NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission summary** from Biogen

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. MS Society
   b. MS Trust
   c. Association of British Neurologists (ABN)
   The Royal College of Physicians has endorsed the ABN statement

4. **Expert personal perspectives** from:
   a. Mrs Lotty Brown– patient expert, nominated by the MS Trust

5. **Evidence Review Group report** prepared by Warwick Evidence
   The Evidence Review Group was updated after the factual accuracy check

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

Post-technical engagement documents

7. **Technical engagement response from company**

8. **Technical engagement responses from experts:**
   a. Dr Declan Chard – clinical expert, nominated by the MS Trust

9. **Technical engagement responses from consultees and commentators:**
   a. MS Society
   b. MS Trust
   c. Association of British Neurologists (ABN)
   d. Novartis

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

11. Final Technical Report

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

Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis [ID 1521]

Document B

Company evidence submission

Submitted by Biogen Idec

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Contents

Tables

Figures

Abbreviations

9-HPT	9-Hole Peg Test
ABN	Association of British Neurology
ADR	adverse drug reaction
AE	adverse event
ALZ	alemtuzumab
ARR	annualised relapse rate
ARR-ST	annualised relapse rate requiring steroids
AWMSG	All Wales Medicines Strategy Group
BBB	blood-brain barrier
BCMS	British Columbia Multiple Sclerosis
BH	black hole
BID	twice daily
BNF	British National Formulary
BOI	burden of illness
BSC	best supportive care
CDP	confirmed disability progression
CDP3M	confirmed disability progression sustained for 3 months
CDP6M	confirmed disability progression sustained for 6 months
CDW	confirmed disability worsening
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CRF	case report form
CrI	credible interval
CSF	cerebral spinal fluid
DCZ	daclizumab
DES	discrete event simulation
DIS	dissemination in space
DIT	dissemination in time
DMF	dimethyl fumarate
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group

FNG	fingolimod
FS	functional system
GA	glatiramer acetate
Gd+	gadolinium enhancing
genGA	generic glatiramer acetate
HCHS	Hospital and Community Health Services
HR	hazard ratio
HRQOL	health-related quality-of-life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ID	identification
IFN	interferon
IFNβ-1a	interferon β-1a
IFNβ-1b	interferon β-1b
IM	intramuscular
INEC	Independent Neurology Education Committee
IQR	interquartile range
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITT	intent to treat
IV	intravenous
JAGS	Just Another Gibbs Sampler
JCV	John Cunningham virus
LCLE	less costly, less effective
LY	life-year
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
MSIS-29	Multiple Sclerosis Impact Scale 29
MTA	multiple technology appraisal
MTC	mixed-treatment comparison
NA	not available
N/A	not applicable
NEDA	no evidence of disease activity
NET2	T2-weighted
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NR	not reported
NS	not significant
NTZ	natalizumab
OR	odds ratio
OWSA	one-way sensitivity analysis
PASAT-3	Paced Audio Serial Addition Test 3
Pbo	placebo
PEG	polyethylene glycolated
pegIFNβ-1a	pegylated interferon β-1a
PICOS	populations, interventions, comparators, outcomes, and study designs of interest
PML	progressive multifocal leukoencephalopathy
POP	Plegridy Observational Programme
PPMS	primary-progressive multiple sclerosis
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q24W	every 24 weeks
Q2W	every 2 weeks
Q4W	every 4 weeks
QAD	every other day
QALY	quality-adjusted life year
QD	once daily
QOL	quality-of-life
QW	once weekly
RDC	remote data capture
RES	rapidly evolving severe
RR	relapse rate
RRMS	relapsing-remitting multiple sclerosis
RSS	Risk Sharing Scheme
SAE	serious adverse event
SAG	scientific advisory group
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-12	SF-12 Health Survey
SF-36	SF-36 Health Survey
SF-6D	SF-6D Health Survey

SLR	systematic literature review
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
SMR	standardised mortality ratio
SOT	suboptimally treated
SPMS	secondary-progressive multiple sclerosis
STA	single technology appraisal
T25FW	Timed 25-Foot Walk
TA	technology appraisal
TID	three times daily
TIW	three times weekly
UK	United Kingdom
US	United States
VAS	visual analog scale

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

B.1.1 Decision problem

The objective of this appraisal is to assess the clinical and cost-effectiveness of pegylated interferon β-1a (pegIFNβ-1a, Plegridy®) within its marketing authorisation for the treatment of adults with relapsing-remitting multiple sclerosis (RRMS).

PegIFNβ-1a is a new molecular entity containing IFNβ-1a that received European marketing authorisation for the treatment of RRMS in 2014.[1] PegIFNβ-1a is currently commissioned across the United Kingdom (UK), following positive recommendations from the Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG) and a commissioning policy in England[2-4] with over 1,500 patients currently receiving therapy.

PegIFNβ-1a has been previously assessed by National Institute for Health and Care Excellence (NICE) in the interferon β (IFN) and glatiramer acetate (GA) multiple technological appraisal (NICE TA527), where the initial assessment group report found pegIFNβ-1a to be the most clinically and cost-effective IFN.[5] However, given the comparator technologies were all participants in the UK MS Risk Sharing Scheme (RSS), a 10-year observational study initiated in 2002 to assess the impact of disease-modifying therapies (DMTs) on disability progression in RRMS patients, this was ultimately used as the primary evidence base for economic modelling and decision making. Under the RSS scheme, the then-licensed formulations of intramuscular (IM) IFNβ-1a 30 (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), SC IFNβ-1b (Betaferon®), and GA (Copaxone®) were provided to patients with multiple sclerosis (MS) under an agreement that the clinical benefit of each drug would be regularly assessed against target outcomes agreed with the manufacturers. The price for each drug would be scaled, as necessary, to reach a target level of cost-effectiveness, set at the start of the scheme as £36,000 per quality-adjusted life-year (QALY). As part of the RSS, patients meeting the criteria for treatment were enrolled in a cohort and monitored regularly for evidence of disability progression and treatment benefit. Analysis of the 10-year data of this clinical cohort compared disease progression against a historical comparator and suggested that the DMTs included in the RSS reduced disability progression overall and did so to the agreed level of cost-effectiveness.

The outcome of NICE TA527 was a positive recommendation for IM IFNβ-1a (Avonex® and Rebif®), IFNβ-1b (Extavia®), and GA (Copaxone®) for people with RRMS. IFNβ-1b (Betaferon®), although included in the RSS and the same compound as Extavia, was not recommended based on the grounds of cost-effectiveness.

PegIFNβ-1a, on the other hand, is a new chemical entity and was licensed in 2014; therefore, it was not part of the RSS. On the basis of this as well as the committee's decision to use the RSS (which pegIFNβ-1a was never part of) as the primary source for evidence base in the multiple technology appraisal (MTA), NICE were unable to provide any recommendation for pegIFNβ-1a at the time and instead referred pegIFNβ-1a for an independent single technology appraisal (STA).

The decision problem as per the final NICE scope for this STA is presented 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-remitting multiple sclerosis	People with RRMS that is not highly active or rapidly evolving severe	PegIFNβ-1a is currently recommended within the NHS England DMT algorithm as a first-line therapy, and not in the highly active MS or rapidly evolving severe subpopulations. People with MS can only be classified as highly active RRMS if they have disease activity despite previous treatment.[a,6] A key exclusion criterion in the pivotal pegIFNβ-1a phase 3 study (ADVANCE) was previous treatment with IFN for more than 4 weeks; subjects had to have discontinued IFN treatment 6 months prior to the start of the study. Subjects also had to have discontinued glatiramer acetate treatment 4 weeks prior to study start.[7] Subjects previously treated with fingolimod or natalizumab were excluded. The majority of the subjects (83%) in the ADVANCE study were MS treatment-naive.[1] The remaining 17% of subjects were previously treated across three treatment groups; the most common pre-study medications were glatiramer acetate (5% of subjects), corticosteroids (4%), and IFNβ-1b (1%) and azathioprine (1%). Thus, there are limited data available to assess the efficacy of pegIFNβ-1a in the highly active subgroup. The EPAR also confirms that only patients with RRMS were included in the studies; they were mildly affected at baseline and mostly naive to MS medication. The CHMP considered lack of data in patients with high disease activity.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Biogen also believe that pegIFNβ-1a should not be assessed in the rapidly evolving severe sub-population[b] as it is highly unlikely to be used in this population in clinical practice
Intervention	PegIFNβ-1a	As per scope	N/A
Comparator(s)	For people with RRMS: ▪ Alemtuzumab ▪ Dimethyl fumarate ▪ Teriflunomide ▪ IFNβ ▪ Glatiramer acetate ▪ Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with rapidly evolving severe RRMS: ▪ Alemtuzumab ▪ Cladribine ▪ Natalizumab ▪ Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with highly active RRMS despite previous treatment: ▪ Alemtuzumab ▪ Fingolimod	For people with RRMS: ▪ Alemtuzumab[c] ▪ Dimethyl fumarate ▪ Teriflunomide ▪ IFNβ ▪ Glatiramer acetate ▪ Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)[d]	As described above, the comparators included in the submission are for people with RRMS that is not highly active or rapidly evolving severe. [c]The EMA has applied a temporary restriction to alemtuzumab due following new reports of immune-mediated conditions (caused by the body's defence system not working properly) and problems with the heart and blood vessels with the medicine, including fatal cases. Under this temporary restriction, alemtuzumab should only be initiated in adults with RRMS that is highly active despite a full and adequate course of treatment with at least two other DMTs, or in adults with highly active RRMS where all other DMTs are contraindicated or otherwise unsuitable. We have included alemtuzumab in all MTC and economic analyses due to the timing of the final scope and the article 20 procedure, however results should be interpreted with the above restriction in mind. [d]Given the NICE recommendation for ocrelizumab is for relapsing forms of MS (only if alemtuzumab is contraindicated or otherwise unsuitable), it is unclear what the impact of the alemtuzumab restriction will have on

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	▪ Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)		prescribing ocrelizumab and whether this is a relevant comparator for pegIFNβ-1a.
Outcomes	The outcome measures to be considered include: ▪ Relapse rate ▪ Severity of relapse ▪ Disability (e.g., EDSS) ▪ Symptoms of MS (such as fatigue, cognition and visual disturbance) ▪ Freedom from disease activity (e.g., lesions on MRI scans) ▪ Mortality ▪ Adverse effects of treatment ▪ HRQOL	As per scope	Some outcomes (severity of relapse, symptoms, and freedom from disease activity) could not be assessed in an MTC due to lack of comparative data or heterogenous definitions or scales.
Economic analysis	▪ Cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. ▪ Time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per scope	A number of comparators have confidential commercial agreements in place. Results are therefore presented using list prices only and should therefore be interpreted with caution.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	▪ Costs will be considered from an NHS and Personal Social Services perspective. ▪ The availability of any commercial arrangements for the intervention or comparator technologies will be taken into account.		
Subgroups to be considered	If the evidence allows, the following subgroups of people will be considered: ▪ People who could not tolerate previous treatment	Due to lack of evidence this subgroup is not included in the submission.	Biogen believes the subgroup "people who could not tolerate previous treatment" is relevant in clinical practice. However, most clinical trials generally have exposure to previous DMTs within a specified time frame (or any exposure at all) as an exclusion criterion.

CHMP = Committee for Medicinal Products for Human Use; DMT = disease-modifying therapy; EDSS = expanded disability status scale; EMA = European Medicines Agency; EPAR = European Public Assessment Report; Gd+ = gadolinium enhancing; HRQOL = health-related quality-of-life; IFN = interferon; MRI = magnetic resonance imaging; MS = multiple sclerosis; MTC = mixed-treatment comparison; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; RRMS = relapsing-remitting multiple sclerosis.

[a] Defined as failure to respond to at least 1 year of treatment with a DMT and either, ≥ 1 relapse in the previous year with either ≥ 9 T2 lesions and/or ≥ 1 Gd+ lesion, or unchanged or increased relapse rate, or ongoing severe relapse compared with the previous year.[6]

[b] Defined as one or more disabling relapses in 1 year, and with ≥ 1 Gd+ lesion or a significant increase in T2 lesion load compared with a previous recent MRI.[6]

B.1.2 Description of the technology being appraised

Table 2 presents the technology being appraised. The European public assessment report can be found in Appendix C.

Table 2. Technology being appraised

UK-approved name and brand name	Plegridy® (pegylated interferon β-1a) Referred to as PegIFNβ-1a throughout this document
Mechanism of action	While the mechanism of action is not fully understood, pegIFNβ-1a is thought to reduce disease activity in MS by a similar mechanism to that of non-pegIFNβ-1a; it binds to the type I IFN receptor on the surface of cells eliciting a cascade of intracellular events, leading to the regulation of IFN-responsive gene expression.[1] PegIFNβ-1a is the first and only DMT in MS to leverage the benefits of pegylation, a modification with the ability to enhance product exposure whilst maintaining an acceptable safety profile. Pegylation of IFN creates a new molecular entity, that increases the circulation time of IFN, facilitating less frequent dosing, providing more continuous drug exposure and allowing treatment-free weeks. In addition, pegylation decreases immunogenicity,[9,10] which is associated with reduced incidence of neutralising antibodies.[11] The incidence of neutralising antibodies has been linked to treatment waning.[12,13]
Marketing authorisation/CE mark status	PegIFNβ-1a received EMA marketing authorisation on 17 July 2014.
Indications and any restriction(s) as described in the SmPC	PegIFNβ-1a is indicated in adult patients for the treatment of RRMS.
Method of administration and dosage	Subcutaneous pegIFNβ-1a (Plegridy®) is available as a 0.5 mL prefilled syringe/autoinjector containing 63/94/125 µg of pegIFNβ-1a with bis-[monomethoxy polyethylene glycol]. The recommended dosage of Plegridy® is 125 µg administered subcutaneously Q2W by self-injection. It is generally recommended that patients start treatment with 63 µg at dose 1, increasing to 94 µg at dose 2, and to the full dose of 125 µg at dose 3. The full dose is then administered Q2W thereafter.
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: Standard Q2W pack, 2 injections, £654 Standard Q2W pack, 6 injections, £1,962 Annual cost: £8,502 per annum
Patient access scheme (if applicable)	No patient access scheme is included in the submission.

DMT = disease-modifying therapy; EMA = European Medicines Agency; IFN = interferon; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon β-1a; Q2W = every 2 weeks; RRMS = relapsing-remitting multiple sclerosis; SmPC = summary of product characteristics; UK = United Kingdom.

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

B.1.3.1 Disease overview

Multiple sclerosis is a chronic, progressive, lifelong disease with no cure, characterised by localised areas of inflammation, demyelination, and axonal degeneration.[14,15] It affects the central nervous system (CNS) and results in the accumulation of irreversible disability. The underlying cause of MS is currently unknown, but it is thought that a complex relationship between genetic and environmental factors result in an autoimmune reaction, in which immune cell subsets in the CNS are activated and recruited, producing the hallmarks of MS pathology.[16-18] There is also evidence suggesting that smoking, obesity during adolescence, and Epstein-Barr virus infection may be associated with an increased risk of developing MS.[19-25]

B.1.3.1.1 Types of MS

MS can develop and progress into one of three major forms:

1. *Relapsing-remitting multiple sclerosis (RRMS):* a form of MS that affects approximately 85% of the people at the time of diagnosis. It is characterised by periods of remission followed by relapses (which may or may not result in residual disability).
2. *Secondary-progressive multiple sclerosis (SPMS):* a period of steady progression of neurological damage with or without relapses. Most patients with RRMS will eventually develop SPMS.
3. *Primary-progressive multiple sclerosis (PPMS):* unlike RRMS, PPMS is characterised by gradual disability progression from the onset with no obvious relapses or remissions.

This appraisal assesses the evidence of pegIFNβ-1a for RRMS, which compromises approximately 85% of the overall MS population.

B.1.3.1.2 Epidemiology

Multiple sclerosis is the leading cause of non-traumatic CNS morbidity and mortality in young and middle-aged adults, and generally manifests between the ages of 25 and 35.[26-28] Multiple sclerosis is two to three times more common in women than in men.[29] Approximately 110,000 people in the UK have MS, with an estimated 90,500 people with MS in England (164 per 100,000), 4,300 in Wales (138 per 100,000), 3,200 in Northern Ireland (175 per 100,000) and 11,300 in Scotland (209 per 100,000).[29] The incidence of MS in the UK is approximately 5,000 newly diagnosed patients per year.[29]

The chronic and progressively debilitating nature of MS, combined with the young age at diagnosis, mean that these patients pose a substantial burden to the healthcare system and society.

B.1.3.1.3 Pathophysiology

Multiple sclerosis is recognised as having neurodegenerative and inflammatory processes, although the exact pathophysiology of either is not fully understood. There is strong evidence of an auto-reactive inflammatory response resulting from the activation of T-helper cells against antigens in the CNS. A subsequent inflammatory cascade results in a disruption to the blood-brain barrier (BBB), allowing for increased migration of activated immune cells, cytokines, and chemokines into the CNS. Once in the CNS, these inflammatory mediators lead the damage to myelin and oligodendrocytes; the latter responsible for maintenance and reparation of myelin.[16,30-32] Demyelination and axonal

degeneration disrupt the ability of neurons to conduct electrical impulses in the brain and spinal cord, causing lesions in the brain, spinal cord, and optic nerve.[16]

Recent studies have suggested both neuroinflammation and neurodegeneration may occur simultaneously and perhaps independently, rather than sequentially.[33]

B.1.3.1.4 Presentation

Clinical symptoms

The clinical symptoms of MS vary from patient to patient, as well as within patients over time; ranging from clinically asymptomatic earlier on in the disease to significant disability in an aggressive form of the disease.[34] The symptoms of MS can be generally categorised as primary (caused by the pathologic state), secondary (complications of primary symptoms), or tertiary (caused by the disease's impact on daily life).[14] Some of the most common presenting symptoms experienced by patients with MS are sensory dysfunction (40% of patients), motor problems (39% of patients), visual disturbances (30% of patients), balance problems (24% of patients), pain (15% of patients), and cognitive problems (10% of patients). Later in the disease course, cognitive problems are the most common symptoms affecting 40%-70% of patients with MS.[35]

Due to the unpredictable nature of MS it is impossible to anticipate when symptoms will occur; however, factors such as infections, heat, sleep deprivation, stress, malnutrition, anaemia, concurrent organ dysfunction, exertion, and childbirth are perceived to aggravate symptoms or lead to a new relapse.[14]

Imaging features

Magnetic resonance imaging (MRI) was added to the diagnostic criteria (see Section B.1.3.1.5) for MS in 2001 and rapidly has become a primary tool for characterising MS severity and progression, as well as a tool used to evaluate treatment response and prognosis and to perform pharmacovigilance surveillance

In patients with active MS, the disruption of the BBB allows acute lesions (sites of active inflammation) to be enhanced after administration of a contrast media, whereas chronic lesions are generally non-enhancing. Therefore, MRI can highlight sites of active inflammation within the CNS.

It is important to note that even in the absence of clinical symptoms described above. MRI scans will also highlight sites of irreversible axonal loss (black holes [BHs]).

