative of permanent disability progression, fewer studies report on the 6 month endpoint and data missingness in NMA for 6 month data would mean an absence of comparison to comparators.
Key issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	No	While there is uncertainty around the data used for the population described in the decision problem addressed in the company submission for ponesimod; people with RRMS (limited to people with active RRMS and people with highly active RRMS), the proposed assumption to model treatment sequencing adds an additional complexity that is unwarranted. Furthermore RRMS patients in the current model discontinue to receive BSC in the treatment sequence, when other DMTs would be offered after treatment discontinuation.

Additional issues

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

Additional issue 1: Clinical advice to the ERG was that some people who have been diagnosed with SPMS will also receive dimethyl fumarate, though this is not considered to be highly efficacious.	ERG report: Key Issue 5; p24	Yes	Other than siponimod and interferon beta-1b, Biogen is not aware of any other treatments licensed in SPMS. If other treatments are used in SPMS then this would be unlicensed use. It is acknowledged that there may be instances or circumstances of delayed diagnosis of SPMS with patients remaining on DMTs for RRMS. Biogen request clarification is made in the report as dimethyl fumarate is not licensed in SPMS (EMC, 2020). "Tecfidera 120Mg Gastro-Resistant Hard Capsules - Summary Of Product Characteristics (Smpc) - (Emc)". *Medicines.Org.Uk*, 2020, https://www.medicines.org.uk/emc/product/5256/smpc#gref. Accessed 7 July 2021.
Additional issue 2: Preferred assumption description does not match scenarios assessed by ERG	ERG report – Table 53: ERG preferred base case assumptions (ITT and HA RRMS), p173	No	The following description in Table 53 should be cross checked; “25% of people receive BSC after converting to SPMS, 75% receive Siponimod”, as the scenario described in section 4.2.6 and 6.1.1.2 assumes “25% of people who converted to SPMS received siponimod, whilst 75% received BSC”.

<table>
<tr>
<td>Additional issue 3:

Progression from RRMS to SPMS</td>
<td>ERG report, p106</td>
<td>Yes</td>
<td>The annual probabilities of the London Ontario data used in the TA624 dossier are based on an analysis undertaken by the ERG in the appraisal of daclizumab (TA441). The ERG utilised the appendix to the original ScHAAR report which provided hazards that were subsequently converted to probabilities by p = 1 – exp (–h). The London Ontario data that underlie these estimates is apparently AIC, with ScHAAR having access to the patient level data.

Table 1: ScHAAR report RRMS to SPMS hazards (TA441 ERG Report p153, table 96)
<table>
<tr><td></td><td colspan="2">ScHAAR appendix</td><td>TA441</td></tr>
<tr><td>EDSS</td><td>Hazards</td><td>Probability</td><td>Original manufacturer submission</td></tr>
<tr><td>0</td><td>0.004</td><td>0.004</td><td>0.000</td></tr>
<tr><td>1</td><td>0.002</td><td>0.002</td><td>0.003</td></tr>
<tr><td>2</td><td>0.030</td><td>0.029</td><td>0.032</td></tr>
<tr><td>3</td><td>0.103</td><td>0.097</td><td>0.117</td></tr>
<tr><td>4</td><td>0.199</td><td>0.181</td><td>0.210</td></tr>
<tr><td>5</td><td>0.256</td><td>0.225</td><td>0.299</td></tr>
<tr><td>6</td><td>0.184</td><td>0.168</td><td>0.237</td></tr>
<tr><td>7</td><td>0.237</td><td>0.211</td><td>0.254</td></tr>
<tr><td>8</td><td>0.066</td><td>0.064</td><td>0.153</td></tr>
<tr><td>9</td><td>0.167</td><td>0.154</td><td>1.000</td></tr>
</table>
Biogen consider the RRMS to SPMS transitions applied in the TA624 to be more accurate as data is based on the patient level analysis. Previous STAs (including TA127, TA254, TA303, TA312, TA320 and T441 manufacturer submission) that all used the London Ontario dataset assumed no transitions reported for EDSS 0 and EDSS 9, where the associated probabilities were assumed to be 0 and 1 respectively.</td>
</tr>
</table>

			Single Technology Appraisal Daclizumab For Treating Relapsing-Remitting Multiple Sclerosis [ID827] Committee Papers. NICE, 2017, p. 826, https://www.nice.org.uk/guidance/ta441/documents/committee-papers. Accessed 10 July 2021.
Additional issue 5: half cycle correction applied to cladribine and alemtuzumab	Manufacturer submission B.3.2.2.1 and economic model	No	Given the posology of alemtuzumab and cladribine administered on an annual or bi-annual basis respectively, have half-cycle corrections been omitted from the acquisition and administration costs?

NICE National Institute for Health and Care Excellence

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RRMs to SPMS			

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

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	No	Novartis agrees with the ERG that comparisons between ponesimod and natalizumab should be undertaken and included in the model to allow consideration of the ICERs for ponesimod vs all relevant comparators (including natalizumab). In addressing the issue of subgroups, it is important to recall that the definitions of the so-called "highly active" (HA) and "rapidly evolving severe" (RES) subgroups were created by the European Medicines Agency (EMA) during the regulatory process for natalizumab in order to define a subgroup of people with MS for whom the risk–benefit balance of treatment would be favourable,[1] i.e. these subgroups were created based on identifying greatest unmet need for treatment at that time, not due to an expectation of differential treatment effect. In approaching the evidence base for comparative effectiveness in the present appraisal it is therefore relevant that the subgroups were defined based on what were expected to be prognostic variables rather than on known treatment effect modifiers. The definitions used have been revised over time by the EMA and have been re-applied to other treatments where questions over the risk–benefit balance of treatment arose, such as fingolimod and, latterly, alemtuzumab.[2, 3] As NICE must appraise a product within its licensed indication, TA127 and TA254 issued guidance related to these prognostic subgroups and they therefore entered the NHS algorithm.[4-6] However, Novartis are not aware of any RCTs conducted specifically in the HA or RES populations. The issue raised by the ERG recurs in some form in each appraisal of a new disease modifying therapy (DMT).