MRI and the type of lesions found are described below[36]:

- T2 lesions are typically chronic, and may be inactive or active; these are considered to reflect the dissemination of disease over time.[37]
- T1 lesions are believed to show reversible oedema and demyelination, as well as irreversible demyelination if persisting more than 6 months (chronic BHs).[37]
- Gd+ lesions indicate the number/volume of lesions with active inflammation.[37]
- Chronic black holes (BHs) developed from acute MRI lesions indicate severe and irreversible tissue injury and axonal damage. These can be used to measure the neuroprotective effect of DMTs.[38]

The characteristic MRI lesion is a cerebral or spinal plaque with high T2 signal (lesion), representing a region of demyelination with axonal preservation.

B.1.3.1.5 Diagnostic criteria

The criteria for a diagnosis of MS are known as the McDonald criteria and were last updated in 2017 with the addition of cerebrospinal fluid (CSF) analysis to investigate the presence of oligoclonal bands in order to demonstrate dissemination in time (DIT) (please see Appendix L for more detail).[39]

The diagnosis of MS is primary clinical (relapses), with supportive roles for neuroimaging (MRI) and laboratory (oligoclonal bands). The fundamental requirement for a diagnosis of MS is the requirement of DIT and dissemination in space (DIS). Historically, the diagnosis of MS has required two or more relapses over a period of time, with two or more objective MRI lesions. However, advances in clinical practice and the updated McDonald criteria (see Appendix L) enable the diagnosis of MS after a single attack (relapse), as long as DIS is satisfied (e.g., by using MRI to identify the development of lesions in distinct anatomical locations within the CNS), as well as DIT (e.g., by using oligoclonal bands as evidence of development of new CNS lesions over time).

The 2005 McDonald criteria 1 to 4 are used to define patients with RRMS in trials for pegIFNβ-1a and they are defined as follows[7]:

1. Two or more relapses, two or more objective lesions
2. Two or more relapses, one objective lesion, and DIS by MRI or positive CSF, and two or more MRI lesions consistent with MS or further clinical attack involving different sites
3. One relapse, two or more objective lesions, and DIT by MRI or second clinical attack
4. One (mono-symptomatic) relapse, one objective lesion, DIS by MRI or positive CSF and two or more MRI lesions consistent with MS, and DIT by MRI or second clinical attack.

B.1.3.1.6 Prognosis and disease monitoring

RRMS is typically preceded by clinically isolated syndrome (defined as a first clinical episode with features suggestive of MS lasting ≥ 24 hours), and if left untreated, most patients with RRMS (50%-60%) will develop SPMS within 15 to 20 years after disease onset.[40,41] One of the goals of the 2017 McDonald criteria was to facilitate earlier diagnosis of RRMS.[39,41]

Risk factors for disease progression

Multiple sclerosis is a heterogeneous disease, and risk factors generally vary between individuals. However, observational data have found that male sex, older age of onset, progressive stage of MS at onset, and a higher MRI activity tend to be associated with a poor prognosis and faster progression. Modifiable risk factors include smoking, exposure to infectious diseases, discontinuation of DMTs; all of which are associated with increased progression.

Disease activity can be measured using a variety of direct and indirect methods and outcomes, including relapse frequency, level of disability, and lesion burden. Therefore, improvements or changes in these can be used to evaluate the efficacy of treatments. Table 3 summarises outcome measures commonly used in MS.

Table 3. Outcome measures commonly used in MS studies

Outcome	Relevance to clinical practice	Definition/scales
Clinical		
Disability progression	Patients with RRMS will accumulate disability as their disease progresses.[42] Therefore, disease progression can be measured using disability severity scales such as the EDSS or MSFC. Treatment differences in relapse reduction and T2 lesion measures may be predictive of EDSS disability progression.[43]	EDSS: an ordinal scale derived from neurological examination findings ranging from 0-10 driven primarily by ambulation assessment, with lower scores indicating a better outcome.[44] EDSS scale is heavily weighted on morbidity but does not capture cognitive disability.
		CDP, also referred to as CDW[45] defined as worsening of ≥ 1.0 point in EDSS score from baseline (or 1.5 points if baseline EDSS is 0) sustained over 12 weeks (12-week CDP, or 3-month CDP), or 24 weeks (24-week CDP, or 6-month CDP).
		MSFC: three tests, the T25FW, 9-HPT, and PASAT-3, assessing ambulation, upper extremity function, and cognitive function, respectively.[46] The MSFC is less heavily weighted towards ambulation than the EDSS.
Relapses	The level of disease activity in patients with RRMS can be directly measured by the frequency at which they experience relapses, that contribute to demyelination and accumulating disability.[47] Therefore, reducing the rate of relapses is pivotal to the efficacy of an MS treatment, and consequent patient benefits.	Clinical relapses are defined as new or recurrent neurological symptoms not associated with fever or infection, lasting for at least 24 hours; at least 30 days are required between relapses to be considered as separate events.[48]
Relapses requiring IV steroids	Patients who require IV steroid therapy for relapse may be considered as those with affected functional abilities to the greater extent. Relapses requiring IV steroids may correlate with more severe relapses.[45]	Relapses requiring IV steroids: relapses treated with IV steroids according to treating doctor.[45]

Outcome	Relevance to clinical practice	Definition/scales
Brain and CNS lesions (radiographic progression)	Changes in the number or volume of brain/CNS lesions on MRI show the degree of MS disease activity. These are indicative of inflammation and myelin destruction, and contribute to accumulating disability. MRI may be predictive of future disease course, and it is expected that compound techniques (combining different types of scans) may enhance the predictive power.[36]	T2 lesions are typically chronic, and may be inactive or active; these are considered to reflect the dissemination of disease over time.[37] These can be measured using MRI.
		T1 lesions are believed to show reversible oedema and demyelination, as well as irreversible demyelination ("BHs").[37] These can be measured using MRI.
		Gd+ lesions indicate the number/volume of lesions with active inflammation.[37] These can be measured using MRI.
		Chronic BHs develop from acute MRI lesions and indicate severe tissue injury. These can be used to measure the neuroprotective effect of DMTs and can be measured by MRI.[38]
No evidence of disease activity (NEDA)	The absence of disease activity is the ultimate goal of MS treatment.[49] NEDA at year 2 is considered a good predictor of long-term disease stability.[33]	Overall NEDA indicates disease stability that compromises no new relapses, no disability progression, and no new or enlarging MRI lesions. Clinical NEDA is defined as no evidence of relapses and onset of CDP, while MRI NEDA is defined as no evidence of Gd+ lesions and no new/newly enlarging T2 lesions.[38]

Outcome	Relevance to clinical practice	Definition/scales
Patient-reported outcomes		
Quality-of-life (QOL)	QOL is an important measure of patients' perceptions of their own condition. Questionnaires can be used to measure the impact of MS upon patients' activities of daily living, and improvements in these scores can reflect significant benefits to the patient.[50]	SF-12: condensed 12-question version of the SF-36 questionnaire. SF-12 measures QOL in eight subscales: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health.[51]
		EQ-5D[52]: standardised instrument with two components, the EQ-5D descriptive system and the EQ-5D VAS. The descriptive system allows the subject to state that they have either "no problems", "some problems", or "severe problems" for five dimensions of health; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D VAS is a 20-cm scale from 0 to 100 where 0 represents "worst imaginable health state" and 100 represents "best imaginable health state".
		VAS: a commonly used generic scale where patients may indicate their pain or QOL on a 0-10 cm or 0-100 mm scale.[53]
		MSIS-29: an MS-specific QOL questionnaire that combines a patient perspective with psychometric methods measuring both the physical and psychological impact of MS from the patient's perspective.[50]

9-HPT = 9-Hole Peg Test; BH = black hole; CDP = confirmed disability progression; CDW = confirmed disability worsening; CNS = central nervous system; DMT = Disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale 29; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity; PASAT-3 = Paced Audio Serial Addition Test 3; QOL = quality-of-life; RRMS = relapsing-remitting multiple sclerosis; SF-12 = SF-12 Health Survey; SF-36 = SF-36 Health Survey; T25FW = Timed 25-Foot Walk; VAS = visual analogue scale.

Measurement of disability

The Expanded Disability Status Scale (EDSS) is the standard measure used in clinical practice (as well as economic evaluation models) to measure disease progression in MS. The EDSS quantifies disability in eight functional systems, specifically focusing on pyramidal, cerebellar brain stem, sensory, bowel and bladder, and cerebral/mental function. An EDSS score of 0.0 would indicate normal neurology with no impairment, an EDSS of 4.0 would suggest full ambulation without aid despite disability, an EDSS of 6.0 would suggest ambulation needing support (cane, crutch) to walk 100 m, and EDSS of 7.0 would suggest wheelchair confinement.[54,55]

Disability progression

A longitudinal cohort study by Leray et al. (2010)[42] suggested that MS may be characterised by two distinct phases: phase 1 lasting from diagnosis until irreversible EDSS 3 and phase 2 lasting from EDSS 3 until EDSS 6. Disability progression in phase 1 did not influence phase 2, and as in previous studies, increased relapse during the first 2 years of MS only influenced time in phase 1. Relapses after EDSS 3 were not associated with continued disability progression. Previously characterised risk factors of sex, age of onset, and relapse history were not related to disability progression in phase 2.[42] These data are in line with previous studies suggesting that while rates of relapse early in disease predicts disease progression, relapses later in RRMS or during SPMS may not significantly predict or influence disability progression.[56,57]

Impact of relapses on disability progression

The risk of accumulating disability from disease onset increases proportionally with relapse frequency in year 1 and 2 after disease onset[56]; there is a strong association between the time to reach mild or severe disability (EDSS 3.0 and 6.0, respectively) and the number of relapses experienced by patients in these first 2 years since diagnosis.[58]

Relapses can significantly contribute to disability progression, with 42% of patients experiencing a permanent residual deficit of ≥ 0.5 EDSS points following a relapse.[47] Consequently, patients could reach mild disability, after which progression to severe disability occurs in 6 to 9 years, following just six relapses.[42]

A typical MS relapse may last for 4 to 6 weeks or up to several months, during which time patients may be unable to work or perform activities of daily living.[59] Therefore, it is vital that relapses are controlled to delay disability progression and to allow patients to avoid disability accumulation for as long as possible.

Impact of ongoing MRI activity on disability progression

Even in the absence of relapses, ongoing MRI activity indicates that pathological inflammatory activity continues to occur despite a lack of clinical symptoms.[54]

Ongoing MRI activity contributes to disability progression, with a significant relationship between the number of T2 lesions at disease onset and the number of patients with EDSS > 3.0 and EDSS ≥ 6.0 at 20 years.[55] MRI activity indicates active inflammation within the CNS (T2 and Gd+ lesions), can occur up to 10 times more frequently than clinical relapses, and is more indicative of poor prognosis. MRI activity may be predictive of disease progression, with patients developing SPMS at 20 years tending to have larger baseline T2 lesion volumes and a greater increase in lesion volume, particularly over the first 5 years after disease onset.[54,55]

B.1.3.2 Burden of multiple sclerosis

B.1.3.2.1 Impact on the patient and care giver

Due to the lack of a cure for MS, the disease poses a significant personal burden for patients and caregivers. Patients are generally diagnosed at a young age, and MS negatively influences their autonomy, independence, dignity, and life planning.[33] The accumulation of physical and mental disabilities associated with MS, along with a range of unpredictable symptoms, can have a devastating effect on patients, impacting both their physical and cognitive functioning and quality-of-life (QOL).[60] Patients with MS have been shown to have worse QOL scores than patients with epilepsy, diabetes, recent myocardial infarction, or hypertension.[61,62]

Physical dysfunction/disability

Physical disability accumulates over time, and it is estimated that untreated patients with MS will become unable to walk 100 m unaided (EDSS 6.0) after a median of 16 to 17 years from disease onset.[44,63-66]

Mobility impairment has a considerable impact on patients' lives; even a mild loss of mobility has a significant effect on employment[67] and walking impairment is also associated with a loss of independence and limitations in daily functioning.[68]

Cognitive dysfunction

Patients with MS face increasing levels of mental disability as their disease progresses, and approximately 43% to 71% of patients with MS experience cognitive dysfunction.[69-71]

Fatigue

Fatigue is one of the most common symptoms of MS and is reported by up to 95% of patients. In MS, fatigue results in an overwhelming sense of tiredness, which often occurs after very little activity.[72] Many patients regard fatigue as among the worst symptoms of MS, regardless of neurologic impairment.[73,74]

Mortality

While MS does not directly result in death, up to 50% of mortality in patients may be caused by MS-related complications.[75] The life expectancy of patients with MS was estimated to be 5 to 7 years lower than that of the general population.[76]

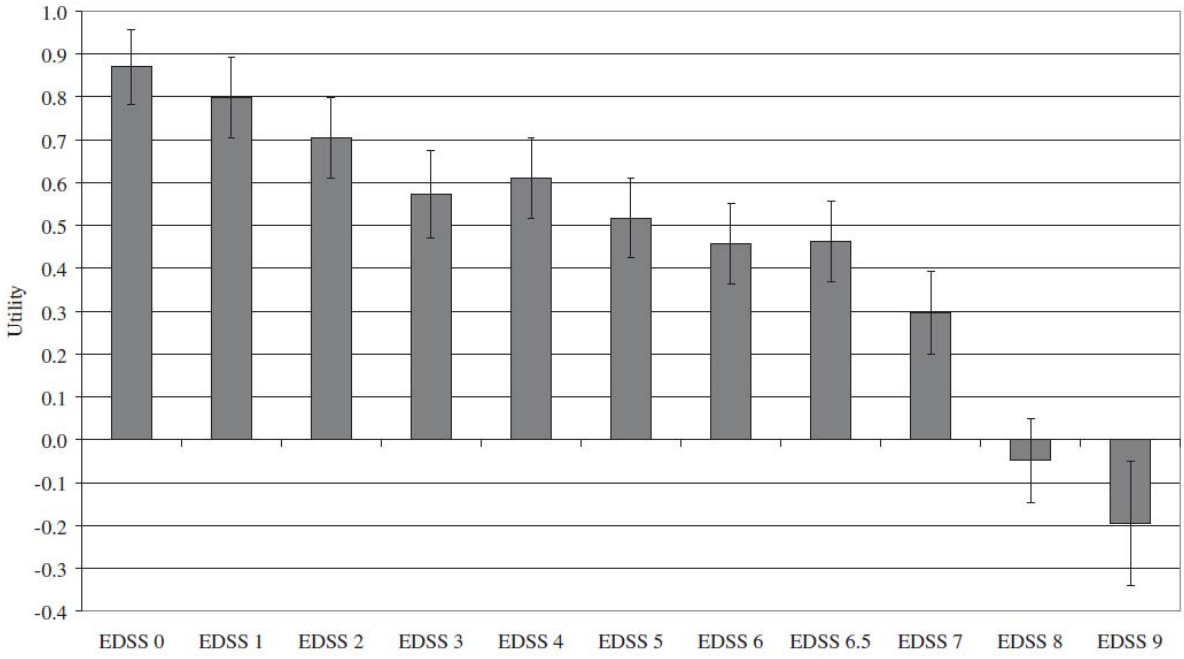
In a UK cohort study, patients with MS were shown to have a significant 1.7-fold increased risk of all-cause mortality compared with the general population.[77]

Quality-of-life

QOL (EQ-5D) scores decline with increasing EDSS scores (Figure 1)[78]

Patients with MS have worse QOL scores than patients with epilepsy, diabetes, recent myocardial infarction, and hypertension.[61,62] This is apparent even in the early stages of the disease, with patients with mild MS reporting scores approximately 30% lower than in the general population.[79]

Figure 1. Mean utility (EQ-5D) by disease severity (EDSS score)



EDSS = Expanded Disability Status Scale.
Source: Orme et al. (2007)[78]

B.1.3.2.2 Societal and healthcare burden

Multiple sclerosis is associated with a significant economic burden.[80,81] Patients develop MS at a young age, and healthcare costs and levels of disability increase over time. Patients may also require hospital admission during severe exacerbations.[60]

Using values from TA320 (inflated 7% using the Hospital and Community Health Services [HCHS] index in the Personal Social Services Research Unit [PSSRU] from 2011/2012 to 2017/2018), which were originally derived from the 2005 UK MS Survey of 2,048 patients, states that the annual cost for patients with RRMS per EDSS state that fall under the National Health Service (NHS) and Personal Social Services (PSS) perspective were £965 for EDSS 0, £4,025 for EDSS 3, £11,621 for EDSS 7, and £22,648 for EDSS 9.[82]

Costs of treating MS-related relapses have been reported as £2,168 (also inflated 7% from 2011/2012 to 2017/2018 values using the HCHS index from PSSRU).[82,83] Therefore, preventing disability progression and relapses through effective management of MS is likely to reduce costs associated with the disease.

While the direct healthcare costs associated with interventions, diagnosis, and monitoring are lifelong and substantial,[60] much of the cost burden of MS falls on the social care system and wider society, with indirect costs contributing significantly to the total reported costs associated with MS. Although these indirect costs are not currently captured as a cost to the NHS, they are substantial and increase with increasing disability levels.[80] With the ongoing and potential further integration of health and social care,[84,85] these indirect costs are likely to become increasingly relevant to calculations of cost-effectiveness considered by NICE.

One of the key indirect costs associated with MS is the accumulating disability resulting in many patients being forced to give up work and needing assistive care as their condition progresses.[60,80,86-88] The UK component of a multinational study on the burden of MS found that 44.3% of patients with MS were forced to retire early,[80] while 10.8% of patients with MS were forced to change their type of work, and 10.9% were forced to change their working

hours as a result of the disease.[80] The proportion of patients in employment was 28.2%, with only 5.5% of patients working full time.[80] Work capacity also decreased significantly with increasing disease severity, with employment rates in patients aged < 65 years diminishing to approximately 11.0% at an EDSS score of 6.5 compared with employment rates of 82.0% in patients with EDSS 0 (if employment is assumed to be unaffected during the very early stages of MS).[80]

A study conducted in Wales found that the strongest predictors of patients with MS remaining in employment were lower disability level, shorter disease duration, and more years of education.[89]

Relapse frequency also has a negative impact on a patient's ability to work. A cross-sectional survey reported that patients with MS who experienced ≥ 1 relapse in the previous year were absent from work for 15 days during those 12 months, compared with 5 days absenteeism in patients with clinically stable disease.[59]

B.1.3.3 Treatments for relapsing multiple sclerosis

B.1.3.3.1 Disease-modifying therapies

MS is an unpredictable, heterogeneous disease, the course of which can be influenced by factors such as sex, relapse frequency, type of relapse, MRI lesion load, and spinal cord involvement. There is currently no cure for MS. The goal of treatment in RRMS is to decrease the frequency and severity of relapses, diminish the accumulation of lesions as observed on brain and spinal MRI scans, slow the accumulation of physical and mental disability, and maintain or improve patient QOL.[49] Disease-modifying therapies (DMTs) are the mainstay for the treatment of RRMS, and have been shown to be effective in reducing relapse rates (RRs), MRI lesions, and disability. There is considerable evidence that initiating a DMT as early as possible is beneficial in the management of patients with MS.