		Novartis notes the approach accepted by the ERG and the Committee in TA699: in that appraisal the NMA conducted using the ITT populations of all included trials was considered to be generalisable across both the HA and RES subgroups.[7]
Key issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	No	Novartis notes that heterogeneity within the NMA has been recognised in other appraisals of DMTs and note that the ERG states in their Report that the NMA presented is consistent with other appraisals. Novartis supports maintaining consistency with prior appraisals in the approach to decision making in this appraisal.
Key issue 3: Insufficient comparative evidence for the safety of ponesimod	No	Novartis disagrees with the ERG proposal to conduct an NMA of discontinuation rates due to adverse events, given the differences in trial protocol definitions of such events. Novartis suggests that the appropriate resolution to the ERG concern regarding positioning of ponesimod is to undertake qualitative comparisons to all DMTs available for RRMS in the NHS. Novartis agrees with the ERG that the evidence does not demonstrate that ponesimod is associated with a better safety profile than fingolimod. A naïve comparison of clinical trial data shows that the incidence of hypertension in patients treated with ponesimod (10.1%)[8] is higher than in those treated with fingolimod (3.7%–6.1%)[9, 10] and the summary of product characteristics for ponesimod suggests that blood pressure should be regularly monitored during treatment with ponesimod.[11] As the ERG reports, rare adverse events, such as progressive multifocal leukoencephalopathy (PML), or also reactivation of disease activity (rebound) and hepatobiliary disorders, may be identified over a longer time period, but there is inherent uncertainty in the long term safety profile of any new treatment which has recently received a marketing authorisation based on available phase 2 and 3 clinical trial data.

Key issue 4: Uncertainty surrounding use of 3 month CDA as the primary measure of disease progression in the economic model	No	Novartis agrees with the ERG that 6-month CDA is the correct measure of disability progression to be used in the model, because it is less likely confounded by incomplete relapse recovery than 3-month CDA, in line with long-established Committee preference across all recent appraisals of DMTs for MS, including TA699.[7] The reduction in the evidence base available to inform the NMA that results from exclusively focussing on 6-month CDA (as opposed to 3-month CDA) is negligible and was not considered a barrier to decision-making in TA699.[7]
Key issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	No	Following the publication of TA656, siponimod is now available for patients with active SPMS.[12] Novartis therefore agrees that it is appropriate to test the effect of this new pathway in the model by considering subsequent treatment after transition to SPMS for a proportion of people in the model. Novartis is however extremely concerned by the ERG approach to implementing this scenario, as the ERG applies the cost of siponimod but does not model its effectiveness and continues to apply transition probabilities for untreated patients. This is not an evidence-based approach to considering the new treatment pathway for SPMS and may in fact introduce more uncertainty and bias. Novartis requests that the Committee rejects any analysis that includes the cost but not the effectiveness of siponimod as biased and misrepresenting the cost-effective nature of siponimod within the treatment pathway, as established by NICE in TA656.[12] If the current model structure does not allow the effectiveness of siponimod to be included within the timeframe of this appraisal, it would be preferable to model 100% BSC in SPMS which would align to previous decision-making models considered by the Committee, including TA699.[7]

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

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Waning of treatment effectiveness	Page 109	No	No evidence has been presented by the Company or the ERG to support the arbitrary reduction in efficacy of 25% after Year 2 and 50% after Year 5 applied to all DMTs by the Company and accepted by the ERG. Indeed, in contrast to this assumption, evidence against waning has been presented in prior appraisals such as TA533 and TA699.[7, 13] In both TA533 and TA699 the Committee instead accepted that using all-cause discontinuation rates in the model acts as a proxy for any waning of treatment effect, as patients are unlikely to stay on a treatment if they experience breakthrough disease.[7, 13] Given this precedent, Novartis requests that the appraisal base case be changed to consider all-cause discontinuation as an adequate proxy for waning.

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Ponesimod for treating relapsing multiple sclerosis [ID1393]

ERG Review of Company's Response to Technical Engagement Response

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1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of ponesimod (ID1393).

In response to technical engagement, the company have: sought expert clinical advice; clarified their intended positioning for ponesimod; presented a series of new analyses; clarified some of their methods; and have updated their economic model to incorporate new clinical efficacy inputs. In addition, the company raised several key issues relevant to this appraisal.

The ERG has reviewed the additional evidence presented by the company to address key uncertainties raised in the ERGs report. A response to each of the issues, including those raised by the company, is presented in the sections below.

In addition, the ERG has provided a response to key issues raised by NICE, and to the responses to technical engagement written by stakeholders.

The ERG response is structured as follows:

- Section 2: ERG response to key issues raised by NICE
- Section 3: ERG response to the company's submission at technical engagement
- Section 4: ERG response to issues raised by the company
- Section 5: ERG response to updates in the company's base case
- Section 6: ERG response to stakeholder comments received during technical engagement.

In addition, this response is accompanied by an appendix containing the results of the company's economic model after confidential patient access scheme (PAS) discounts have been applied for comparators to ponesimod. Please note that the results in this document therefore only contain the PAS discount agreed for ponesimod.

2. ERG RESPONSE TO KEY ISSUES RAISED BY NICE

In a communication between the ERG and NICE on 12/07/2021, several issues were raised for ERG review. A response to each of these issues is provided below.

1. *Issue with using hazard ratios (HRs) as relative risks (RRs) - The HRs from the CDA NMA are handled as if they are RRs. This has potential to overstate treatment effect for all active treatments vs placebo. Therefore, some artificial caps have been set at 1 in various places which shouldn't have been necessary on the appropriate rate scale.*

ERG response: We acknowledge that it is optimal to use the appropriate rate scale to estimate transition probability matrices. However, numerous previous MS appraisals have acknowledged the challenges of estimating transition probability matrices given the numerous possible forward transitions and the limitations of existing NMA evidence; for example, nearly all trials of MS therapies use Cox proportional hazards models to estimate disability progression. As a result, HRs are commonly used as risk ratios to estimate changes to transition probability matrices. While acknowledging that this is suboptimal, we do not believe this is a critical issue and is in fact a necessary compromise between the data we have and the model structure now commonly accepted for RRMS appraisals.

2. Reconsideration of source of discontinuation data - *Using data from all-cause discontinuation could double count some modelled events (e.g. progression to SPMS). Pooling the 24-week and 108-week trial could overstate the expected rate. The higher discontinuation in the 24-week trial suggests that there could be exploration of a non-constant rate of discontinuation (i.e. AEs have an immediate reaction and these would be rarer in those that continue past the first 24 weeks).*

ERG response: We believe that we have appropriately raised the key challenges in quality of safety data in this appraisal, and as a recurring issue in MS appraisals generally. Previous meta-analyses of adverse events in RRMS trials (e.g. Melendez-Torres et al., 2017) have found these data to be of consistently low quality and unlikely to be provided in the relevant time frames. Indeed, in the cited meta-analysis, the modal follow-up time was 24 months, despite time-varying discontinuation rates likely falling off after year 1. Previous MS appraisals have also acknowledged these challenges with discontinuation rates and acknowledged that despite these likely differences, there exist little data to address this problem systematically.

3. Structural uncertainty of pairwise comparisons in the model - *The pairwise setup of the model could overlook critical correlations between treatment effects, this is because NMA estimates are sampled independently (see TSD6).*

Additional potential errors in the probabilistic sensitivity analysis – Some potential issues surrounding parameters used in the probabilistic sensitivyt including fixed starting distributions, arbitrary uncertainty and parameters with perfect correlation. An error was identified that led to increased certainty with higher number of PSA runs.

ERG response: The ERG agree that the uncertainty in the results should be expressed via 95% credibility intervals rather than confidence intervals. The PSA results for the revised model have yet to be provided and the ERG have requested that the intervals are corrected before these results are generated. The ERG agree that it would be preferable for potential correlations between the treatment effects to be accounted for when sampling (without assuming perfect correlation), but are mindful of the timeline to which the company is working and so have decided not to request that possibly substantial structural changes are made to the model at this stage. While the minor points on the choice of certain distributions in the PSA are valid, the ERG note that these do not concern parameters to which the results are noticeably sensitive and so the PSA results are unlikely to be significantly affected by related adjustments.

3. ERG RESPONSE TO COMPANY'S SUBMISSION AT TECHNICAL ENGAGEMENT

This section contains the ERG's response to the company's submission at technical engagement, including the additional evidence presented by the company in an appendix to their response. For ease, the ERG has retained the company's response in this document.

Key issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population

The ERG welcome clarification from the company that they do not wish to target ponesimod towards the RES population, which was a query unresolved during clarification.

The ERG thanks the company for providing analyses relevant to the HA RRMS population as defined using NHS criteria, and believe that these analyses are most relevant to decision-making for the HA RRMS due to potential differences in clinical efficacy and costs between people with HA and RES RRMS.

The results of the updated NMAs are broadly similar to those presented by the company using the broader OPTIMUM trial definition, with only subtle changes in the effect estimates and respective 95% confidence intervals. These changes had no material impact on the ERG's conclusions regarding the comparative effectiveness of ponesimod. The impact of these data on the company's economic findings are summarised in Section 5.

Finally, the ERG consider that the company misunderstood a statement made during the technical engagement call regarding disease progression in people with RES RRMS, and is aware that people with RES RRMS may progress while receiving treatment. As stated in its report, the ERG is aware that there is a lack of a universal definition surrounding the different subgroups of RRMS, and that high quality evidence comparing treatment effectiveness and costs between subgroups are lacking. This is one of the uncertainties in appraisals of disease-modifying treatments for RRMS. However, by adjusting the subgroup analyses to the NICE definition of HA RRMS and the treatments currently, the ERG consider that this evidence will be most relevant to decision-making for this group.

Key issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators

The ERG thanks the company for providing these amended NMAs, which seek to resolve an issue of uncertainty surrounding the effect estimates for treatment with interferons. Of the two approaches, the ERG considered that the class-based analysis treating interferons as a

class was the most useful analysis, as this can account for outliers in treatment effects without losing data.

The ERG agrees with the company that the treatment effects reported from the class-based NMA are broadly comparable to those from the company's original analyses. The ERG's conclusions about the relative efficacy of ponesimod in the trial ITT population are therefore unchanged. However, as stated in its report, the ERG noted that even small changes in treatment effects could materially impact on cost effectiveness. Larger change was seen for comparisons with ocrelizumab and alemtuzumab, where relative effects moved closer to the line of null effect. The impact on the ICER is discussed further in Section 5.

However, the ERG wishes to stress that the approach taken by the company, while reasonable in addressing this one source of uncertainty, does not resolve the major limitations with the analyses. As stated by the company, the ERG noted in its report that the company's NMAs appeared to include all relevant evidence to the decision problem, and generated effect estimates consistent with those reported by previously published NMAs. However, as also stated by stakeholders in their response to technical engagement, there are significant limitations with these NMAs due to extreme heterogeneity in trial design that is highly likely to bias effect estimates. This view is also mirrored by the company's feasibility assessment provided during technical engagement, which identified multiple sources of heterogeneity in the evidence base for all analyses, most notably trial follow-up duration and previous treatments at baseline. As shown in the ERG report, the impact of this heterogeneity is demonstrated by vast differences in the effect of placebo reported across trials for all outcomes. The ERG therefore consider that the clinical efficacy estimates for ponesimod and its comparators continue to be highly uncertain. This is a pervasive issue relevant to evaluations of RRMS treatments in all populations, meaning that there is a high degree of uncertainty in how these treatments will perform in practice.

The ERG further notes that it was agreed during the technical engagement call that the company would present missing outcome data for its NMAs, including confidence intervals around rank data and investigations about inconsistency in the networks. However, these have not been presented for any of the company's NMA (note that NMAs presented during technical engagement were not accompanied by rank data).

Finally, the ERG thanks the company for clarifying the domains assessed as part of their risk of bias assessment, and consider that this item has been resolved.