The availability of a number of DMTs allows treatment to be tailored to each patient's need in terms of efficacy, safety profile, and administration preferences. Thus, it is important to have shared conversations between clinicians and patients to determine the most appropriate treatment choice for each individual. The following should be discussed with patients during their discussions:

- Possible outcomes of MS with no, inadequate, or suboptimal response, and potential next steps
- Benefits of early treatment
- Treatment goals of minimising disease activity while optimising the safety profile
- Potential benefits and risks of DMTs
- Patient management of disease through living a brain-healthy lifestyle and making informed, shared decisions about treatment
- Limitations in the current understanding of MS and DMTs

In order to meet the clinical and individual needs for each patient, it is essential that the full range of DMTs are available to prescribe; in line with the UK Association of British Neurology (ABN) guidelines 2015.[54]

Recent advances in therapy for MS have raised questions regarding the selection of the appropriate patients for treatments and, if switching treatments, the most appropriate sequencing of therapies. Most patients require a change in therapy over the course of their disease, and achieving treatment goals requires careful planning. MS is a chronic, progressive, lifelong disease, and therapeutic needs may change across a lifetime. Patients

may require multiple DMTs over the course of their disease. Therefore, DMT sequencing planning is important for individual patients to maximise disease control and minimise the risks associated with DMTs; consideration should be given to the mechanism of action, pharmacokinetics, and pharmacodynamic properties of each therapy. In addition to clinical efficacy, safety profile, and administrative burden, reversibility of the immune system effects and flexibility to switch should also be key factors when selecting a DMT. This particularly important now as newer treatments become available. The approach selected for a patient should provide optimal levels of disease management without limiting future therapeutic options.[90,91]

B.1.3.3.2 NICE guidance and clinical guidelines

Current clinical practice in England and Wales is driven by NICE guidance. The key guidelines and technology appraisals in RRMS are as follows:

- Related guidelines and pathways:
  - Multiple sclerosis in adults (2014). NICE guideline 186 (currently under review). https://www.nice.org.uk/Guidance/CG186[92]
  - Multiple sclerosis (2014) NICE pathway. https://pathways.nice.org.uk/pathways/multiple-sclerosis[93]
- Related NICE technology appraisals:
  - TA533: Ocrelizumab for treating relapsing-remitting multiple sclerosis (July 2018). https://www.nice.org.uk/guidance/TA533[94]
  - TA527: Beta interferons and glatiramer acetate for treating multiple sclerosis (2018). https://www.nice.org.uk/guidance/TA527[5]
  - TA493: Cladribine tablets for treating relapsing-remitting multiple sclerosis (2017). https://www.nice.org.uk/guidance/TA493[95]
  - TA320: Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (2014).https://www.nice.org.uk/Guidance/TA320[82]
  - TA312: Alemtuzumab for treating relapsing-remitting multiple sclerosis (2014). https://www.nice.org.uk/Guidance/TA312[96]
  - TA303: Teriflunomide for treating relapsing-remitting multiple sclerosis (2014). https://www.nice.org.uk/Guidance/TA303[97]
  - TA254: Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (2012). https://www.nice.org.uk/Guidance/TA254[98]
  - TA127: Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (2007). https://www.nice.org.uk/Guidance/TA127[99]

B.1.3.3.3 Treatment guidelines

The ABN published clinical guidelines for MS in 2015, which discuss the treatment pathway of patients with RRMS.[54] These guidelines recommend that all patients with active RRMS are considered for treatment, and that treatment should be initiated as early as possible in eligible patients. Neurologists should discuss the risks, benefits, and monitoring requirements of DMTs with patients, as well as other factors that are personally important to patients, such as work and family. Clinicians should take into account patient views when selecting a treatment.[54]

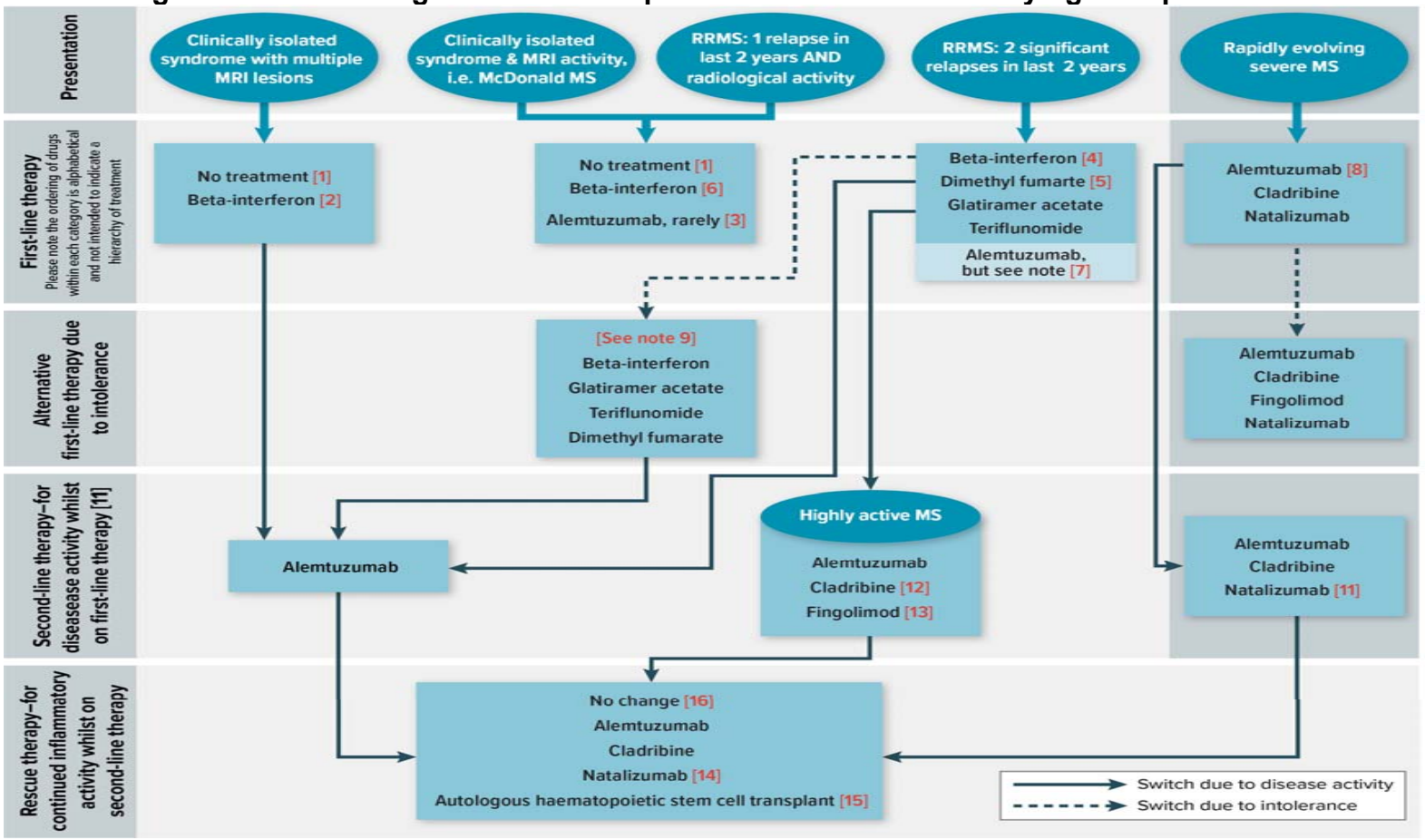
The ABN divides DMTs into two categories based on efficacy:

- Category 1 - drugs of moderate efficacy: IFNβ-1a 30 µg, IFNβ-1a 22 µg, IFNβ-1a 44 µg, IFNβ-1b 250 µg, pegIFNβ-1a, GA, teriflunomide 14 mg, dimethyl fumarate (DMF) 240 mg, fingolimod 0.5 mg
- Category 2 - drugs of high efficacy: alemtuzumab 12 mg, natalizumab 300 mg, ocrelizumab 600 mg, cladribine 10 mg (The latter two got their marketing authorisation after ABN guidelines were published and thus do not officially have a category, but are likely to be category 2 based on their marketing authorisation efficacy data.)

B.1.3.3.4 Treatment pathway

Figure 2 summarises the treatment algorithm for MS DMTs outlined by NHS England.

Figure 2. NHS England: treatment algorithm for multiple sclerosis disease-modifying therapies



Beta-interferon = IFNβ-1a (Avonex®, Rebif®), IFNβ-1b (Extavia®), and pegIFNβ-1a (Plegridy®); CIS = clinically isolated syndrome; DMT = disease-modifying therapy; EMA = European Medicines Agency; GA = glatiramer acetate; IFN = interferon; JCV = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PML = progressive multifocal leukoencephalopathy; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis; UK = United Kingdom.
Notes:
1. Trials of first-line therapies in people with CIS at high risk of conversion have NOT shown a convincing long-term effect on the accumulation of disability. Therefore, it is reasonable to opt for no treatment in many patients in this situation.
2. Under 2014 NHS England guidance, IFNβ may be offered for patients within 12 months of a clinically significant CIS when MRI evidence predicts a high likelihood of recurrent episodes (i.e., development of MS).
3. In exceptional circumstances, clinical or radiological markers may indicate a poor prognosis for rapidly developing permanent disability even after just one clinical episode, in which case, alemtuzumab may be considered. Doctors and patients should weigh up the considerable risks and burden of monitoring associated with this drug, against the potential benefit.
4. For RRMS (that is not RES), IFNβ, GA, and teriflunomide are effective and safe.
5. There is some evidence that dimethyl fumarate may be more effective at suppressing relapses than IFNβ, GA, and teriflunomide.
6. NHS England (2014) policy allowed the use of IFNβ in “patients with only a single major relapse in the preceding 2 years but combined with MRI evidence of continuing disease activity”.
7. For RRMS (that is not RES), alemtuzumab is an option that may be considered, but we note it is considerably more high risk than the other options. It should be used only when the patient and MS specialists accept the significant risks and burden of monitoring.
8. Alemtuzumab and cladribine may be considered by some patients and clinicians as a safer option than natalizumab when JCV serology is high-index positive.
9. If a patient satisfies the eligibility criteria for a first-line therapy, and then is relapse-free on a drug to which he/she becomes intolerant, they may be switched to another DMT even though their relapses may now fall outside the eligibility window.
10. NHS England (2014) policy states that fingolimod can be used as an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing PML as defined by: (i) JCV exposure indicated by anti-JCV antibody positive status, (ii) receiving an immunosuppressant prior to receiving natalizumab, or (iii) natalizumab treatment duration of > 2 years. If patients develop a severe adverse effect to natalizumab (e.g., anaphylaxis), and they have not previously received fingolimod, then it may be appropriate to use fingolimod.
11. Definition of disease activity: treatment failure may be indicated by either clinical or radiological relapse-related changes, after significant exposure to the treating drug, with changes indicating a poor prognosis for future disability. For instance, alemtuzumab is specifically licensed for “active disease defined by clinical or imaging features”.
12. For cladribine, NICE specifically defined treatment failure as “1 relapse in the previous year and MRI evidence of disease activity”.
13. Under previous guidance, fingolimod may be given if patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with IFNβ or GA. This is now extended to include disease activity on teriflunomide and dimethyl fumarate.
14. The risk of PML on natalizumab is likely to be increased after alemtuzumab or cladribine, given the prolonged lymphopenia induced by these drugs. But, where the patient is negative for JCV serology, this may be appropriate.
15. Autologous haematopoietic stem treatment for autoimmunity is commissioned at specialised centres and is currently being offered to some people with MS in parts of the UK. But there is not yet an adequate controlled trial of its efficacy relative to other potent therapies. We recommend that it is made available equitably to all people with MS, but we propose that it should only be considered for people with relapsing disease (not progressive) who have failed high-activity licensed DMTs and are prepared to accept the significant risks of the procedure. We recommend that this treatment is offered only by units with expertise both in the management of aggressive MS and the use of autologous haematopoietic stem treatment.
16. After considering all these options, it may be appropriate to continue the second-line therapy, despite evidence of disease activity.
Source: Dias et al. (2013)[100]

B.1.3.3.5 Interferons

Interferons are the most widely used DMTs. They have a proven track record of efficacy, a favourable safety profile, and have been used successfully for over 16 years.[101-104] There are currently five IFNβs licensed in the market for the treatment of RRMS; two IFNβ-1a (Avonex®, Rebif®), two IFNβ-1b (Extavia®, Betaferon®), and only one pegIFNβ-1a (Plegridy®). Due to their track record of efficacy and favourable safety profile, IFNs and GA are commonly used first line. In general, they offer approximately a 30% reduction in ARR, with IFNβ-1a also providing significant reductions in disability progression.[101-103,105-109] IFNβ-1b and GA (Copaxone®) have not been shown to decrease the risk of disability progression versus placebo significantly in their pivotal clinical trials.[101,105,108-110]

All IFNs are recombinant forms of natural IFN, which is a 166 amino-acid glycoprotein that is produced by most body cells in response to a viral infection. Interferon β-1a are structurally indistinguishable from natural IFN, whereas IFNβ-1b are non-glycosylated forms that carry two structural changes compared with natural IFN. PegIFNβ-1a is a pegylated IFNβ-1a.

Depending on the formulation, there are marked differences in the dose regimen of the different preparations (ranging from once daily [GA 20 mg] to once every 2 weeks [Q2W] [pegIFNβ-1a]), however, there are no marked differences from a safety profile. More frequent injections have been correlated with poor patient compliance resulting in reduced efficacy and poorer outcomes.[111]

Frequent DMT dosing has been shown to negatively affect adherence, which may impact clinical and economic outcomes by increasing a patient's risk of disease activity and MS-related costs.[111-114] It has been estimated that up to 25% of RRMS patients are non-adherent to their DMT and the most commonly reported reasons for non-adherence are forgetting to administer the injection (50.2%; including but not limited to: tiredness of taking medication [20.4%]), injection-related reactions (32.0%; fatigue [14.5%], flu-like symptoms [12.9%], pain at injection site [11.7%], inconvenient dosing schedule [9.5%]).[115]

Non-adherent RRMS patients are more likely to have a relapse or severe relapse, require more MS-related hospitalisations and emergency department visits, thereby, increasing healthcare costs.[113,116] These patients demonstrate worse QOL, physical, mental and emotional well-being compared with patients who are adherent to their DMT.[113,117] In addition, patients with higher adherence may experience lower EDSS scores and are more likely to be employed than patients with lower adherence.[117] The burden of frequent injections may also result in patients stopping therapy, with 16% to 18% of patients reporting treatment burden as the main reason for stopping their IFN, especially when it requires once-daily administration.[118]

B.1.3.4 Pegylated interferon β-1a for RRMS

PegIFNβ-1a is the first pegylated IFN for the treatment of RRMS, with a convenient dosing Q2W. IFNs have had a proven track record of efficacy and a favourable safety profile in the treatment of RRMS for almost two decades.

Pegylation of IFN creates a new molecular entity with an increased biological half-life, resulting in less frequent administration. Pegylation has also shown to decrease immunogenicity (neutralising antibodies), which may have an impact on efficacy.

B.1.3.4.1 Mechanism of action

As with the other IFNs, the mechanism of action for pegIFNβ -1a is not fully understood, but is likely to involve a number of complex pathways, including:

- Increasing production of anti-inflammatory cytokines (interleukin-10)/decreasing production of pro-inflammatory cytokines (interleukin-7 and osteopontin): Inflammation is one of the main factors involved in MS; therefore, these effects are likely to reduce disease activity.
- Preventing leukocyte migration across the BBB[119]: In MS, there is an increase of leukocyte migration across the BBB (due to its increased permeability) into the CNS.[119,120] Interferon treatment decreases the serum levels of adhesion molecules that regulate the interaction of T cells with endothelial cells, while increasing the levels of tissue inhibitors. These mechanisms help to oppose disruption of the migration of activated leukocytes across the BBB.[119]
- Assisting in CNS repair and recovery: Interferon treatment promotes nerve growth factor expression, which increases tissue repair and neuroprotection.[119]
- Increasing production of natural killer cells: Natural killer cells are primary producers of anti-inflammatory cytokines and may also control adaptive immune responses.[119] Therefore, increased production of natural killer cells may counter the inflammation observed in the CNS of patients with MS.

B.1.3.4.2 Pegylation

Pegylation was achieved by attaching a 20 kDa methoxy-PEG-O-2-methyl-propionaldehyde group to the N-terminus of IFNβ-1a, forming a shield-like structure around the protein, which protects from proteolysis (pegylation); this site is not critical to the biological activity of IFNβ-1a. Pegylation has been shown to modify the pharmacokinetics of a drug as well as decrease neutralising antibodies and has been used for over 40 years. More than 10 products are available that use this technique in disease areas such as hepatitis, kidney disease, and cancer.

The potential benefits of pegIFNβ-1a (pegylation) compared with other IFNs and GA drugs include the following:

- Less frequent and lower dosing: PegIFNβ-1a has a prolonged circulation time in comparison to other IFNs and GA, which results in reduced frequency of administration (Q2W).
- Improved stability: PegIFNβ-1a does not require cold chain and can be kept at room temperature for 30 days.
- Reduced immunogenicity: Pegylation can decrease drug immunogenicity by shielding antigenic determinants, which may result in a lower incidence of neutralising antibodies. This could potentially have an impact on efficacy.[121,122]

B.1.4 Equality considerations

No equity issues are foreseen.

B.2 Clinical effectiveness

ADVANCE – Year 1 results: pegIFNβ-1a Q2W vs. placebo

- PegIFNβ-1a Q2W significantly reduced the frequency and severity of relapses at 1 year. Compared with placebo at 1 year, patients had a relative:
  - 36% reduction in annualised relapse rate (ARR); rate ratio, 0.644 (95% confidence interval [CI], 0.500-0.831; *P* = 0.0007)
  - 39% reduction in the proportion of patients relapsed
  - 34% reduction in the proportion of relapses requiring intravenous (IV) steroids
- Patients treated with pegIFNβ-1a Q2W had a 44% lower rate of MS-related hospitalisations, compared with placebo.
- Patients treated with pegIFNβ-1a Q2W were 38% less likely to experience confirmed disability progression sustained for 3 months (CDP3M) and 54% less likely to experience confirmed disability progression sustained for 6 months (CDP6M) (post hoc analysis), compared with placebo.
- Patients treated with pegIFNβ-1a Q2W who experienced a relapse were 30% less likely to experience CDP following the relapse.
- Among patients who experienced disability progression following a relapse, pegIFNβ-1a patients were significantly more likely to recover completely; the likelihood of disability progression in the 180 days following a relapse was reduced by 56%, compared with placebo.
- PegIFNβ-1a Q2W patients had 67% fewer new/newly enlarging T2 lesions, 67% fewer new active lesions, 86% fewer Gd+ lesions, and 53% fewer T1 lesions compared with placebo.
- PegIFNβ-1a Q2W patients were significantly more likely to demonstrate no evidence of disease activity (NEDA) compared with placebo, based on clinical (80.3% vs. 69.9%; *P* = 0.0013) and radiological criteria (62.6% vs. 41.2%; *P* < 0.0001), or combination of both (34.8% vs. 14.7%; *P* < 0.0001).

ADVANCE – Year 2 results: PegIFNβ-1a Q2W vs. delayed treatment

- In year 2 of ADVANCE, patients were switched from placebo to pegIFNβ-1a Q2W (delayed treatment arm), whereas patients initially randomised to pegIFNβ-1a Q2W continued the same treatment:
- Patients who continued treatment with pegIFNβ-1a had a further reduction in the adjusted ARR at year 2:
  - 37% reduction in the adjusted ARR compared with delayed treatment; rate ratio, 0.630 (95% CI, 0.499-0.794; *P* < 0.0001)
  - 39% reduction in the proportion of patients relapsed
- Patients who continued with pegIFNβ-1a Q2W were 37% less likely to experience CDP3M when compared with delayed treatment; hazard ratio (HR), 0.63 (95% CI, 0.43-0.94; *P* = 0.0223).