Key issue 3: Insufficient comparative evidence for the safety of ponesimod

Additional AE and SAE NMAs

The ERG thanks the company for undertaking additional NMAs related to AEs and SAEs, both as a full network and an S1P network, in seeking to address the need for further comparative safety evidence. Point estimates in comparisons with most DMTs suggest a broadly similar safety profile for ponesimod in terms of overall AEs, [redacted]

However, the ERG stresses that as with the other NMAs provided by the company, the evidence base is very heterogeneous and point estimates in both AE and SAE analyses are surrounded by wide 95% credible intervals. These intervals frequently extend widely on each side of the line of null effect, suggesting that the true difference in AEs and SAEs between treatments is highly uncertain. In addition to variation in trial methods, consistent with the company's other NMAs, there is also likely to be variation in the definition and measurement of AEs across trials.

On the basis of the available evidence, the ERG considers that a high degree of uncertainty remains around the relative safety of ponesimod. In general, ponesimod may be broadly comparable in safety to other DMTs; [redacted].

Long-term safety of ponesimod

The ERG acknowledges the company's position that ponesimod has one of the longest data collection periods. However, the ERG remains concerned that long-term safety has not been demonstrated in a large enough group of participants. The long-term follow-up period in the trial only includes 145 participants treated with the licensed dose (20mg) of ponesimod. Clinical advice to the ERG confirms that rare serious side effects, such as PML - a known concern with S1P modulators, take both many years and many patients to detect.

Safety vs. efficacy plots

The ERG thanks the company for providing plots showing the relative balance of safety vs. efficacy of ponesimod and its comparators. As stated in the ERG report, the ERG consider that these plots may be informative for considering the likely positioning of ponesimod,

although cautions that the plots be interpreted with caution, given uncertainty in the estimates of clinical efficacy and safety in this field. The ERG further note that the plots are based on data from the trial ITT population (i.e. separate plots are not provided for trial populations with HA RRMS). The ERG notes two minor errors on one of the figures provided (Figure 16): first, the x-axis is incorrectly labelled as serious adverse events; and second, alemtuzumab is omitted from the plot.

Overall, the ERG considers these plots to suggest that [redacted]. Overall, the ERG interpreted the plots to suggest that ponesimod may be most comparable as a treatment option to first-line DMTs, although there may be situations where people with RRMS would choose ponesimod as an appropriate alternative to a 2nd line DMT.

Comparative safety of ponesimod and fingolimod

As stated in the ERG report, the ERG agrees with the company that naïve comparisons of safety data can be misleading, and should be interpreted with caution. In the absence of a head-to-head comparison, and in consideration to the limitations of the NMA data for safety, the ERG considers that the comparative safety profile of ponesimod and fingolimod remains uncertain. While the ERG acknowledges that there is biological plausibility for an improved safety profile of ponesimod relative to fingolimod, the ERG does not agree with the company that evidence has demonstrated an improved safety profile for ponesimod.

In detailed response to the additional information provided by the company from the SmPC of fingolimod and ponesimod (in effect a naive comparison itself), the ERG thanks the company for pointing out the inconsistency between trials of ponesimod and fingolimod in respect of ULN reference ranges for ALT; it further notes the transient nature of elevated liver transaminases resolving with continued ponesimod treatment, as juxtaposed with the evidence for a suggested dose-response relationship with fingolimod. Furthermore, the ERG notes the evidence presented for a comparable cardiac safety profile for ponesimod versus fingolimod; it also notes the incidence of macular oedema in trials for both treatments, and the role of a history of eye disorders in patients with MS. However, the ERG considers all these factors to be encompassed in the new NMAs conducted by the company and therefore still views the comparative evidence for these AEs to be uncertain. Furthermore, in the

absence of comparative evidence of treatment discontinuations due to AEs, the ERG would like to reiterate that the best available evidence on this remains a more than two-fold increase in treatment discontinuations due to AEs between ponesimod (8.7%) and fingolimod (2.2 to 3.1%).

Key issue 4: Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model

The ERG does not change its view about its preference for the CDA-6 outcome over CDA-3. The benefit of CDA-6 is that it provides a more reliable measure of disability progression, given the natural fluctuations in disease that are common for people with RRMS. While historically CDA-6 has been measured less frequently in trials, in the company's analyses the difference was negligible (N=23 vs. N=26 trials), and there was no major drop in participant numbers (16,029 vs. 17,266). The ERG note the point raised by the company that there are fewer closed loops in the CDA-6 analyses than for CDA-3, however on balance consider that limitations of measuring disability using CDA-3 outweigh this. Therefore, the ERG preference is consistent with previous appraisals that CDA-6 should have greater weight in decision-making. CDA-3 outcomes may be considered as supportive evidence, and the ERG have provided a commentary on both CDA-3 and CDA-6 in its report.

Key issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive best supportive care (BSC)

The ERG thanks the company for conducting expert elicitation on this issue, which is obviously an area of uncertainty until such time as data on siponimod uptake are available. The findings of the company's analyses are similar to those reported by the ERG; i.e. that incorporating treatment costs for subsequent uptake of siponimod has little impact on the ICER. However, as stated in its report, the ERG noted that this is a limited approach, as it does not account for the clinical effect of siponimod, for which there was a lack of robust long-term data available. The true impact of the availability of siponimod therefore remains uncertain.

4. ERG RESPONSE TO ADDITIONAL ISSUES RAISED BY THE COMPANY

In this section, the ERG responds to additional key issues raised by the company during technical engagement. Some of these issues relate to those raised in the NICE technical engagement response.

Additional issue 1: Induction treatments (cladribine and alemtuzumab) as appropriate comparators

The company proposed that "Higher efficacy treatments (in particular those used as "induction treatments") are not appropriate comparators to moderate efficacy treatments such as ponesimod, and the results should be interpreted with caution". The ERG acknowledges that there are likely differences in treatment strategy between induction and escalation approaches. However, the ERG remains unconvinced that the classification the company propose in their response has meaningful impact in respect of which comparators should be considered in cost-effectiveness modelling, instead suggesting which comparators are most likely to be considered as 'of a kind' in patient-clinician shared decision-making.

Put otherwise, what Janssen are proposing in their response is not a difference in treatment pathway as such, as all included comparators are relevant for consideration in highly active RRMS. Thus, the ERG do not regard that it is appropriate to exclude or include comparators on the basis of difference in treatment strategy. For this proposed distinction between induction and escalation therapy to be amenable of inclusion in the ERG's economic analysis, a considerably different treatment pathway would need to be proposed with formalisable criteria for patients selecting into either an 'induction pathway' or an 'escalation pathway'. As currently proposed, Janssen have not suggested these formalisable criteria.

Additional issue 2: Plausibility of trials for interferon-beta-1B (INCOMIN) and peginterferon (ADVANCE)

As stated in response to Key Issue 2, the ERG thanks the company for providing these new analyses, which help to address one source of uncertainty in the NMA results. Of the two approaches, the ERG prefers the analysis treating interferons as a class, as evidence suggests they have comparable efficacy, and this approach helps to address outlier data points while retaining all the available data.

The ERG accepted the inclusion of these data in the company's revised economic evaluation. The ERG's appraisal of the results of this analysis are reported in Section 5. For the reason stated above, the ERG did not consider the company's revised model that

excluded evidence from the INCOMIN and ADVANCE trials to be appropriate for consideration.

Additional issue 3: NEDA-3 NMA results

The ERG did not consider this to be a new issue; however, thanks the company for providing an additional NMA in the trial ITT RRMS population to evaluate the comparative efficacy of ponesimod for the risk of NEDA-3. As stated by the company, their primary definition of NEDA-3 was the absence of confirmed relapses, absence of 3-month CDA, and no new or enlarging MRI lesions. Generally speaking, the results were consistent with the comparative efficacy of ponesimod for ARR.

As stated in the ERG report, the association between NEDA-3 and predicting long-term disease progression has not been established, and the reliance on CDA-3 in determining the outcome has limitations (as discussed for Key Issue 4 above). Furthermore, the provision of this additional NMA, while providing additional validation of the other analyses, does not resolve the uncertainty in the NMAs. While the company's feasibility assessment did not find a major cause for concern in the different definitions of NEDA-3 used across the trials, the broader issues of heterogeneity remain.

5. ERG RESPONSE OF CHANGES TO THE COMPANY'S COST-DEFFECTIVENESS ESTIMATE(S)

The ERG's response to the changes made by the company to their base case are summarised in Table 1. The ERG accepts all these changes, and does not present an alternative preferred base case.

As several of the changes made by the company were included in the ERG preferred base case presented in its original report, the impact of these changes has been explored previously. In Table 2, the ERG reports the impact of using a class-based effect for interferon treatment on the company's base case (ITT population), and in Table 4 the ERG reports the impact of using the NHS definition of HA RRMS on the company's base case (HA RRMS population). In Table 3 and Table 5, the ERG reports the impact of accepting all the revisions on the ERG's original base case in the ITT RRMS and HA RRMS populations, respectively.

It should be noted that these results do not include the relevant cPAS information and therefore do not reflect accurate treatment costs. Please see the appendix to this document, which contains results incorporating those discounts.

Table 1: Summary of changes made to the company's base case

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made by the company in response to technical engagement	Impact on the base-case ICERs
Issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	Treatment effects for ponesimod in the highly active subpopulation were based on evidence from the prespecified highly active subgroup from the OPTIMUM trial	Treatment effects for ponesimod in the highly active subpopulation are based on patients with highly active RRMS as defined by NICE/NHSE and obtained from post hoc analyses of the OPTIMUM trial	Please see Tables 4 & 5 for details of changes in the base case ICERs for the full set of comparators considered in this appraisal
Issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	Treatment effects for interferons were considered separately for each DMT in the ITT population	Treatment effects for interferons are considered as a pooled average of all DMTs, since all of these DMTs are considered to have equivalent clinical effectiveness	Please see Tables 2 & 3 for details of changes in the base case ICERs for the full set of comparators considered in this appraisal

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made by the company in response to technical engagement	Impact on the base-case ICERs
Issue 4: Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model	3-month CDA was used as the primary measure of disease progression in the economic model	6-month CDA is used as the primary measure of disease progression in the economic model, in line with the ERG's preferred assumptions	Please see section 6.2 of the ERG report for the impact of this change on the company's original base case results.
Issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	100% of patients that convert to SPMS will receive best supportive care (BSC)	25% of patients that convert to SPMS will receive siponimod, while 75% of patients will receive BSC, in line with the ERG's preferred assumptions and based on clinical expert feedback to Janssen	Please see section 6.2 of the ERG report for the impact of this change on the company's original base case results

Table 2: ICERs for ponesimod vs comparator DMTs in the ITT population: impact of including the class-based effect for interferon treatment (Key Issue 2)

	TER	DMF	GA	IFNB-1a 22 mg	IFNB-1a 30 mg	IFNB-1a 44 mg	IFNB-1b	OCR	OFA	OZA	PEG
Original company base case ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER with change for Key Issue 2	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	NA

Table 3: ICERs for ponesimod vs comparator DMTs in the ITT population: comparison of original ERG base case and revised base case

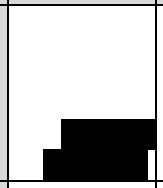
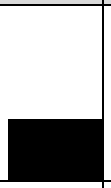
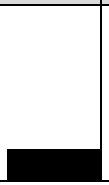
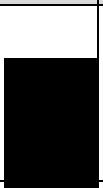
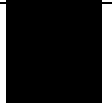
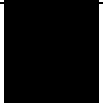
	TER	DMF	GA	IFNB–1a 22 mg	IFNB-1a 30 mg	IFNB-1a 44 mg	IFNB-1b	OCR	OFA	OZA	PEG
Original ERG base case ICER											
Revised base case ICER											

Table 4: ICERs for ponesimod vs comparator DMTs in the highly active population: impact of using the NHS definition of HA RRMS (Key issue 1)