ATTAIN

In the continuous pegIFNβ-1a Q2W treatment:

- The long-term results from the ATTAIN study demonstrated sustained efficacy of pegIFNβ-1a Q2W over 6 years.

- The adjusted ARR, relapses requiring IV steroids, and hospitalisation rate decreased year-after-year and remained lower versus first-year period with placebo control in the ADVANCE study.
- Low numbers of MRI lesions shown at year 1 continued to be low over 4 years of pegIFNβ-1a Q2W treatment (mean number of Gd+ lesions: 0.2-0.3, new/newly enlarging T2 lesions: 1.6-1.7, new T1 lesions: 0.7-0.8).
- Consistent with year 1 findings in the ADVANCE study, the proportion of patients with NEDA was maintained at a high level in each year during years 2 to 4 (> 80% based on clinical criteria, > 60% based MRI criteria, and > 50% for combination of both).

In the continuous versus delayed initiation of pegIFNβ-1a Q2W:

- The delayed pegIFNβ-1a Q2W group (i.e., patients who switched from placebo to pegIFNβ-1a Q2W after year 1 in the ADVANCE study) experienced treatment effects similar to those of the continuous pegIFNβ-1a Q2W group in terms of low RRs and hospitalisation rates, but results were numerically lower (worse) in the delayed group than in the continuous group.
- Both groups experienced a similar trend towards a reduced risk of 24-week CDP over up to 5 years of treatment
- Mean changes of Multiple Sclerosis Impact Scale 29 (MSIS-29) psychological subscale, SF-12 Health Survey (SF-12) mental component score, and EQ-5D visual analog scale (VAS) demonstrated a slight improvement in QOL over up to 6 years, irrespective of the time of pegIFNβ-1a Q2W initiation (early or delayed by 1 year).

Subgroup/post hoc analysis from ADVANCE

- Subgroup analysis suggested that the efficacy of pegIFNβ-1a was similar in all patients regardless of their sex, age, body weight, geographical region, or disease status at the initiation of treatment.
- A post hoc analysis of the ADVANCE study evaluating chronic BH development over 2 years found fewer BHs developed at week 48 from new or enlarging T2-weighted (NET2) lesions (0.44 vs. 0.99; 56% reduction, $P < 0.0001$) and from new Gd+ lesions (0.09 vs. 0.19; 53% reduction, $P = 0.0003$) in Q2W continuous treatment patients than in the delayed treatment group.

B.2.1 Identification and selection of relevant studies

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

B.2.2 List of relevant clinical-effectiveness evidence

Only one relevant randomised controlled trial was identified in the clinical systematic review that evaluated clinical effectiveness of pegIFNβ-1a in adult patients with RRMS. This was the pivotal phase III trial, ADVANCE, which compared dosing pegIFNβ-1a Q2W and every 4 weeks (Q4W) with placebo over 1 year and demonstrated the efficacy and safety profile of pegIFNβ-1a Q2W. In the second year of ADVANCE, patients originally randomised to receive placebo were re-randomised to receive pegIFNβ-1a Q2W or Q4W; therefore, comparisons were made between the group of patients who received pegIFNβ-1a Q2W or Q4W treatment continuously versus those for whom treatment was delayed.[11]

Based on mechanistic considerations, it may be assumed that pegIFNβ-1a is at least as effective as currently available IFNβs, so a superiority study against an active comparator was not deemed scientifically appropriate. A formal non-inferiority study versus an active comparator was considered but, following scientific advice and regulatory guidance, this option was not adopted because the number of patients required to characterise the relative efficacy of pegIFNβ-1a and a comparator with sufficient confidence was deemed to be too large to be feasible and realistic.[7]

In view of the potential ethical concerns at the time of study conceptualisation, a placebo-controlled design was chosen for this study. Given the number of treatment options for patients with RRMS that were available at the time, it was decided that a 1-year placebo-controlled phase with a second year to demonstrate the longer-term safety profile and efficacy of pegIFNβ-1a was most appropriate ethically. Given that IFNs have been used for over 16 years and have a well-established efficacy and safety profile[101-104,108], pegIFNβ-1a was able to proceed directly to phase III testing following phase I studies. All evidence from ADVANCE is taken from the year 1 clinical study report,[7] the ADVANCE primary publication,[11] or the final data tables for the data over 2 years.[7,123] Table 4 summarises the study design of ADVANCE.

Table 4. Clinical-effectiveness evidence: ADVANCE

Study	ADVANCE[11,123]		
Study design	Multicentre, randomised, double-blind, placebo-controlled,[a] phase III study		
Population	Adults aged 18-65 years (inclusive) with RRMS, EDSS ≤ 5.0		
Intervention(s) and comparator(s)	Year 1: ▪ SC pegIFNβ-1a Q2W (n = 512) ▪ SC pegIFNβ-1a Q4W (n = 500) ▪ Placebo (n = 500) At the end of year 1, all placebo patients were randomised to active treatment: ▪ Continued SC pegIFNβ-1a Q2W (n = 438) ▪ Continued SC pegIFNβ-1a Q4W (n = 438) ▪ Switched to SC pegIFNβ-1a Q2W (n = 228) ▪ Switched to SC pegIFNβ-1a Q4W (n = 228)		
Study length	96 weeks (year 1: 48 weeks; year 2: 48 weeks)		
Indicate if trial supports application for marketing authorisation	Yes	Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	Pivotal phase III, randomised controlled trial for clinical efficacy data		
Reported outcomes specified in the decision problem	▪ **Relapse rate** ▪ Severity of relapse ▪ **Disability (e.g., EDSS, CDP3M, and CDP6M)** ▪ Symptoms of MS (such as fatigue, cognition, and visual disturbance – visual function test, MS functional component, etc.) ▪ Freedom from disease activity (for example lesions on MRI scans) ▪ Mortality ▪ **Adverse effects of treatment** ▪ HRQOL		
All other reported outcomes	▪ Brain atrophy ▪ Magnetisation transfer ratio ▪ ARR-ST ▪ MS-related hospitalisation ▪ Treatment discontinuation ▪ Life-years ▪ Direct cost outcomes		

ARR-ST = annualised relapse rate requiring steroids; CDP3M = confirmed disability progression sustained for 3 months; CDP6M = confirmed disability progression sustained for 6 months; EDSS = Expanded Disability Status Scale; HRQOL = health-related quality-of-life; pegIFNβ-1a = pegylated interferon β-1a; MRI = magnetic resonance imaging; MS = multiple sclerosis; Q2W = every 2 weeks; Q4W = every 4 weeks; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.
Outcomes marked in **bold** are incorporated into the model
[a] Year 1 only.
Source: Calabresi et al. (2014)[11]

ATTAIN is a 2-year extension study for ADVANCE which supplements data from ADVANCE (Table 5) (the study was deemed complete when the last patient reached week 96 assessment, hence for some patients data up to 6 years are available). ATTAIN was not used to populate the economic model which is based on ADVANCE but is included in Sections B.2.2 to B.2.6 as it provides supplementary evidence for the long-term efficacy and safety profile of pegIFNβ-1α 125 µg up to 6 years.[124]

Table 5. Clinical-effectiveness evidence: ATTAIN

Study	ATTAIN (2-year extension of ADVANCE)[124]
Study design	A dose-frequency blinded extension study of ADVANCE
Population	Patients who completed 2 years in ADVANCE
Intervention(s) and comparator(s)	pegIFNβ-1a Q2W (n = 376) pegIFNβ-1a Q4W (n = 354)
Study length	2 years (completed when the last patients reach the week 96 assessment)
Indicate if trial supports application for marketing authorisation	No
Indicate if trial used in the economic model	No
Rationale for use/non-use in the model	Not applicable
Reported outcomes specified in the decision problem	▪ Adverse effects of treatment ▪ Mortality ▪ Relapse rate ▪ Severity of relapse ▪ Disability (e.g., EDSS CDP6M) ▪ Freedom from disease activity (for example lesions on MRI scans)
All other reported outcomes	▪ Immunogenicity

CDP6M = confirmed disability progression sustained for 6 months; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; pegIFNβ-1a = pegylated interferon β-1a; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: Newsome et al. (2018)[124]

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

B.2.3.1 ADVANCE

B.2.3.1.1 Methodology

ADVANCE was an international, multicentre, randomised, double-blind, parallel-group, placebo-controlled study (year 1). The methods for the ADVANCE study are summarised in Table 6. Patients were randomised in a 1:1:1 ratio to receive either SC pegIFNβ-1a 125 mcg Q2W or Q4W, or placebo. All randomisation took place using a centralised, interactive voice/web recognition system and was stratified by site.[11]

ADVANCE was double-blind for patients in the first year, while assessors performing clinical assessments were blind throughout. All patients and study staff were blinded to the patient's randomised treatment assignment. To ensure treatment blinding within the first year, each patient received one injection of pegIFNβ-1a or placebo Q2W. In the second year, all patients were permitted to know they were receiving pegIFNβ-1a treatment but remained blinded to the treatment frequency (Q2W or Q4W).[11]

Table 6. Study methodology: ADVANCE

Study	ADVANCE
Location	26 countries
Trial design	An international, multicentre, phase III, randomised, 2-year double-blind study, assessing the efficacy of two pegIFNβ-1a treatment regimens in adults with RRMS. Patients were randomised in a 1:1:1 ratio to receive either pegIFNβ-1a Q2W or Q4W, or placebo. A 1-year placebo-controlled treatment period was followed by a second year of treatment, during which all patients initially allocated to placebo were re-randomised to receive either pegIFNβ-1a Q2W or Q4W. To ensure treatment blinding within the first year, each patient received one injection of pegIFNβ-1a or placebo Q2W. At the end of year 1, patients randomised to placebo were re-randomised to pegIFNβ-1a (Q2W or Q4W). In year 2, all patients were permitted to know that they were receiving pegIFNβ-1a treatment but were to remain blinded to the treatment frequency (Q2W or Q4W).
Objectives	**Year 1** To determine the safety profile and efficacy of two different treatment regimens of pegIFNβ-1a (Q2W and Q4W) in adult patients with RRMS at 1 year in terms of reducing ARR, reducing the proportion of patients who relapsed, slowing disability progression, and reducing the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans. **Year 2** To determine the maintenance of efficacy and the safety profile, tolerability, and immunogenicity of pegIFNβ-1a over a 2-year treatment period.
Settings and locations where the data were collected	183 neurology practices, including hospitals, academic medical centres, and private practices, in 26 countries.

Study	ADVANCE
Interventions	**Year 1** In year 1, patients were randomised in a 1:1:1 ratio to receive either: ▪ PegIFNβ-1a Q2W (n = 512) ▪ PegIFNβ-1a Q4W (alternate injections of placebo and pegIFNβ-1a Q2W) (n = 500) ▪ Placebo (n = 500) **Year 2** In year 2, the delayed treatment group (those who received placebo in year 1) were re-randomised in a 1:1 ratio to receive pegIFNβ-1a Q2W (n = 228) or Q4W (n = 228). Patients who received pegIFNβ-1a Q2W or Q4W in year 1 remained on their assigned treatment regimen in year 2 (Q4W, n = 438; Q2W, n = 438).
Key inclusion criteria	▪ Aged 18-65 years at time of informed consent ▪ Confirmed diagnosis of relapsing MS, as defined by McDonald criteria 1 through 4 ▪ EDSS score 0.0-5.0 ▪ ≥ 2 relapses within the last 3 years with ≥ 1 of these in the last 12 months prior to randomisation ▪ Able and willing to practice effective contraception during the study and for 3 months after the last dose of study treatment
Key exclusion criteria	Medical history ▪ Relapse within 50 days prior to randomisation and/or not stabilised from a previous relapse ▪ Primary progressive, secondary-progressive, or progressive relapsing MS ▪ Known allergy to any component of the pegIFNβ-1a formulation ▪ History of hypersensitivity or intolerance to paracetamol, ibuprofen, naproxen, or aspirin that would preclude use of at least one of these during the study Treatment history ▪ Prior treatment with interferon could not exceed 4 weeks, and patients must have discontinued interferon treatment 6 months prior to day 1 of the study (baseline) ▪ Previous treatment with pegIFNβ-1a, total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, fingolimod, any therapeutic monoclonal antibody (including natalizumab), or GA within 4 weeks prior to randomisation

Study	ADVANCE
Efficacy outcomes	**Year 1** Primary efficacy outcome: ▪ ARR at 1 year Secondary efficacy outcomes: ▪ Proportion of patients relapsed at 1 year ▪ CDP3M at 1 year, and post hoc analysis of CDP6M at 6 months that was defined as a ≥ 1.0-point increase on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 3 or 6 months, or a ≥ 1.5-point increase on the EDSS from baseline EDSS = 0.0 that was sustained for 3 or 6 months ▪ Number of new or newly enlarging T2 hyperintense lesions at 1 year **Year 2** Secondary/tertiary end points included the following key clinical and MRI measures: ▪ ARR ▪ Proportion of patients relapsed ▪ Disability progression (CDP3M and CDP6M) ▪ Mean number of new or newly enlarging T2 hyperintense lesions and Gd+ lesions
Pre-planned subgroups	▪ ARR between patients who withdrew before the end of year 1 and those who completed year 1. ▪ Baseline EDSS (EDSS < 4.0 vs. EDSS ≥ 4.0) ▪ Age at baseline (< 40 vs. ≥ 40 years)* ▪ Sex* ▪ Region ▪ Baseline weight* ▪ Baseline number of relapses in the 3 years prior to study entry ▪ Time since most recent pre-study relapse (months) (≤ 4 vs. > 4 months ▪ Baseline McDonald criteria ▪ Prior MS treatment ▪ Baseline Gd+ lesions* ▪ Baseline T2 lesion volume

ARR = annualised relapse rate; CDP3M = confirmed disability progression sustained at 3 months; CDP6M = confirmed disability progression sustained at 6 months EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium enhancing; MRI = magnetic resonance imaging; McDonald criteria 1-4 = see Section B.2.3.1.2; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.

Note: Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting ≥ 24 hours, and accompanied by new objective neurological findings upon examination by a neurologist. Relapses were required to be confirmed by an independent committee consisting of 8 blinded neurologists with expertise in MS (3 neurologists were voting members, with 1 substitute member at any one time). New or recurrent neurologic symptoms that occurred < 30 days following the onset of a protocol-defined relapse were considered part of the same relapse (i.e., if 2 relapses had onset days that were ≤ 29 days apart, they were counted only as 1 relapse, and the onset date used in the analysis was the onset date of the first relapse).[11]

* Due to the number of outcomes and subgroups, only those which were felt to be relevant will be presented. Therefore, results for those subgroups marked with an asterisk (*) will not be presented.

Sources: Calabresi et al. (2014)[11]; Biogen Idec Inc (2013)[7]; Kieseier et al. (2015)[123].

B.2.3.1.2 Baseline characteristics

In the intent-to-treat (ITT) population, the three treatment groups were generally well-balanced with respect to baseline demographics (Table 7). ADVANCE was conducted in mainly treatment-naive patients (approximately 83% overall) with mild to moderate disease.[125-127] The majority of patients were women (71%), < 40 years old (62%), and white (82%). In total, 14 patients were enrolled in the UK.[7,11]

The three treatment groups were also similar regarding proportions of patients meeting the 2005 McDonald criteria 1 to 4 at screening (please see Section B.1.3.1.5 for more detail), baseline EDSS scores, relapse history, and MS disease history. Most patients (88%) were diagnosed with MS based on McDonald criterion 1. EDSS scores at baseline were similar (0.0-5.5 across treatment groups). One patient (< 1%) had scores greater than the protocol-specified upper limit of 5.0. Most patients (84%) had an EDSS < 4 at baseline, and 16% of patients had a baseline EDSS ≥ 4.[7,11] The McDonald criteria are defined as follows[7]:

1. Two or more relapses, two or more objective lesions.
2. Two or more relapses, one objective lesion, and DIS by MRI or positive CSF and two or more MRI lesions consistent with MS or further clinical attack involving different site.
3. One relapse, two or more objective lesions, and DIT by MRI or second clinical attack.
4. One (mono-symptomatic) relapse, one objective lesion, DIS by MRI or positive CSF and two or more MRI lesions consistent with MS, and DIT by MRI or second clinical attack.

During the 12 months before the start of the study, most patients (53%) had one relapse, 40% of patients had two relapses, and 6% of patients had three or more relapses. The mean number of relapses that occurred during this period was 1.5. During the 3 years prior to study entry, the mean number of relapses was 2.5. The mean time since the most recent relapse was 5.0 months. The mean time since the occurrence of the first symptoms of MS was 6.6 years, with a wide range of individual subject values (0-40 years). The mean time since MS diagnosis was 3.6 years (0-40 years).[7,11]

Table 7. Patient demographics and baseline characteristics, ADVANCE, intent-to-treat population

Characteristic		PeglFNβ-1a Q2W (N = 512)	Placebo (N = 500)	PeglFNβ-1a Q4W (N = 500)
Age, mean ± SD		36.9 ± 9.8	36.6 ± 9.8	36.4 ± 9.9
Female, n (%)		361 (71)	358 (72)	352 (70)
Race, n (%)	White	416 (81)	412 (82)	409 (82)
	Asian	59 (12)	56 (11)	56 (11)
	Other	33 (6)	29 (6)	32 (6)
	Black	3 (< 1)	3 (< 1)	1 (< 1)
	Not reported	1 (< 1)	0	2 (< 1)

Characteristic		PegIFNβ-1a Q2W (N = 512)	Placebo (N = 500)	PegIFNβ-1a Q4W (N = 500)
Region, n (%)	India	58 (11)	56 (11)	56 (11)
	North America	19 (4)	17 (3)	16 (3)
	Western Europe	41 (8)	38 (8)	39 (8)
	Eastern Europe	355 (69)	354 (71)	355 (71)
	Rest of world	39 (8)	35 (7)	34 (7)
Height (cm), mean ± SD		167.8 ± 9.55	167.5 ± 9.11	167.6 ± 9.17
Weight (kg), mean ± SD		69.57 ± 17.38	69.19 ± 16.16	68.32 ± 14.63
Body mass index (kg/m^2), mean ± SD		24.59 ± 5.10	24.61 ± 4.90	24.25 ± 4.53
EDSS score	Mean ± SD	2.47 ± 1.25	2.44 ± 1.18	2.48 ± 1.24
	< 4, %	83	86	83
	≥ 4, %	17	14	17
Relapses in previous year, mean ± SD		1.6 ± 0.7	1.6 ± 0.7	1.5 ± 0.6
Relapses in previous 3 years, mean ± SD		2.6 ± 1.0	2.6 ± 1.0	2.5 ± 0.8
Time since MS diagnosis, years ± SD		4.0 ± 5.1	3.5 ± 4.63	3.4 ± 4.3
McDonald criteria	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]
Prior MS treatment, n (%)[a]	Any	89 (17)	86 (17)	85 (17)
	GA	27 (5)	24 (5)	28 (6)
	IFNβ-1b	8 (2)	6 (1)	5 (1)
	IFNβ-1a	4 (< 1)	5 (1)	6 (1)
	Other	58 (11)	58 (12)	56 (11)
Number of lesions, mean± SD	T2	48.7 ± 36.83	50.6 ± 35.65	51.4 ± 35.99
	T1	[redacted]	[redacted]	[redacted]
	Gd+	1.2 ± 3.44	1.6 ± 3.81	1.8 ± 5.38

EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation.
Note: PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
[a] Patients may have received more than one therapy.
Sources: Calabresi et al. (2014)[11]; Biogen Idec Inc (2013)[7]

B.2.3.2 ATTAIN

B.2.3.2.1 Methodology

ATTAIN was a dose-blinded extension of ADVANCE, in which patients received the same dosing regimen that they received in year 2 of ADVANCE. ATTAIN was completed in quarter 4, 2015.[124,128]

Table 8 summarises the methodology and results of ATTAIN.

Table 8. Study methodology and key results: ATTAIN

Study	ATTAIN
Location	26 countries
Trial design	A phase IIIb, multicentre, parallel-group, dose-frequency blinded, 2-year extension of ADVANCE. When the last patient reached 96 weeks, the ATTAIN study was considered complete; therefore, some patients received treatment for up to 6 years. A protocol amendment changed ATTAIN to an open-label study where all ongoing patients on pegIFNβ-1a Q4W dosing were switched to Q2W dosing; the original dosing schedules remained blinded.
Objectives	To evaluate the long-term efficacy and safety profile of pegIFNβ-1a (2 years in ADVANCE and 2 years in ATTAIN; 5-year and 6-year data also presented).
Settings and locations where the data were collected	183 neurology practices, including hospitals, academic medical centres, and private practices, in 26 countries.
Interventions	Patients received one of the following treatment regimens depending on their treatment assignment in year 2 in ADVANCE: ▪ PegIFNβ-1a Q2W (n = 740; 512 received continuous treatment, and 228 received treatment beginning in year 2). ▪ PegIFNβ-1a Q4W (n = 728; 500 received continuous treatment, and 228 received treatment beginning in year 2). – Following implementation of the protocol amendment, all ongoing patients on pegIFNβ-1a Q4W were switched to Q2W for the remainder of the study
Eligibility criteria for participants	Inclusion: Diagnosis of RRMS as defined by the 2005 McDonald criteria, age 18-65 years, a score of 0.0-5.0 on the EDSS, and at least two clinically documented relapses in the previous 3 years, of which at least one occurred within 12 months of screening visit. Exclusion: Progressive forms of MS, prespecified laboratory abnormalities, and previous treatment with IFNs for MS for more than 4 weeks, or discontinuation of treatment less than 6 months before baseline visit.

Study	ATTAIN
Outcomes assessed	Primary outcomes: ▪ Incidence of AEs. ▪ Incidence of SAEs. ▪ Number of patients discontinued due to AEs. ▪ Laboratory abnormalities. Secondary outcomes: ▪ ARR and proportion of patients relapsed. ▪ Proportion of patients with CDP sustained for 6 months over 3 years. ▪ Mean numbers of Gd+ lesions, new or newly enlarging T2 lesions, and new T1 hypointense lesions.
Pre-planned subgroups	Not reported

AE = adverse event; ARR = annualised relapse rate; BH = black hole; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; IFN = interferon; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon; Q2W, every 2 weeks; Q4W, every 4 weeks; RRMS = relapsing-remitting multiple sclerosis; SAE = serious adverse event; SC, subcutaneous.
Note: Definition of relapses is the same as described in the ADVANCE study (Table 6).
Sources: Newsome et al. (2018)[124]

B.2.3.2.2 Baseline characteristics

In total, 1,076 patients took part in the ATTAIN study, of whom 376 received continuous pegIFNβ-1a Q2W, 354 received continuous pegIFNβ-1a Q4W from year 1 of ADVANCE, 171 received delayed treatment with pegIFNβ-1a Q2W, and 175 received delayed treatment with pegIFNβ-1a Q4W.[124,128]

When the last patient reached 96 weeks, the ATTAIN study was considered complete; therefore, some patients received treatment for up to 6 years. The mean duration of exposure (for all patients who received active treatment during the study) was 149.9 weeks (range 2-278). Due to the limited number of patients completing 6 years, some of the outcomes reported are over 5 years.

Patient demographic and baseline characteristics were generally balanced across treatment arms (Table 9).

Table 9. Baseline characteristics: ATTAIN (continuous treatment groups)

Characteristic	pegIFNβ-1a Q2W (n = 376)	pegIFNβ-1a Q4W (n = 354)
Age, years	39.0 (9.73)	38.1 (9.91)
Gender, % female	72	71
Time since first MS symptoms, years	8.5 (6.27)	8.1 (6.11)
Mean EDSS score	2.39 (1.34)	2.41 (1.37)[a]
Number of T2 lesions	5.8 (12.23)[b]	14.8 (23.39)[c]
Volume of T2 lesions, cm^3	10.51 (12.58)	11.30 (13.37)
Number of T1 hypointense lesions	29.1 (28.98)	29.0 (31.06)
Number of Gd+ lesions	0.2 (1.18)[d]	0.6 (1.74)[e]

EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.
Note: PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
[a] n = 352.
[b] n = 374.
[c] n = 353.
[d] n = 375.
[e] n = 353.
Sources: Newsome et al. (2018)[124]; Biogen Idec Inc (2016)[128]

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

Table 10 presents a summary of the statistical analysis and definition of study groups for the ADVANCE and ATTAIN trials.[11]

Table 10. Summary of statistical analyses

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ADVANCE	That treatment with pegIFNβ-1a would result in a statistically significant reduction in ARR at 48 weeks, compared with placebo.	The primary end point was analysed using negative binomial regression, adjusted for baseline EDSS score (< 4 vs. ≥ 4), baseline age (< 40 vs. ≥ 40 years), and baseline relapse rate (number of relapses in 3 years prior to study entry divided by 3). A sequential closed testing procedure was used to control the type I error rate. For the primary end point, the pegIFNβ-1a Q2W group was compared with placebo; if the difference between the pegIFNβ-1a Q2W group vs. placebo was statistically significant ($P \leq 0.05$), the comparison of pegIFNβ-1a Q4W group vs. placebo could also be performed and considered statistically significant if $P \leq 0.05$; however, if statistical significance was not achieved with the pegIFNβ-1a Q2W group vs. placebo, the comparison of the pegIFNβ-1a Q4W group vs. placebo was not considered statistically significant, regardless of *P* value. Five sensitivity analyses (three prespecified and two post hoc) of ARR at year 1 were performed; these differed from the primary analysis by using: ▪ The per protocol population (prespecified) ▪ Poisson regression model (prespecified), all relapses recorded on the unscheduled relapse assessment CRF (prespecified)	The sample size calculation was based on the type I error rate of 0.05 and a dropout rate of 10%. It was assumed that the treatment effect for pegIFNβ-1a would be a 32% reduction from placebo in ARR at year 1. A sample size of 420 per treatment group was initially planned to provide approximately 90%, 87%, and 85% power for a year 1 placebo ARR of 0.6, 0.55, or 0.5, respectively. It was specified that the pooled year 1 ARR would be monitored and that the placebo year 1 ARR would be estimated by back-calculating from the pooled ARR and the assumed treatment effect. If the placebo year 1 ARR was estimated to be lower than 0.5, the sample size could increase for the study. As a result of this monitoring, the sample size was increased from 420 to 500 subjects per group.	Data management was performed by Biogen Idec personnel and a Functional Service Provider (Client Associated Businesses, Inc.) using the web-based Oracle® Clinical RDC onsite version 4.5 data management system. Relapses that occurred after patients received any alternative approved MS treatments such as chronic immunosuppressant therapy or other immunomodulatory treatments were excluded from the analyses of relapse rate, and the patient's time on study was censored at the time the alternative MS medication was started. If patients withdrew from the study or switched to an alternative MS medication before 1 year, the total number of days was defined as the number of days from the date of

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		▪ Protocol-defined objective relapses recorded on the unscheduled relapse assessment CRF (post hoc) ▪ Baseline Gd+ lesion (presence vs. absence) as a covariate in the model (post hoc)		the first dose to the last date on study or last date prior to the switch.
ATTAIN	The incidence of AEs, SAEs, discontinuations of study treatment due to an AE, and laboratory abnormalities.	All summary analyses of AEs were based on the principle of treatment emergence. In a given data set, an event was considered to be treatment emergent if it had an onset date on or after the date of first study treatment, or if it was present before the start of study treatment and subsequently worsened. In general, AEs were analysed based on incidence, defined as the proportion of patients who had at least one occurrence of an event out of the number of patients in the relevant safety analysis population. The MedDRA Version 18.0 was used to code and group AEs by system organ class and preferred term.	The safety population was the ATTAIN intent to treat population and was defined as all patients who received at least one dose of treatment while enrolled in ATTAIN. The Q2W continuously dosed analysis group included only those patients who received pegIFNβ-1a Q2W from the start of ADVANCE; it did not include patients who switched to Q2W dosing at the time of the protocol amendment.	Data management was performed by Biogen personnel and a Functional Service Provider (Client Associated Businesses, Inc.) using the onsite web-based Oracle® Clinical RDC, version 4.5, data management system.

AE = adverse event; ARR = annualised relapse rate; CRF = case report form; EDSS = Expanded Disability Status Scale; MedDRA = Medical Dictionary for Regulatory Activities; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon β-1a; Q2W = every-2-weeks; Q4W = every-4-weeks; RDC = Remote Data Capture; SAE = serious adverse event.
Sources: Calabresi et al. (2014)[11]; Newsome et al. (2018)[124]; Biogen Idec Inc (2013)[7]; Biogen Idec Inc (2016)[128]

B.2.5 Quality assessment of the relevant clinical-effectiveness evidence

The quality assessment conducted for ADVANCE using the established risk-of-bias tools recommended for HTA submissions found that there was a low risk of bias reported across all risk-of-bias items assessed. Please see Appendix D for further detail.

B.2.6 Clinical-effectiveness results of the relevant trials

The primary, secondary, and some of the tertiary end points for the ADVANCE study are presented in this section (further end points presented in Appendix L). The primary outcomes for the ATTAIN study were safety outcomes, summarised in Section B.2.3.2, with secondary outcomes of efficacy. Results for pegIFNβ-1a Q4W are presented here in some tables and figures; however, only pegIFNβ-1a Q2W is discussed in detail as this is the only licensed posology.

B.2.6.1 Annualised relapse rate (ARR) at 1 year

B.2.6.1.1 ADVANCE

During year 1, 116 (23%) patients receiving pegIFNβ-1a Q2W experienced an Independent Neurology Education Committee (INEC)-confirmed relapse, compared with 181 (36%) placebo patients. ARR at 1 year was significantly reduced by 35.6% (rate ratio 0.644; 95% CI, 0.500-0.831; *P* = 0.0007) following treatment with pegIFNβ-1a Q2W, compared with placebo (Table 11). Analyses of the per patient RRs were consistent with the analysis of ARR at year 1. A reduction in the ARR is an important treatment goal as relapses indicate an acute worsening of neurological function that substantially impairs QOL in patients with RRMS and relapses are thought to be associated with development of residual deficits [11]

Table 11. Primary efficacy outcome: ARR at year 1

	PegIFNβ-1a Q2W N = 512	**Placebo N = 500**	**PegIFNβ-1a Q4W N = 500**
ARR (95% CI)	**0.256 (0.206-0.318)**	0.397 (0.328-0.481)	0.288 (0.234-0.355)
Rate ratio vs. placebo (95% CI)	**0.644 (0.500-0.831)**	-	0.725 (0.565-0.930)
P vs. placebo	**0.0007**	-	0.0114

ARR = annualised relapse rate; CI = confidence interval; pegIFNβ = pegylated interferon β; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: Bold text indicates a significant difference for pegIFNβ-1a Q2W versus placebo. PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
Source: Calabresi et al. (2014)[11]

Sensitivity analysis

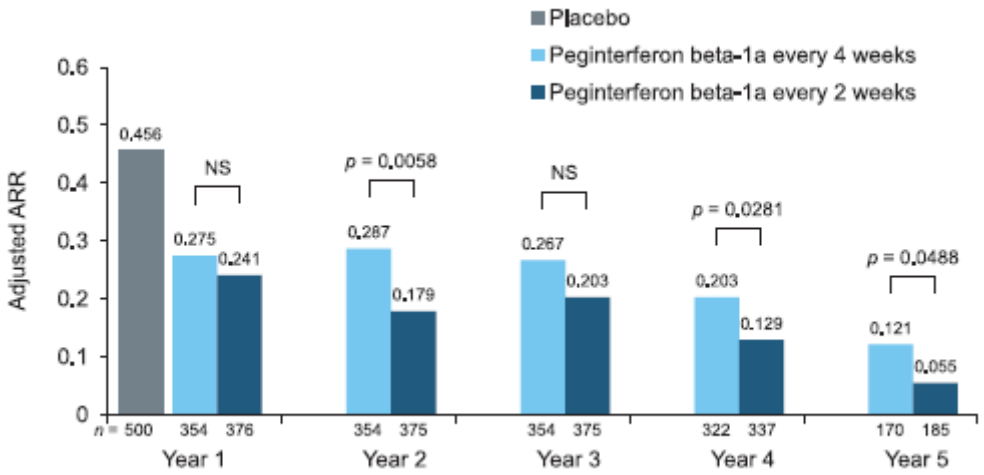
Five sensitivity analyses (three prespecified and two post hoc) of the ARR at year 1 were performed as described in Table 10 in Section B.2.4. The results of all five analyses were consistent with the primary efficacy results, showing that pegIFNβ-1a Q2W resulted in statistically significant reductions in the ARR compared with placebo, ranging from 33.8% to 38%.[7]

B.2.6.1.2 ATTAIN

ARR

The ARR for pegIFNβ-1a Q2W remained low and was maintained throughout years 1 to 5 in ATTAIN. In fact, the adjusted ARRs were generally reduced year-over-year in the Q2W group, with the difference compared with the Q4W groups being statistically significant in years 2, 4, and 5. Thus, it would seem reasonable to assume that if the placebo arm was continued, pegIFNβ-1a Q2W would have also potentially resulted in a significantly lower ARR compared with placebo.[124] The difference between the Q2W and Q4W groups was statistically significant in years 2, 4, and 5 (Figure 3).

Figure 3. Annualised relapse rate by year



ARR = annualised relapse rate; NS = not significant.
Source: Newsome et al. (2018)[124]

B.2.6.2 Risk of confirmed disability progression

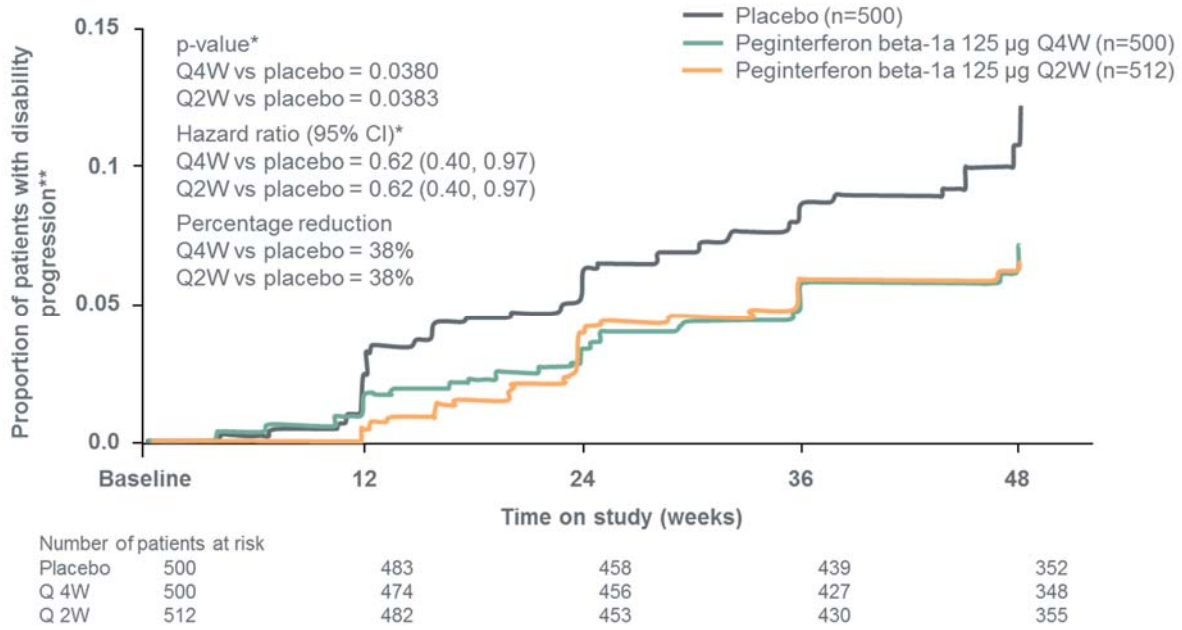
B.2.6.2.1 Risk of CDP3M

ADVANCE

Year 1

In the ITT population, pegIFNβ-1a Q2W significantly reduced the risk of CDP3M at year 1 compared with placebo by 38% (estimated proportion of patients who progressed for Q2W vs. placebo: 0.068 vs. 0.105), resulting in an HR of 0.62 (95% CI, 0.40-0.97; *P* = 0.0383) (Figure 4). This demonstrates that patients can achieve lower EDSS scores when given pegIFNβ-1a Q2W treatment compared with placebo and therefore less disability.[11]

Figure 4. Secondary efficacy outcome: risk of CDP3M at year 1



pegIFNβ-1a = pegylated interferon β-1a; CDP3M = confirmed disability progression sustained at 3-months; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; Q2W = every 2 weeks; Q4W = every 4 weeks.
* *P* value and HR (active/placebo) are based on a Cox proportional hazards model, with adjustment for baseline EDSS and age (< 40 vs. ≥ 40).
Source: Calabresi et al. (2014)[11]

Year 2

After year 1, patients receiving placebo were re-randomised to pegIFNβ-1a Q2W or Q4W for year 2, and patients receiving pegIFNβ-1a Q2W and Q4W in year 1 remained on the same dosing regimen for year 2.

Early initiation of pegIFNβ-1a Q2W significantly reduced the CDP3M over 2 years by 37% when compared with delayed treatment (HR, 0.63; 95% CI, 0.43-0.94; *P* = 0.0223).