	OCR	OFA	OZA	ALE	CLA	FIN
Original company base case ICER						
ICER with change for Key Issue 1						

Table 5: ICERs for ponesimod vs comparator DMTs in the highly active population: comparison of original ERG base case and revised base case after technical engagement

	OCR	OFA	OZA	ALE	CLA	FIN
Original ERG base case ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6. ERG RESPONSE TO ISSUES RAISED BY STAKEHOLDERS

Responses to technical engagement were received by the following stakeholders:

- A representative of the Association of British Neurologists (ABN)
- Representative for companies who manufacture comparator products to ponesimod (Biogen: manufacturer of: interferon beta-1a, peginterferon beta-1a, dimethyl fumarate and natalizumab; and Novartis: manufacturer of ofatumumab and siponimod).
- A representative of the Multiple Sclerosis Trust
- A patient with MS who is also an employee of a patient organisation
- A specialist in the treatment of RRMS (Professor of Neurology)

Overall, stakeholders considered ponesimod to be most appropriate for the treatment of active RRMS, or potentially as an alternative to fingolimod for those with HA RRMS. It was noted that the availability of an oral treatment with a short half-life would be an appealing treatment option for people RRMS; however, the risk of relapse, disability, and safety concerns were nevertheless paramount. It was noted that a reduction in fatigue would also be valuable to people with RRMS, and that this could have knock-on benefits for their quality of life and mental health.

A stakeholder noted that uncertainty in whether evidence in the trial ITT RRMS population could be generalised to subgroups of people with HA and RES RRMS is a recurring issue in NICE appraisals of treatments for RRMS. Further evidence to evaluate whether treatment effects can be generalised across populations would be informative.

Stakeholders supported the approach taken by the company to evaluate ponesimod, which is consistent with the approach taken in previous NICE appraisals of treatments for RRMS. It was noted that the measurement of disability in RRMS is complex, and that more robust measures are needed. Of the two measures, however, stakeholders stated that CDA-6 provides a more robust measure of disability than CDA-3. Stakeholders also noted the uncertainty in the company's NMAs, noting that this is a feature of the evidence base in this field. Stakeholders noted that without more direct head-to-head comparisons of treatments for RRMS, uncertainty in the clinical evidence base will continue to be a key issue for future appraisals.

On the basis of the available trial evidence, stakeholders considered that ponesimod had an acceptable safety profile. However, stakeholders noted that longer follow-up data with a

larger sample would give a more reliable representation of safety. Furthermore, it was considered that further evidence may be needed to evaluate the comparative safety of ponesimod and fingolimod.

Stakeholders considered that it was appropriate for subsequent treatment with siponimod to be considered in the company's model; however, stakeholders noted that the uptake of siponimod is as yet unknown. It was noted that consideration of the costs of siponimod without also modelling its clinical effects lacks validity, and the results should be interpreted with caution.

In addition to the above appraisal, the ERG has provided specific feedback to several issues raised by stakeholders:

1. *Biogen request clarification is made in the report as dimethyl fumarate is not licensed in SPMS (EMC, 2020).*

ERG response: The ERG report does not state that dimethyl fumarate is licensed for the treatment of SPMS, but rather repeats a statement from clinical experts to the ERG that the treatment is nevertheless used.

2. *The following description in Table 53 should be cross checked; "25% of people receive BSC after converting to SPMS, 75% receive Siponimod", as the scenario described in section 4.2.6 and 6.1.1.2 assumes "25% of people who converted to SPMS received siponimod, whilst 75% received BSC".*

ERG response: The ERG thank the stakeholder for raising this error in the text.

3. *Biogen consider the RRMS to SPMS transitions applied in the TA624 to be more accurate as data is based on the patient level analysis. Previous STAs (including TA127, TA254, TA303, TA312, TA320 and T441 manufacturer submission) that all used the London Ontario dataset assumed no transitions reported for EDSS 0 and EDSS 9, where the associated probabilities were assumed to be 0 and 1 respectively.*

ERG response: The ERG acknowledge that different approaches have been taken in previous appraisals, with different data sources, but believe that the approach taken by the company in this appraisal is defensible.

4. *Given the posology of alemtuzumab and cladribine administered on an annual or bi-annual basis respectively, have half-cycle corrections been omitted from the acquisition and administration costs?*

ERG response: Yes, half-cycle corrections have been omitted from the acquisition and administration costs for alemtuzumab and cladribine.

5. *Novartis requests that the appraisal base case be changed to consider all-cause discontinuation as an adequate proxy for waning*

ERG response: The ERG does not think that all-cause discontinuation should be used as a proxy for waning in the base case, since this includes discontinuation for reasons other than treatment effectiveness. Adverse events are a major cause of discontinuation among patients with MS, and the degree to which all-cause discontinuation is a proxy for treatment waning is likely to vary systematically by drug.

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Addendum to the ERG Review of Company's Response to Technical Engagement: Appraisal of PSA results

August, 2021

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
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1. INTRODUCTION

This document is an addendum to the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of ponesimod (ID1393). Due to time constraints, the company were unable to submit the results of their probabilistic sensitivity analyses (PSAs) with their response to technical engagement. These were subsequently submitted to the ERG after the end of the technical engagement period. This addendum contains the ERG's appraisal of these results.

It should be noted that the revised PSA results are based on company changes to the model, which were accepted by the ERG (see Section 2). Due to the limitations surrounding deterministic sensitivity analysis, the PSA results may be useful in exploring the impact of uncertainties in the cost effectiveness results highlighted by the ERG in its report.

The ERG response is structured as follows:

- An overview of the company's revised changes (Section 2)
- Presentation of company PSA results, scatter plots and cost effectiveness acceptability (CEAC) curves for the ITT and HA RRMS populations (Section 3)
- A brief conclusion describing the PSA results (Section 4)

In addition, this response is accompanied by an appendix containing the results of the company's economic model after confidential patient access scheme (PAS) discounts have been applied for comparators to ponesimod. Please note that the results in this document therefore only contain the PAS discount agreed for ponesimod.