ATTAIN

The long-term analysis found that the risk of CDP3M remained low over 5 years of treatment with pegIFNβ-1a Q2W. The Q2W dose continued to be associated with low risk of CDP3M (15.3%).[128]

B.2.6.2.2 Risk of CDP6M

ADVANCE

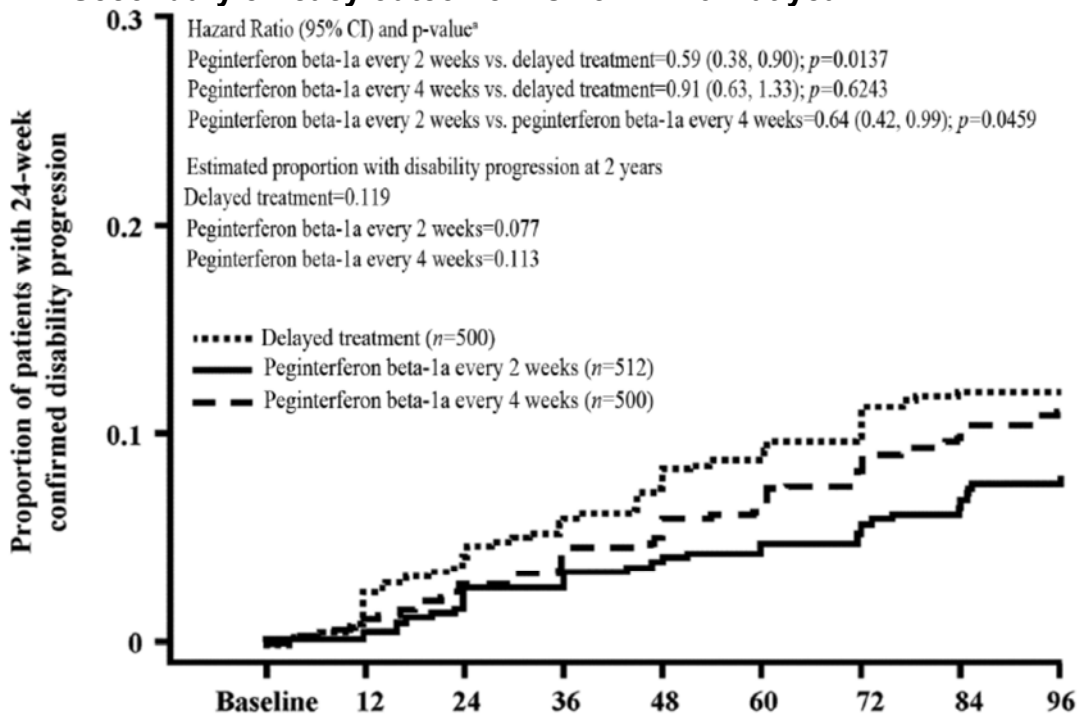
Year 1

In a post hoc analysis, pegIFNβ-1a Q2W significantly reduced the risk of CDP6M at year 1 compared with placebo by 54%, resulting in an HR of 0.46 (95% CI, 0.26-0.81; *P* = 0.0069).[11,123]

Year 2

In the ITT population, early initiation of pegIFNβ-1a Q2W significantly reduced the risk of CDP6M by 41% compared with delayed treatment (estimated proportion of patients who progressed for Q2W vs. delayed treatment: 0.077 vs. 0.119), resulting in an HR of 0.59 (95% CI, 0.38-0.90; *P* = 0.0137) (Figure 5).

Figure 5. Secondary efficacy outcome: risk of CDP6M at year 2



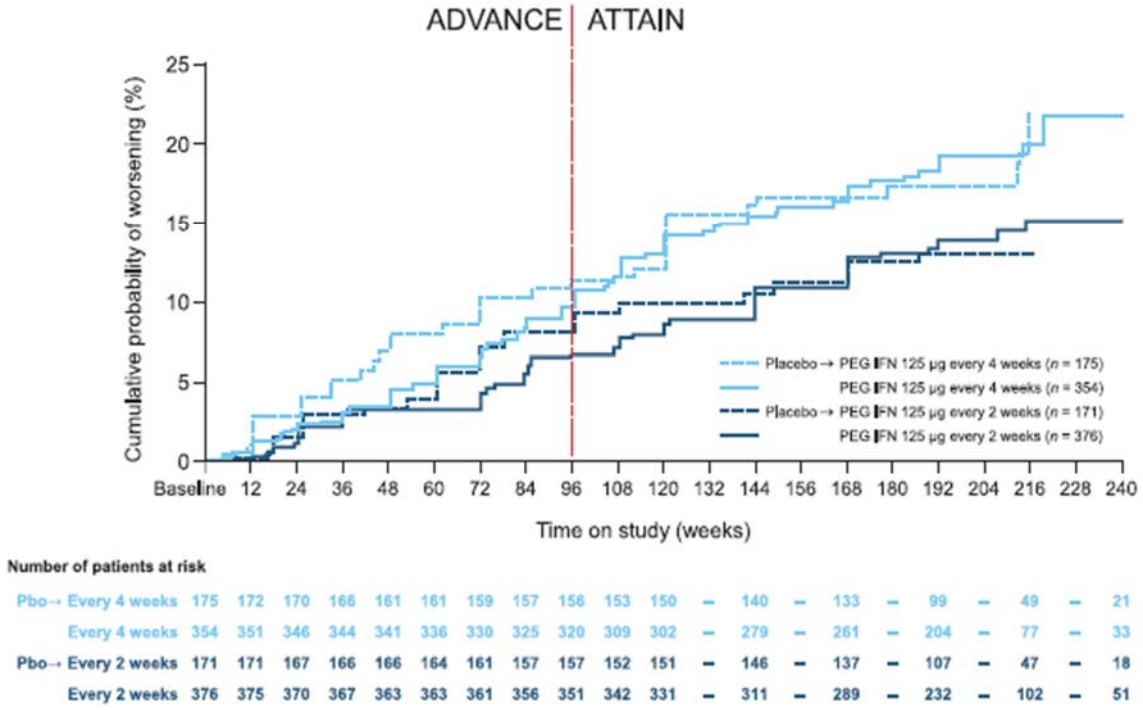
Number of patients at risk									
Delayed treatment	500	483	460	444	424	405	387	367	258
Peginterferon beta-1a every 2 weeks	512	480	455	438	428	415	405	397	301
Peginterferon beta-1a every 4 weeks	500	475	457	438	421	400	383	361	252

pegIFNβ-1a = pegylated interferon β-1a; CDP6M = confirmed disability progression at 6 months; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; Q2W = every 2 weeks; Q4W = every 4 weeks.
[a] *P* value and HR (active/delayed treatment) are based on a Cox proportional hazards model, with adjustment for baseline EDSS and age (< 40 vs. ≥ 40).
Source: Kieseier et al. (2015)[123]

ATTAIN - Proportion of patients with CDP6M over 5 years

Over 5 years, there was a trend towards a reduced risk of CDP6M in patients receiving continuous or delayed pegIFNβ-1a Q2W (13% and 15%, respectively) (Figure 6).[124]

Figure 6. CDP6M over ATTAIN



CDP6M = confirmed disability progression at 6-months; Pbo = placebo; PEG IFN = pegylated interferon.
Source: Newsome et al. (2018)[124]

B.2.6.3 MRI outcomes

B.2.6.3.1 ADVANCE

Number of new or newly enlarging T2 hyperintense lesions at year 1

Patients treated with pegIFNβ-1a Q2W had low numbers of new or newly enlarging T2 lesions at 1 year and achieved a statistically significant reduction in the number of new or newly enlarging T2 lesions compared with placebo at year 1 (Table 12). The adjusted lesion mean ratio was 0.33 (95% CI, 0.27-0.40; $P < 0.0001$) for pegIFNβ-1a Q2W versus placebo, representing a reduction of 67% in the number of T2 lesions over 1 year. Lesions detected in NET2 sequences represent a range of histopathological MS events and indicate the "footprint" of inflammatory events or remyelination and can determine the total number of lesions (cumulative "burden of disease"). A reduction in the number of T2 lesions can indicate a reduction of the accumulated burden of focal inflammatory disease in patients with MS.[11]

Table 12. Secondary efficacy outcome: number of new or newly enlarging T2 lesions at year 1

	PegIFNβ-1a Q2W N = 512	**Placebo N = 500**	**PegIFNβ-1a Q4W N = 500**
N	**457**	476	462
Mean± SD	**4.1± 8.55**	13.3± 19.51	9.2± 15.84
Adjusted mean[a]	**3.6**	10.9	7.9
Lesion mean ratio (95% CI)[a]	**0.33 (0.27-0.40)**	-	0.72 (0.60-0.87)
P value[a]	**< 0.0001**	-	0.0008

CI = confidence interval; pegIFNβ-1a = pegylated interferon β-1a; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation.
Notes: Bold text indicates a significant difference for pegIFNβ-1a Q2W vs. placebo. PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
[a] Adjusted mean, lesion mean ratio (95% CI) and *P* value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for region and baseline T2 lesion number.
Source: Calabresi et al. (2014)[11]; Biogen Idec Inc (2013)[7]; [1]

The results of sensitivity analyses were consistent with the primary analysis, showing that pegIFNβ-1a Q2W resulted in a statistically significant reduction in the number of new or newly enlarging T2 hyperintense lesions at 1 year compared with placebo, ranging from 67% to 68%.[7] The number of new or newly enlarging T2 hyperintense lesions at year 2 are presented in Table 14.

Tertiary MRI end points at 1 year

Table 13 summarises tertiary MRI outcomes at year 1. PegIFNβ-1a Q2W was significantly better than placebo for all outcomes at 1 year (except for brain atrophy), with a reduced number of lesions and reduced volume lesions reported versus placebo. In particular, pegIFNβ-1a Q2W patients had 86% and 53% fewer new active Gd+ and T1 lesions, respectively, at 1 year compared with placebo.[7] The results for brain atrophy are as expected due to the short treatment duration and in the view of the potential effect of pseudoatrophy (shrinkage of the brain after cessation of inflammation) during the first year of treatment.[11]

Table 13. Summary of tertiary MRI efficacy outcomes at 1 year in ADVANCE

Outcome		PegIFNβ-1a Q2W N = 512	Placebo N = 500	PegIFNβ-1a Q4W N = 500
No. new active lesions	Adjusted mean	**3.7**	11.2	7.3
	% reduction	**67%**	-	-
	Lesion mean ratio (95% CI)	**0.33 (0.27-0.40)**	-	0.65 (0.54-0.79)
	P	**< 0.0001**	-	< 0.0001
No. new T2 lesions and volume change (cm^3)	Adjusted mean	**3.6**	10.9	
	% reduction	**67%**	-	-
	Lesion mean ratio (95% CI)	**0.33 (0.27-0.40)**	-	
	P	**< 0.0001**		
	Volume change from baseline ± SD	**-0.26 ± 1.66624**	0.77 ± 2.52	0.06 ± 2.02
	P	**< 0.0001**	-	< 0.0001
No. Gd+ lesions and volume change (cm^3)	Mean ± SD	**0.2 ± 0.96**	1.4 ± 3.69	0.9 ± 3.31
	% reduction vs. placebo	**86%**	-	36%
	P	**< 0.0001**	-	0.0738
	Volume change from baseline ± SD	**-0.13 ± 0.45**	0.06 ± 1.25	-0.13 ± 0.76
	P	**< 0.0001**	-	< 0.0001
No. T1 lesions and volume change (cm^3)	Mean ± SD	**1.8 ± 4.37**	3.8 ± 6.78	3.1 ± 6.29
	% reduction vs. placebo	**53%**	-	18%
	P	**< 0.0001**	-	0.0815
	Volume change from baseline ± SD	**0.32 ± 0.96**	0.54 ± 1.14	0.57 ± 1.72
	P	**< 0.0001**	-	0.1795
Brain atrophy	% change from baseline, mean ± SD	**-0.72 ± 0.75**	- 0.62 ± 0.90	-0.67 ± 0.83
	P	**0.0841**	-	0.3747
Magnetisation transfer ratio	% change from baseline, mean ± SD	**-0.13 ± 1.61**	- 0.38 ± 1.61	-0.43 ± 1.57
	P	**0.0438**	-	0.6873

CI = confidence interval; Gd+ = gadolinium enhancing; pegIFNβ-1a = pegylated interferon β-1a; Q2W, every 2 weeks; Q4W, every 4 weeks; SD = standard deviation.
Notes: Bold text indicates a significant difference for pegIFNβ-1a Q2W vs. placebo. PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
Source:[11]

Tertiary MRI end points over 2 years

Table 14 summarises tertiary MRI outcomes for all patients over 2 years (ITT population).[7,123] The number of new or newly enlarging T2 lesions was further reduced in year 2 compared with year 1 in the continuous pegIFNβ-1a groups compared with the delayed treatment group, with greater reductions observed for pegIFNβ-1a Q2W than for pegIFNβ-1a Q4W. Statistically significant reductions in the number of Gd+ lesions over 2 years were also observed in the Q2W group versus the placebo + pegIFNβ-1a Q2W or Q4W group (delayed treatment group). These reductions in T2 lesions and Gd+ lesions can indicate a reduction in the presence of active inflammation which contributes to many of the complications associated with MS.[11,123]

Table 14. Summary of tertiary MRI end points for all patients over 2 years in ADVANCE

		PegIFNβ-1a Q2W (N = 512)	Placebo + pegIFNβ-1a Q2W or Q4W (N = 500)	PegIFNβ-1a Q4W (N = 500)
No. T2 lesions	Adjusted mean	**5.0**	14.8	12.5
	Mean ratio vs. delayed treatment (95% CI)	**0.33 (0.27-0.41)**	-	0.84 (0.69-1.03)
	P vs. delayed treatment	**< 0.0001**	-	0.0973
	Mean ratio vs. Q4W (95% CI)	**0.40 (0.32-0.49)**	-	-
	P vs. Q4W	**< 0.0001**	-	-
No. Gd+ lesions	Mean ± SD	**0.2 ± 1.15**	0.5 ± 1.58	0.7 ± 2.31
	% reduction vs. delayed treatment	**60**	-	40
	P vs. delayed treatment	**0.0002**	-	0.2169
	% reduction vs. Q4W	**71**	-	-
	P vs. Q4W	**< 0.0001**	-	-
No. T1 lesions	Mean ± SD	**2.3 ± 5.48**	5.6 ± 9.35	4.9 ± 9.29
	% reduction vs. delayed treatment	**59**	-	12
	P vs. delayed treatment	**< 0.0001**	-	0.1056
	% reduction vs. Q4W	**53**	-	-
	P vs. Q4W	**< 0.0001**	-	-

CI = confidence interval; Gd+ = gadolinium enhancing; pegIFNβ-1a = pegylated interferon β-1a; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation.
Notes: Bold text indicates a significant difference for pegIFNβ-1a Q2W vs. placebo. PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
Sources: Kieseier et al. (2015)[123]; Biogen Idec Inc (2013)[7]

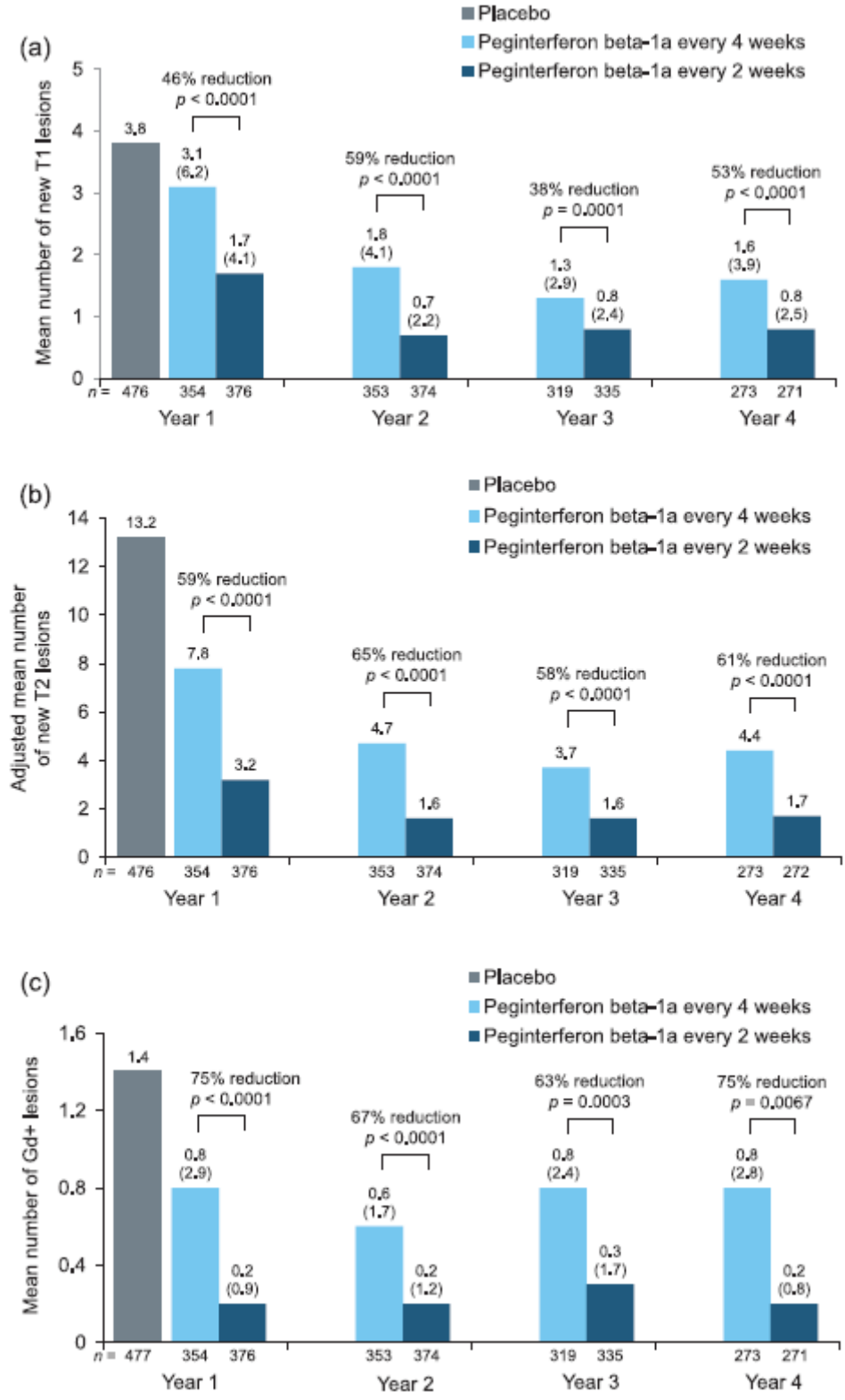
B.2.6.3.2 ATTAIN

MRI outcomes

The mean number of MRI lesions continued to be significantly lower in the pegIFNβ-1a Q2W treatment group compared with the Q4W group over the course of the ATTAIN study. In year 4, patients treated with pegIFNβ-1a Q2W displayed 53% fewer new T1 lesions ($P < 0.0001$), 61% fewer new or newly enlarging T2 lesions ($P < 0.0001$), and 75% fewer Gd+ lesions ($P = 0.0067$) compared with patients treated Q4W (Figure 7).[124]

The mean numbers of new T1 lesions (1.7 at year 1; 0.7 at year 2; 0.8 at year 3; 0.8 at year 4), new or newly enlarging T2 lesions (3.9 at year 1; 1.9 at year 2; 2 at year 3; 1.9 at year 4), and Gd+ lesions (0.2 at year 1; 0.2 at year 2; 0.3 at year 3; 0.2 at year 4) continued to be low with pegIFNβ-1a Q2W in each study year.