2. SUMMARY OF THE COMPANY'S REVISED CHANGES

The company's revised analysis results presented within this document are based on the following:

- Treatment effects for ponesimod in the highly active subpopulation are based on patients with highly active RRMS as defined by NICE/NHSE and obtained from post hoc analyses of the OPTIMUM trial
- Treatment effects for interferons are considered as a pooled average of all DMTs, since all of these DMTs are considered to have equivalent clinical effectiveness
- Six-month CDA is used as the primary measure of disease progression in the economic model, in line with the ERG's preferred assumptions
- 25% of patients that convert to SPMS will receive siponimod, while 75% of patients will receive BSC, in line with the ERG's preferred assumptions and based on clinical expert feedback to Janssen.

As stated by the company, two of these changes (6-month CDA and siponimod uptake) were incorporated into the original ERG base case. The ERG considers the other changes made by the company to be appropriate, and does not present PSA results using an alternative ERG base case.

3. COMPANY PSA RESULTS

3.1. ITT population

Table 1: Company PSA results (ITT population)

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER (Probabilistic)	ICER (Deterministic)
	Mean (Probabilistic)	95% CrI lower	95% CrI upper	Deterministic (base case)	Mean (Probabilistic)	95% CrI lower	95% CrI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Abbreviations: CrI; credible interval; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years

Figure 1 Cost-effectiveness scatter plot (ITT population)

Abbreviations: ITT, intention-to-treat; QALYs, quality adjusted life years

Figure 2 Cost-effectiveness acceptability curve (ITT population)

Abbreviations: ITT, intention-to-treat; QALYs, quality adjusted life years

3.2. HA RRMS Subgroup

Table 2 Company PSA results (HA RRMS subgroup)

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER (Probabilistic)	ICER (Deterministic)
	Mean (Probabilistic)	95% CrI lower	95% CrI upper	Deterministic (base case)	Mean (Probabilistic)	95% CrI lower	95% CrI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI; credible interval; HA, highly active; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

Figure 3 Cost-effectiveness scatter plot (HA RRMS subgroup)

Abbreviations: HA, highly active; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

Figure 4 Cost-effectiveness acceptability curve (HA RRMS subgroup)

Abbreviations: HA, highly active; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis

4. CONCLUSION

Based on these results, the ERG concluded the following:

4.1. PSA results (ITT and HA RRMS population)

- For both the ITT and the HA RRMS populations, probabilistic ICERs were broadly comparable to the deterministic ICERs, albeit in the HA RRMS subgroup [redacted]

4.2. Cost effectiveness scatter plot (ITT population)

- Compared to ocrelizumab and ofatumumab, the majority of ICERs [redacted]
- Compared to the interferon class, teriflunomide, dimethyl fumarate, ozanimod and glatiramer acetate, [redacted]

4.3. CEAC (ITT population)

- Based on the CEAC results, the probability of ponesimod being the most cost-effective treatment was approximately [redacted], at a willingness to pay threshold of £30,000.

4.4. Cost effectiveness scatter plot (HA RRMS population)

- Compared to cladribine, [redacted]
- Compared to ocrelizumab, ofatumumab and alemtuzumab [redacted]
  - [redacted]

4.5. CEAC (HA RRMS population)

- Based on the CEAC results, ponesimod had a [redacted] probability of being the most cost-effective treatment, at a willingness to pay threshold of £30,000.

It should be reiterated that the company's PSA results presented in this document do not account for comparator PAS discounts. Please see the accompanying cPAS appendix for the most relevant results for decision making.

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Addendum #2 to the ERG Review of Company's Response to Technical Engagement: Appraisal of PSA results

August, 2021

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1. INTRODUCTION

This document is the second addendum to the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of ponesimod (ID1393).

Following the completion of the ERG's response to technical engagement, the company submitted for approval a new patient access scheme (PAS) discount. At the time of writing, the proposed PAS had not yet been formalised. However to aid the NICE committee and in respect of the available time prior to the committee meeting, the ERG integrated the new proposed company PAS into (a) the company's new base case analysis submitted at technical engagement (and accepted by the ERG) and (b) the ERG's deterministic sensitivity analyses. Within the timeframe, it was not possible to update the probabilistic sensitivity analyses (PSAs). The updates made to the company's economic analyses at technical engagement are outlined in the ERG's response to technical engagement, and are not repeated in this document.

The ERG response is structured as follows:

- The results of the company's new base case analysis (Section **Error! Reference source not found.**)
- The results of the ERG's deterministic scenario analyses (Section **Error! Reference source not found.**)

In addition, this response is accompanied by an appendix containing the results of the company's economic model after confidential patient access scheme (PAS) discounts have been applied for comparators to ponesimod. Please note that the results in this document therefore only contain the PAS discount agreed for ponesimod.

2. COMPANY BASE CASE

2.1. ITT population

Table 1: Company revised analysis (ITT population)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years

2.2. HA RRMS subgroup

Table 2: Company revised base case results (HA RRMS subgroup)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	Cost per QALY gained (ICER)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	Cost per QALY gained (ICER)
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

3. ERG scenario analysis

In this section, the ERG report the results of the ERG's scenario analyses after incorporating the revisions made by the company at technical engagement and the updated PAS for ponesimod. Scenario analyses 1 (using CDA-6) and 2 (25% of people converting to SPMS receive siponimod) are not shown, as these are no longer needed following the revisions made to the base case.