Figure 7. Mean number of MRI lesions by year: (a) mean number of new T1 lesions; (b) adjusted mean number of new or newly enlarging T2 lesions; (c) mean number of Gd+ lesions



Gd+ = gadolinium enhancing; MRI = magnetic resonance imaging.
Source: Newsome et al. (2018)[124]

B.2.7 Subgroup analysis

Prespecified subgroup analyses were performed for the ADVANCE study and are described in Section B.2.3.2.[7]

Results are presented in Appendix E and were generally consistent with those for the overall population.[7]

B.2.7.1 ARR at 1 year

The ARR across the prespecified subgroups were similar. There were some differences in the point estimates for the ARR for pegIFNβ-1a Q2W compared with placebo among the subgroups, but there was a considerable overlap in the CIs. This suggests that the efficacy of pegIFNβ-1a was similar in all patients regardless of their sex, age, body weight, geographical region, or disease status at the initiation of treatment (Figure 8).[7]

Figure 8. ARR (INEC-confirmed relapses) at 1 year—rate ratio and 95% CI by baseline disease characteristics subgroup: pegIFNβ-1a Q2W vs. placebo

CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; INEC = Independent Neurology Education Committee; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon β-1a; Q2W = every 2 weeks.
Note: Rate ratio (active/placebo) and (95% CI) based on negative binomial regression model, adjusted for baseline EDSS (< 4 v s. > = 4), baseline relapse rate, baseline age (< 40 v s. > = 40), except for the subgroup factor of interest.
Source: Biogen Idec Inc (2013)[7]

B.2.7.2 Post hoc analysis of ADVANCE

A post hoc analysis was performed for the ADVANCE study to evaluate the correlation of clinical outcomes with the evolution of acute lesions into chronic BHs and the effect of pegIFNβ-1a on the development of chronic BHs.[38,129]

Chronic BHs are an indication of irreversible tissue injury and axonal loss. They are used as a marker of therapeutic outcomes in patients with RRMS as the number of chronic BHs that develop from acute MRI lesions can be used to quantify the neuroprotective effects of MS therapy. Patients who do not develop BHs from T2 lesions and Gd+ lesions have less clinical disease activity than those patients who do. A lower risk of BH development from acute MRI lesions is beneficial for patients with RRMS as there will be less potential for irreversible tissue damage to occur.[38,129]

Another post hoc analysis assessed NEDA status during the ADVANCE and ATTAIN studies and explored clinical outcomes (including ARR and CDP) among patients stratified by NEDA achievement at year 2. NEDA is a composite measurement, incorporating clinical and MRI elements of disease activity to evaluate sensitively the therapeutic efficacy of treatments for RRMS.[130]

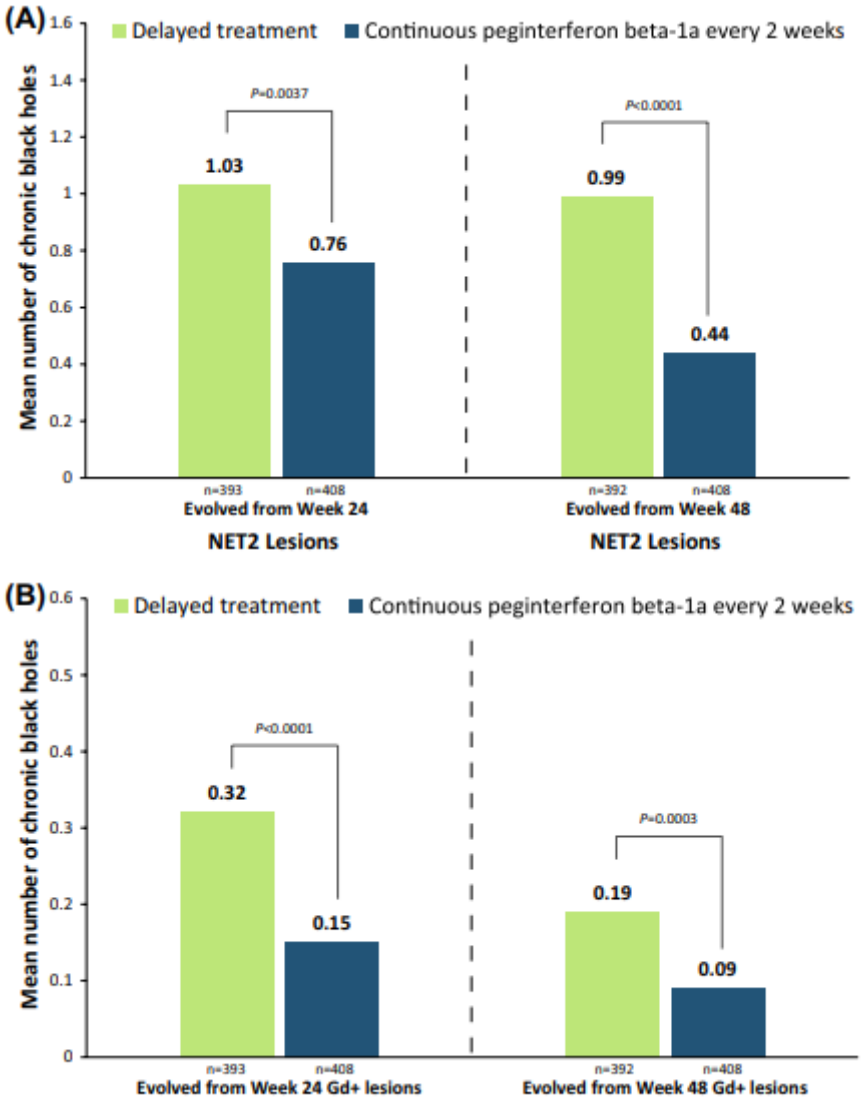
B.2.7.2.1 Black hole conversion

There were significantly fewer BHs at year 2, converted from the NET2 lesions present during year 1, in patients receiving continuous treatment with pegIFNβ-1a Q2W versus those receiving delayed treatment: 0.99 in the delayed treatment group versus 0.44 in the continuous treatment group, a 56% reduction ($P < 0.0001$) (Figure 9).

Similarly, there were also significantly fewer BHs at year 2, converted from Gd+ lesions present during year 1, in patients receiving continuous treatment with pegIFNβ-1a Q2W versus those receiving delayed treatment: 0.19 in the delayed treatment group versus 0.09 in the continuous treatment group, a 53% reduction ($P = 0.0003$).[129]

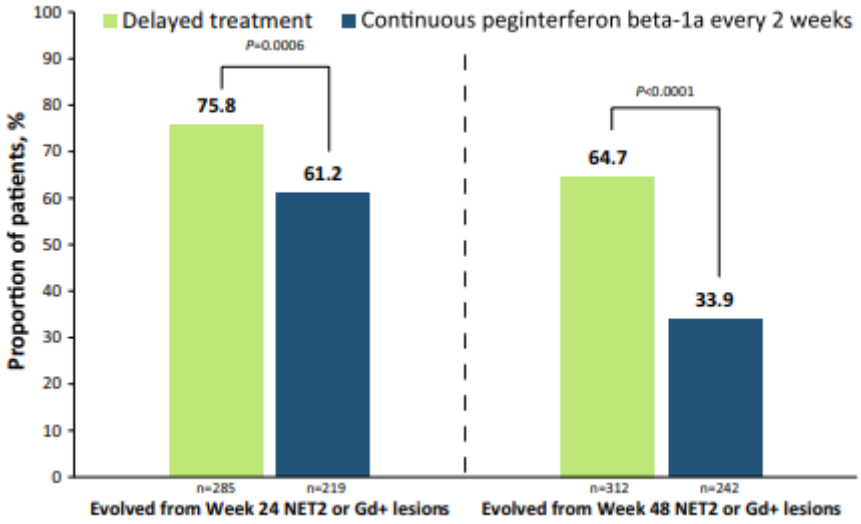
The proportion of patients who had BHs at year 2, converted from either the NET2 lesions or the Gd+ lesions present during year 1, was significantly lower in the patients receiving continuous treatment with pegIFNβ-1a Q2W versus those receiving delayed treatment: 64.7% in the delayed treatment group versus 33.9% in the continuous treatment group, a 48% reduction ($P < 0.0001$) (Figure 10).

Figure 9. Evolution of NET2 or Gd+ lesions detected at weeks 24 and 48 into black holes at 2 years: a) NET2 lesions; b) Gd+ lesions



Adjusted mean and *P* value for comparison between the delayed and continuous Q2W treatment, based on negative binomial regression; adjusted for age, sex, baseline EDSS score, and number of NET2 or Gd+ lesions at week 24 or 48 compared with baseline.
EDSS = Expanded Disability Status Scale; Gd+ = gadolinium enhancing; NET2 = new/newly enlarging T2.
Source:Arnold et al. (2017)[129]

Figure 10. Proportion of patients with NET2- or Gd+-to-black hole evolution at 2 years

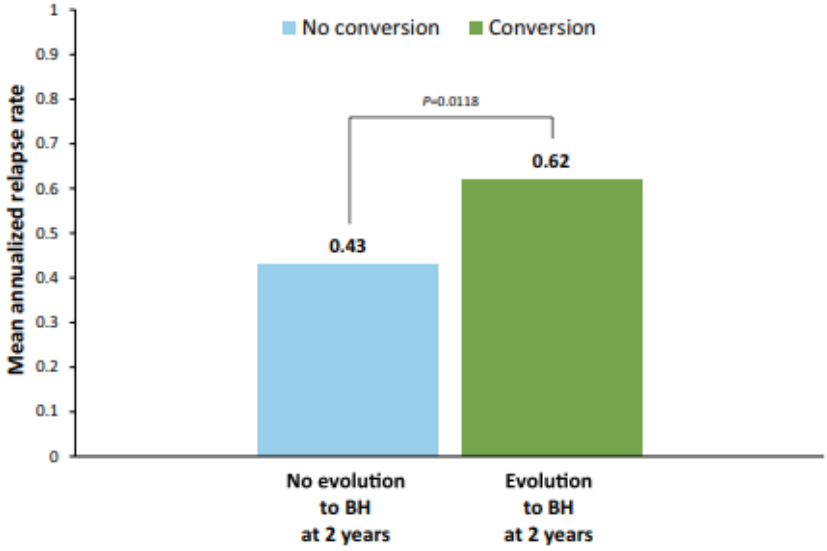


The proportions of patients with at least one Gd+ or NET2 lesion at week 24 or 48 that evolved to a black hole at week 96 were compared using a two-sample Chi-square test for difference in treatment arms.
Gd+ = gadolinium enhancing, NET2 + new/newly enlarging T2.
Source: Arnold et al. (2017)[129]

B.2.7.2.2 Clinical outcomes by BH conversion

For patients with either NET2 or Gd+ lesions at week 24 (n = 760 for all treatment groups), 71.7% (n = 760) of patients had lesions that developed into BHs. The mean ARR at 2 years was significantly higher in patients who had BH evolution (0.62 vs. 0.43; *P* = 0.0118), than in patients without (Figure 11). In addition, a significantly higher proportion of patients with BH evolution at 2 years had both relapsed (38.0 vs. 27.9%; *P* = 0.0088) and changed EDSS score from baseline (0.13 vs. −0.01; *P* = 0.0392).[129]

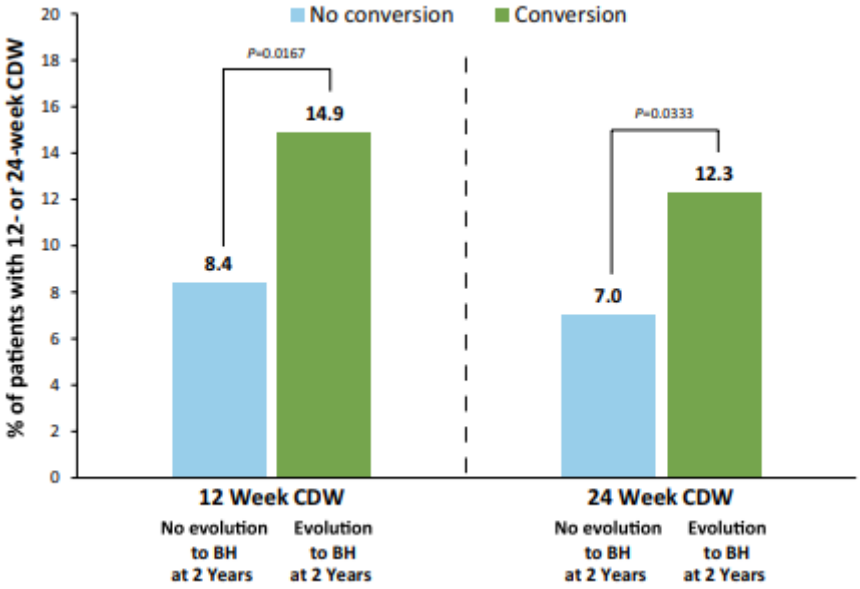
Figure 11. ARR at 2 years in patients with and without black hole evolution



P value is from Wilcoxon rank sum test
ARR = annualised relapse rate; BH = black hole.
Source: Arnold et al. (2017)[129]

A significantly higher proportion of patients who developed BHs at 96 weeks had CDP3M (14.9 vs. 8.4%; *P* = 0.0167) or CDP6M (12.3 vs. 7.0%; *P* = 0.0333) over 2 years (Figure 12).

Figure 12. CDP over 2 years in patients with and without black hole evolution

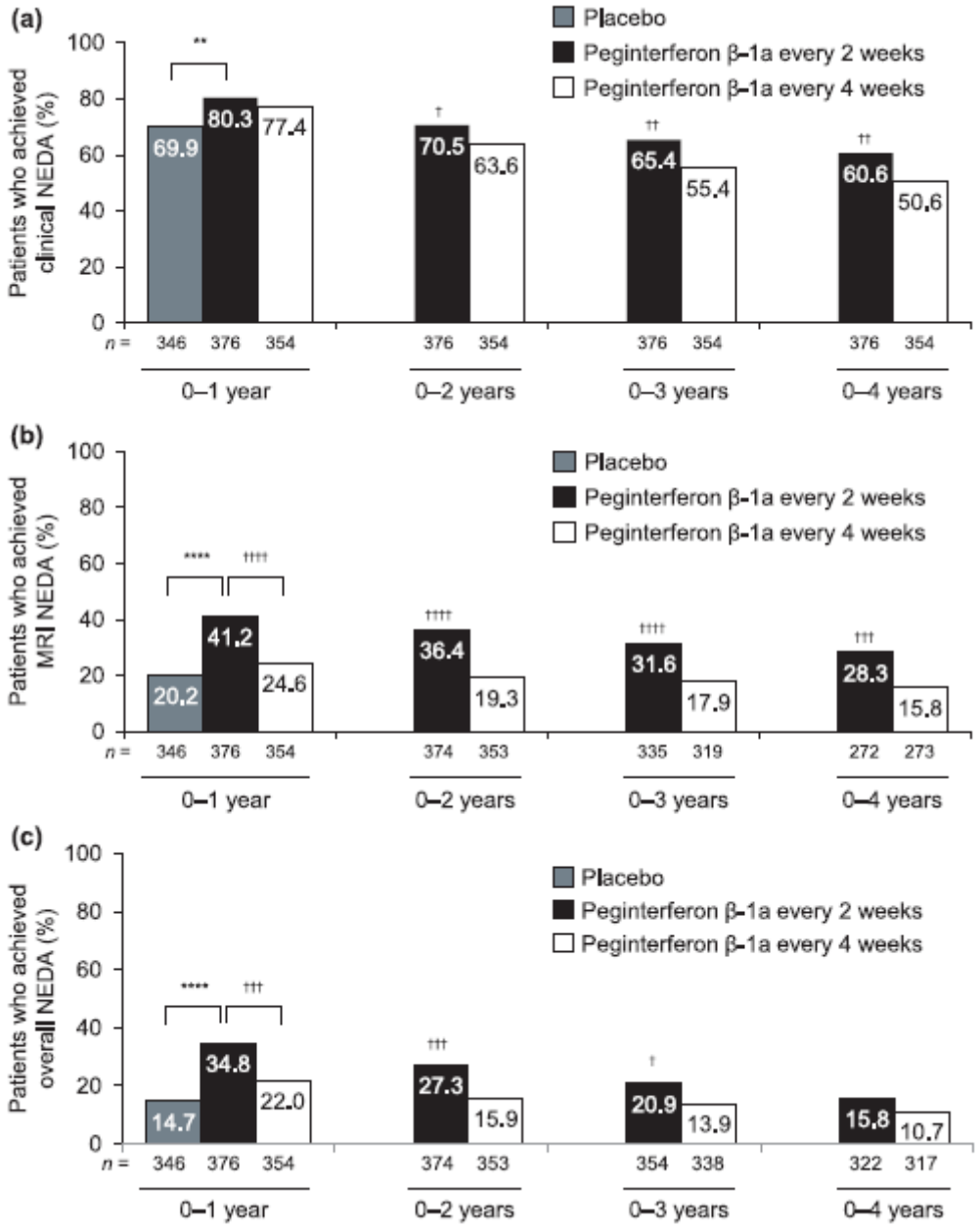


P value is from Chi-square test.
BH = black hole; CDW = confirmed disability worsening.
Source: Arnold et al. (2017)[129]

B.2.7.2.3 NEDA status in patients treated with pegIFNβ-1a

Evidence has suggested that NEDA is a more sensitive measure of treatment efficacy than more traditional efficacy end points and it has been proposed as the main aim of treatment for neurologists. NEDA is composed of MRI parameters and is defined as no evidence of relapses, no onset of CDP, and no active MRI lesions. Achievement of NEDA, MRI NEDA, or overall NEDA was calculated cumulatively or year by year over 4 years. The analysis found that significantly more patients treated with pegIFNβ-1a Q2W (60.6%) than Q4W (50.6%) achieved NEDA (*P* = 0.0063) and MRI NEDA (28.3% vs. 15.8%, *P* = 0.0005) through year 4 and overall NEDA through year 3 (20.9% vs. 13.9%, *P* = 0.0160) (Figure 13). In the Q2W group, 15.8% of patients maintained overall NEDA over 4 years. These data support the sustained efficacy of pegIFNβ-1a Q2W as it continues to provide significant improvement in clinical and MRI end points though 4 years of treatment.[130]

Figure 13. Patients who achieved (a) clinical NEDA, (b) MRI NEDA, and (c) overall NEDA over 4 years (cumulative)



MRI = magnetic resonance imaging; NEDA = no evidence of disease activity.
** *P* < 0.01.
**** *P* < 0.0001 for peginterferon β-1a every 2 weeks versus placebo.
† *P* < 0.05.
†† *P* < 0.01.
††† *P* < 0.001.
†††† *P* < 0.0001 for pegIFNβ-1a β-1a every 2 weeks versus pegIFNβ-1a every 4 weeks.
Source: Arnold et al. (2018)[130]

B.2.8 Meta-analysis

A meta-analysis requires two or more studies that contain the intervention of interest. Therefore, a meta-analysis was not possible, as only one study included pegIFNβ-1a.

B.2.9 Indirect and mixed-treatment comparisons

- The clinical systematic review identified 27 studies that were eligible for inclusion in the analysis of at least one outcome.
- PegIFNβ-1a 125 mcg Q2W reduced the ARR relative to IM IFNβ-1a 30 mcg, teriflunomide, and placebo; however, only the difference versus placebo was statistically significant.
  - The ARR was similar (RR, ≥ 0.9 and ≤ 1.1) for patients treated with pegIFNβ-1a relative to IFNβ-1a 44 mcg, IFNβ-1b, GA 20 mg, and GA 40 mg.
  - There was an increase in the ARR for patients treated with pegIFNβ-1a compared with DMF and a statistically significant increase for alemtuzumab and ocrelizumab.
- PegIFNβ-1a reduced the CDP3M relative to IM IFNβ-1a 30 mcg, IFNβ-1b, GA 20 mg, and placebo; however, only the difference versus placebo was statistically significant
  - The CDP3M was similar (RR, ≥ 0.9 and ≤ 1.1) for patients treated with pegIFNβ-1a relative to IFNβ-1a 44 mcg, IFNβ-1a 22 mcg, teriflunomide, and DMF
  - There was an increase in the CDP3M for patients treated with pegIFNβ-1a compared with alemtuzumab and ocrelizumab (not statistically significant)
- PegIFNβ-1a reduced the CDP6M relative to IM IFNβ-1a 30 mcg, IFNβ-1a 44 mcg, IFNβ-1b, GA 20 mg, DMF, teriflunomide, and placebo; however, only the difference versus placebo was statistically significant.
  - There was an increase in the CDP6M for patients treated with pegIFNβ-1a compared with alemtuzumab 12 mg once daily and ocrelizumab.
- Sensitivity analysis combined studies with a range of follow-up times to analyse CDP3M and CDP6M.
  - These sensitivity analyses identified that CDP6M was statistically significantly improved for pegIFNβ-1a compared with placebo; no further statistically significant differences were observed in comparison with any other treatments.
- Due to the lack of relevant studies no mixed-treatment comparisons (MTCs) could be performed for relapse severity, NEDA, mortality or safety outcomes. Please see Appendix L for further details.