3.1.1.1. ITT population

Table 3: ERG scenario analysis results (ITT population)

ERG Scenario	Outcome PON vs comparator	TER	DMF	GA	INT class	OCR	OFA	OZA
Company base case	Incremental QALYs							
	Incremental Costs							
	ICER							
S3: UK RSS population	Incremental QALY							
	Incremental Costs							
	ICER							
S4: Alternative subsequent treatments	Incremental QALY							
	Incremental Costs							
	ICER							

ERG Scenario	Outcome PON vs comparator	TER	DMF	GA	INT class	OCR	OFA	OZA
S5: 5% discontinu-ation rate	Incremental QALY							
	Incremental Costs							
	ICER							
S6: No treatment waning	Incremental QALY							
	Incremental Costs							
	ICER							
S7: Alternative modelled clinical effectiveness parameters	Incremental QALYs							
	Incremental Costs							
	ICER							
S8: Monitoring costs	Incremental QALYs							
	Incremental Costs							
	ICER							
	Incremental QALYs							

ERG Scenario	Outcome PON vs comparator	TER	DMF	GA	INT class	OCR	OFA	OZA
S9: EDSS health state costs	Incremental Costs							
	ICER							
S10: Relapse costs	Incremental QALYs							
	Incremental Costs							
	ICER							
S11: EDSS health state utilities	Incremental QALYs							
	Incremental Costs							
	ICER							
S12: Conversion to SPMS	Incremental QALYs							
	Incremental Costs							
	ICER							

Abbreviations: DMF, dimethyl fumarate 240mg PO; ERG, Evidence Review Group; GA, glatiramer acetate 20mg SC; ICER, incremental cost-effectiveness ratio; IFNB-1a 22 µg, interferon beta-1a 22 µg subcutaneously; IFNB-1a 30 mcg, interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg, interferon beta-1a 44 µg subcutaneously three times weekly; ITT, intention-to-treat; OCR, ocrelizumab 600 mg every six months; ofatumumab 20mg SC; ozanimod 1.0mg PO; PBO, placebo; PEG, peginterferon beta-1a 125mcg subcutaneously; PON, ponesimod 20 mg once daily; QALYs, quality adjusted life years; TER, teriflunomide 14 mg once daily

3.1.1.2. HA RRMS subgroup

Table 4: ERG scenario analysis results (HA RRMS subgroup)

Scenario	Outcome PON vs comparator	OCR	OFT	OZA	ALE	CLA	FIN
Company HA subgroup analysis	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S3: UK RSS population	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S4: Alternative subsequent treatments	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S5: 5% discontinu-ation rate	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs comparator	OCR	OFT	OZA	ALE	CLA	FIN
S6: No treatment waning	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S7: Alternative modelled clinical effectiveness parameters	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S8: Monitoring costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S9: EDSS health state costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S10: Relapse costs	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome PON vs comparator	OCR	OFT	OZA	ALE	CLA	FIN
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S11: EDSS health state utilities	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S12: Conversion to SPMS	Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Incremental Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; ERG, Evidence Review Group; FIN, fingolimod 0.5 mg once daily; HA, highly active; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OCR, ocrelizumab 600 mg every six months; Ofatumumab 20mg SC; Ozanimod 1.0mg PO; PBO, placebo; PON, ponesimod 20 mg once daily; QALYs, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Addendum #3 to the ERG Review of Company's Response to Technical Engagement
August, 2021

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1. INTRODUCTION

This document is the third addendum to the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of ponesimod (ID1393).

The analysis reported herein includes:

- Use of the 108-week discontinuation rate; and
- Adjustment of transition probabilities to use hazard ratios re-expressed as risk ratios.

This applies across all analyses labelled as 'Company base case' as the company and ERG base cases now coincide.

For probabilistic sensitivity analyses (PSAs; Section 3), we also provide credible intervals for costs and QALYs to support interpretation of probabilistic ICERs.

We further present scenario analyses in Section **Error! Reference source not found.** relating to:

- Independently costed and independently effective interferons (Section 4.1); and
- Independently costed and identically effective interferons (Section 4.2).

In addition, this response is accompanied by an appendix containing the results of the company's economic model after confidential patient access scheme (PAS) discounts have been applied for comparators to ponesimod. Please note that the results in this document therefore only contain the PAS discount agreed for ponesimod.

2. COMPANY BASE CASE

2.1. ITT population

Table 1: Company revised results (ITT population)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years

2.2. HA RRMS subgroup

Table 2: Company revised results (HA RRMS subgroup)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

3. Probabilistic sensitivity analysis

3.1. ITT population

Table 3: Company revised PSA results (ITT population)

	Incremental costs (£)			Incremental QALYs			ICER (£/QALY) Probabilistic	ICER (£/QALY) Deterministic
Treatment	**Mean (Probabilistic)**	**95% CrI lower**	**95% CrI upper**	**Mean (Probabilistic)**	**95% CrI lower**	**95% CrI upper**		
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years

Figure 1: Cost-effectiveness scatter plot (ITT population)

Abbreviations: ITT, intention-to-treat; QALYs, quality adjusted life years

Figure 2: Cost-effectiveness acceptability curve (ITT population)

Abbreviations: ITT, intention-to-treat; QALYs, quality adjusted life years

3.2. HA RRMS subgroup

Table 4: Company revised PSA results (HA RRMS subgroup)

	Incremental costs (£)			Incremental QALYs			ICER (£/QALY) Probabilistic	ICER (£/QALY) Deterministic
Treatment	**Mean (Probabilistic)**	**95% CrI lower**	**95% CrI upper**	**Mean (Probabilistic)**	**95% CrI lower**	**95% CrI upper**		
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

*Figure 3: Cost-effectiveness scatter plot (*HA RRMS subgroup*)*

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

Figure 4: Cost-effectiveness acceptability curve (HA RRMS subgroup)

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

4. ERG scenario analysis

4.1. Independently costed and independently effective interferons

4.1.1. ITT population

Table 5: ERG scenario analysis results (ITT population)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30mcg IM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years

4.1.2. HA RRMS subgroup

Table 6: ERG scenario analysis results (HA RRMS subgroup)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis

4.2. Independently costed and identically effective interferons

4.2.1. ITT population

Table 7: ERG scenario analysis results (ITT population)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Interferon beta-1a 30mcg IM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon beta-1a 125mcg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years

4.2.2. HA RRMS subgroup

Table 8: ERG scenario analysis results (HA RRMS subgroup)

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs (£)	Incremental discounted QALYs	ICER (£/QALY)
Company deterministic base case					
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HA, highly active; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RRMS, relapsing-remitting multiple sclerosis