B.2.9.1 Study selection

The systematic review detailed in Appendix D was used to identify studies included in the MTC for the treatment under consideration (pegIFNβ-1a) and relevant comparators. Only DMTs with a positive reimbursement decision for patients with RRMS that was not highly active or rapidly evolving severe (RES) by NICE were included in the MTC (i.e., natalizumab, daclizumab, fingolimod, and cladribine were excluded).[131] Of note, daclizumab was withdrawn from the market in March 2018 after safety concerns. However, it was initially included in the systematic review as it was still in use when the review was first conducted.

B.2.9.2 Methods

Mixed-treatment comparison was performed using a Bayesian approach using the gemtc package.[132] All Bayesian MTC models used in this report were carried out based on the recommendations of the NICE Decision Support Unit.[133] The gemtc package implements the models recommended by the NICE Decision Support Unit using Just Another Gibbs Sampler (JAGS) to provide the underlying Markov Chain Monte Carlo simulations. A burn-in of 50,000 simulations was used, followed by an additional run of 50,000 simulations to obtain parameter estimates. Model convergence was assessed using the Brooks-Gelman-Rubin statistic,[134] and if there were any doubts about convergence of the estimates, additional simulations were run. Model fit was assessed using residual deviance and the Deviance Information Criterion. The primary analysis used random-effects models. A sensitivity analysis using fixed effect models was also performed. Data were extracted for all outcomes identified in Appendix D; however, MTC and supporting analyses will focus on the following key outcomes:

- ARR was analysed based on MTC of treatment differences using the rate ratio as the effect estimate. The RR is an annualised measure; therefore, we considered it reasonable to combine data across multiple time points for this outcome. For the primary analysis of ARR, we pooled data from studies that reported randomised outcome data for follow-up periods greater than 11 months (see protocol modifications).
- CDP3M and CDP6M were typically reported as an HR for the risk of experiencing disability progression. The analysis for this outcome was based on MTC of treatment differences using the HR as the effect estimate at 24 months follow-up.
- To achieve a comparison with pegIFNβ-1a, a key comparator for this systematic literature review (SLR), 11-month data from ADVANCE and 18- and 24-month data for comparator treatments were pooled for CDP3M and CDP6M outcomes. This limited the accuracy of the comparison but without combining data from different time points, comparative effectiveness would not be possible.
- All other outcomes (including relapses requiring hospitalisation, relapses requiring IV corticosteroids, mortality, NEDA, symptoms of MS [cognition, fatigue, and visual impairment], QOL, any adverse event [AE], any serious adverse event [SAE], treatment discontinuation due to any cause, or treatment discontinuation due to AE) were informed by 12-month follow-up data alone.
- There was some variation in the follow-up time between studies. Several studies reported 1-year outcomes after 48 weeks (11 months) of follow-up. Therefore, any study where 1-year outcomes were reported at ≥ 11 months and ≤ 13 months was considered for potential inclusion in the analysis of 12-month outcomes. The actual follow-up period for 2-year outcomes ranged from 96 weeks (22.2 months) to 108 weeks (24.9 months). Therefore, any study where 2-year outcomes were reported at ≥ 22 months and ≤ 25 months was considered for potential inclusion in the analysis of 24-month outcomes.
- Any SAE was analysed as a dichotomous outcome based on the proportion of patients who experienced at least one event after 24 months follow-up using odds ratios (ORs) as the effect measure. We analysed SAE excluding MS relapses where data were available and performed sensitivity analyses of SAE, including MS relapses. Any AE was reported as a narrative synthesis as heterogeneity in study design, and AE reporting was too great to allow pooling of data in an MTC.
- Treatment discontinuation due to any cause was analysed as a dichotomous outcome based on the proportion of patients who discontinued after 24 months

follow-up using ORs as the effect measure. However, only studies of 12 months follow-up were included in the network analysing treatment discontinuation. Treatment discontinuation due to AE was reported as a narrative synthesis, as heterogeneity in study design and AE reporting was too great to allow pooling of data in an MTC.

The OR (for dichotomous outcomes), HR (for time-to-event outcomes), rate ratios (for rate outcomes) are reported with either 95% credible intervals (CrI, Bayesian methods) or 95% CI (frequentist methods).

B.2.9.3 Results

The selection of studies for inclusion in the final MTC was conducted in two stages. In the first stage studies were selected for inclusion in the systematic review based on the PICOS criteria. These studies were then considered for inclusion in the analysis based on the similarity criteria (trials should be similar for moderators of relative treatment effect). As described in Section B.2.1, 32 studies were considered for inclusion in the MTC.

Seven studies that did not report relevant outcome data at either 12 months or 24 months were included in the systematic review (CombiRx,[135-138] TENERE,[139] TOWER[140]). It was decided after a protocol modification in May 2015 to consider time points other than 12 or 24 months for ARR, as this is an annualised measure expressed as relapses per patient-year. Four studies reported ARR data at time points other than 12 or 24 months (CAMMS223, 36 months; CombiRx, 36 months; TENERE, ~14-15 months; TOWER, ~18-19 months). These studies were consequently considered for inclusion in the analysis of ARR but were not considered for any other outcomes. One study (CAMMS223) also reported ARR at 36 months follow-up, which allowed this study to be considered for inclusion in the combined analysis of ARR (in addition to other outcomes). Two additional studies (EVIDENCE, TOWER) providing 11 months or 18 months of data, respectively, were further considered for inclusion in the base-case analysis for CDP3M and CDP6M.

Two studies[136,137] also failed to report all of the necessary values required as inputs to a MTC or enough information to be able to calculate the required values for at least one outcome.

There was some heterogeneity between studies in the disease duration of the patient populations. There is no clear basis on which to set a threshold for the inclusion/exclusion of studies in the analysis based on disease duration. Any choice of threshold would be arbitrary, and alternative choices may substantially affect the results; therefore, we did not exclude any studies based on clinical heterogeneity. Following the assessment of study similarity and clinical heterogeneity, there were 31 studies eligible for inclusion in the analysis of ARR and 30 studies eligible for inclusion in the analysis of other outcomes.

Ultimately, there were five studies that could not be incorporated in any analysis and were not considered further in this review (Table 15). This resulted in a total of 23 studies that could be considered for inclusion in the analysis of ARR, and 27 studies that could be considered for inclusion in the analysis of other outcomes (Table 16). Table 17 presents baseline characteristics of the patient population in the included trials.

The results for ARR, CDP3M, and CDP6M are presented in this section and results for all other outcomes are presented in Appendix L. Appendix L also presents the run analysis code used in the meta-analysis for each outcome.

Table 15. Studies excluded from key analyses

Study ID	Reason for exclusion from analysis
Crentsil 2012	No relevant outcome data at 12 or 24 months Conference abstract only. No outcome data. Follow-up unclear
GLOW	Only reported data for any AE excluding SAE. Not comparable to other studies reporting SAE
Mokhber 2014	No relevant outcome data at 12 or 24 months Only reported EDSS at baseline and follow-up
Mokhber 2015	No relevant outcome data at 12 or 24 months
O'Connor 2006	No relevant outcome data at 12 or 24 months Core study was only 36 weeks. Extension study maintained randomisation up to 7 years

AE = adverse event; EDSS = Expanded Disability Status Scale; ID = identification; SAE = serious adverse event.

Table 16. Final inclusion in the mixed-treatment comparison for the overall relapsing-remitting multiple sclerosis population

Study ID	ARR	CDP3M	CDP6M
ADVANCE	✓	✓[a]	✓[a]
APEX	x[b]	x[b]	x[b]
BEYOND	✓	✓	x[b]
Boiko 2017	x[b]	x[b]	x[b]
Bornstein 1987	✓	x[b]	x[b]
BRAVO	✓	✓	✓
Calabrese 2012	✓	x[b]	x[b]
CAMMS223	✓	✓	✓
CARE MS I	✓	x[b]	✓
CARE MS II	✓	x[b]	✓
CombiRx	✓	x[b]	x[b]
CONFIRM	✓	✓	✓
Copolymer I	✓	x[b]	x[b]
DEFINE	✓	✓	✓
Etemadifar 2006	x[c]	x[b]	x[b]
EVIDENCE	✓	✓[a]	✓[a]
GALA	✓	x[b]	x[b]
IFNB MS	✓	x[b]	x[b]
INCOMIN	✓	x[b]	x[b]
MSCRG	✓	x[b]	x[b]
OPERA I	✓	✓	✓
OPERA II	✓	✓	✓
PRISMS	x[b]	✓	✓
REGARD	✓	x[b]	x[b]
TEMSO	✓	✓	x[b]
TENERE	✓	x[b]	x[b]
TOWER	✓	✓[c]	✓[c]

ARR = annualised relapse rate; CDP3M = confirmed disability progression sustained for 3 months; CDP6M = confirmed disability progression sustained for 6 months.
[a] Included with 11 or 18 months of follow-up.
[b] This outcome was not reported by the indicated study.
[c] Data were not reported in the appropriate patient population.

Table 17. Baseline characteristics of participants in the randomised controlled trials across randomised groups

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
ADVANCE	pegIFNβ-1a 125 mcg Q2W	512	151 (29) 361 (71)	36.9 (9.8)	2.47 (1.26)	6.9 (6.6) (first MS symptoms)	1.6 (0.67)
	pegIFNβ-1a 125 mcg Q4W	500	148 (30) 352 (70)	36.4 (9.9)	2.48 (1.24)	6.5 (6.1) (first MS symptoms)	1.5 (0.62)
	Placebo	500	142 (29) 358 (71)	36.3 (9.7)	2.44 (1.18)	6.3 (6.3) (first MS symptoms)	1.6 (0.67)
APEX	Dimethyl fumarate 240 mg BID	56	NR	NR	NR	NR	NR
	Placebo	58	NR	NR	NR	NR	NR
BEYOND	GA 20 mg QD	448	142 (32) 306 (68)	35.2 (NR) Median (IQR) = 35 (27-43)	2.28 (NR) Median (IQR) = 2 (1.5-3)	5.1 (NR) Median (IQR) = 3 (1-7) (MS diagnosis)	1.6 (NR) Median (IQR) = 1 (1-2)
	IFNβ-1b 250 mcg QAD	897	270 (30) 627 (70)	35.8 (NR) Median (IQR) = 35 (28-43)	2.35 (NR) Median (IQR = 2 (1.5-3)	5.3 (NR) Median (IQR) = 3 (1-7) (MS diagnosis)	1.6 (NR) Median (IQR) = 1 (1-2)
	IFNβ-1b 500 mcg QAD	899	270 (30) 629 (70)	35.9 (NR) Median (IQR) = 36 (28-43)	2.33 (NR) Median (IQR = 2 (1.5-3)	5.4 (NR) Median (IQR) = 3 (1-8) (MS diagnosis)	1.6 (NR) Median (IQR) = 1 (1-2)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
Boiko 2017	GA 20 mg QD(Copaxone, Teva)[a]	61	NR	NR	NR	Median = 3.0 (range: 1.0-21.0) (MS symptoms)	1.28 (95% CI, 1.12-1.44)
	GA 20 mg QD (Timexon, Biocad)[a]	61	NR	NR	NR	Median = 5.0 (range: 0.0-37.0) (MS symptoms)	1.28 (95% CI, 1.15-1.40)
	Placebo	28	NR	NR	NR	Median = 4.0 (range: 2.0-18.0) (MS symptoms)	1.21 (95% CI, 1.05-1.38)
Bornstein 1987	GA 20 mg QD	25	11 (44) 14 (56)	30 (NR)	NR	4.9 (NR) (unclear)	2 years: 3.8 (unclear average)
	Placebo	25	10 (40) 15 (60)	31 (NR)	NR	6.1 (NR) (unclear)	2 years: 3.9 (unclear average)
BRAVO	IFNβ-1a 30 mcg QW	447	140 (31.3) 307 (68.7)	Median (IQR) = 38.5 (30.3-45.9)	Median (IQR) = 2.5 (1.5-3.5)	Median (IQR) = 1.4 (0.3-4.7) (MS diagnosis)	Median (IQR) = 1 (1-2)
	Laquinimod 0.6 mg QD	434	152 (35) 282 (65)	Median (IQR) = 36.7 (29.6-44)	Median (IQR) = 2.5 (1.5-3.5)	Median (IQR) = 1.2 (0.3-3.8) (MS diagnosis)	Median (IQR) = 1 (1-2)
	Placebo	450	129 (28.7) 321 (71.3)	Median (IQR) = 37.5 (30.3-45.4)	Median (IQR) = 2.5 (1.5-3.5)	Median (IQR) = 1.2 (0.3-4) (MS diagnosis)	Median (IQR) = 1 (1-2)
Calabrese 2012	GA 20 mg QD	48	13 (27.1) 35 (72.9)	38.9 (10.2)	Mean (range) = 2.1 (1-5)	Mean (range) = 5.5 (0-9) (unclear)	NR
	IFNβ-1a 30 mcg QW	47	15 (32) 32 (68)	34.8 (9.6)	Mean (range) = 1.9 (1-5)	Mean (range) = 5.3 (0-8) (unclear)	NR
	IFNβ-1a 44 mcg TIW	46	14 (30.5) 32 (69.5)	35.9 (9.1)	Mean (range) = 1.9 (1-5)	Mean (range) = 5.7 (0-9) (unclear)	NR

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
CAMMS223	Alemtuzumab 12 mg QD	112	39 (35.5) 71 (64.5)	31.9 (8) Median (range) = 31 (18-49)	2 (0.73) median (range) = 2 (0-3)	NR	NR
	Alemtuzumab 24 mg QD	110	40 (35.7) 72 (64.3)	32.2 (8.8) Median (range) = 31 (18-54)	2 (0.73) Median (range) = 2 (0-3.5)	NR	NR
	IFNβ-1a 44 mcg TIW	111	40 (36) 71 (64)	32.8 (8.8) Median (range) = 31 (18-60)	1.9 (0.81) Median (range) = 2 (0-3.5)	NR	NR
CARE MS I	Alemtuzumab 12 mg QD	376	132 (35) 243 (65)	33 (8)	2 (0.8) Median (range) = 2 (0-4)	2.1 (1.4) Median (range) = 1.7 (0.1-5.2) (first MS symptoms)	1.8 (0.8) Median (range) = 2 (0-5)
	IFNβ-1a 44 mcg TIW	187	65 (35) 122 (65)	33.2 (8.5)	2 (0.8) Median (range) = 2 (0-3.5)	2 (1.3) Median (range) = 1.5 (0.2-5) (first MS symptoms)	1.8 (0.8) Median (range) = 2 (0-5) 2 years: Mean (SD) = 2.4 (0.85)
CARE MS II	Alemtuzumab 12 mg QD	426	145 (34) 281 (66)	34.8 (8.36)	2.7 (1.26) Median (range) = 2.5 (0-6.5)	4.5 (2.68) Median (range) = 3.8 (0.2-14.4) (first MS symptoms)	1.7 (0.86) Median (range) = 1 (0-5)
	Alemtuzumab 24 mg QD	170	49 (29) 120 (71)	35.1 (8.4)	2.7 (1.17) Median (range) = 2.5 (0-6)	4.3 (2.77) Median (range) = 3.7 (0.2-16.9) (first MS symptoms)	1.6 (0.86) Median (range) = 1 (0-6)
	IFNβ-1a 44 mcg TIW	202	71 (35) 131 (65)	35.8 (8.77)	2.7 (1.21) Median (range) = 2.5 (0-6)	4.7 (2.86) Median (range) = 4.1 (0.4-10.1) (first MS symptoms)	1.5 (0.75) Median (range) = 1 (0-4)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
CombiRx	IFNβ-1a 30 mcg QW	250	77 (30.8) 173 (69.2)	37.6 (10.2)	2.0 (1.2)	1.4 (4.0) (first MS symptoms)	1.7 (0.9)
	GA 20 mg QD	259	74 (28.6) 185 (71.4)	39 (9.5)	1.9 (1.2)	1 (2.9) (first MS symptoms)	1.6 (0.7)
CONFIRM	DMF 240 mg BID	359	114 (32) 245 (68)	37.8 (9.4)	2.56 (1.2)	4.9 (5.1) (MS diagnosis)	1.3 (0.6)
	DMF 240 mg TID	345	95 (28) 250 (72)	37.8 (9.4)	2.52 (1.19)	4.6 (5.2) (MS diagnosis)	1.4 (0.7)
	GA 20 mg QD	350	103 (29) 247 (71)	36.7 (9.1)	2.57 (1.22)	4.4 (4.7) (MS diagnosis)	1.4 (0.6)
	Placebo	363	112 (31) 251 (69)	36.9 (9.2)	2.59 (1.17)	4.8 (5) (MS diagnosis)	1.4 (0.8)
Copolymer I Study	GA 20 mg QD	125	37 (29.6) 88 (70.4)	34.6 (6)	2.8 (1.2)	7.3 (4.9) (unclear)	2 years: mean (SD) = 2.9 (1.3)
	Placebo	126	30 (23.8) 96 (76.2)	34.3 (6.5)	2.4 (1.3)	6.6 (5.1) (unclear)	2 years: mean (SD) = 2.9 (1.1)
DEFINE	DMF 240 mg BID	410	114 (28) 296 (72)	38.1 (9.1)	2.4 (1.29)	5.6 (5.4) (MS diagnosis)	1.3 (0.7)
	DMF 240 mg TID	416	110 (26) 306 (74)	38.8 (8.8)	2.36 (1.19)	5.1 (5.3) (MS diagnosis)	1.3 (0.6)
	Placebo	408	102 (25) 306 (75)	38.5 (9.1)	2.48 (1.24)	5.8 (5.8) (MS diagnosis)	1.3 (0.7)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
Etemadifar 2006	IFNβ-1a 30 mcg QW	30	6 (20) 24 (80)	28.1 (1.2)	1.9 (1.1)	2.9 (2.3) (unclear)	2 (0.8)
	IFNβ-1a 44 mcg TIW	30	7 (23) 23 (77)	27.4 (1.2)	2.1 (1)	3 (2.2) (unclear)	2.4 (1)
	IFNβ-1b 250 mcg QAD	30	9 (30) 21 (70)	29.9 (1.4)	1.9 (0.7)	3.7 (2.3) (unclear)	2.2 (0.7)
EVIDENCE	IFNβ-1a 30 mcg QW	338	86 (25.4) 252 (74.6)	Mean (range) = 37.4 (18-55)	2.3 (NR) Median (range) = 2 (NR)	6.7 (NR) Median (range) = 4.1 (NR) (unclear)	2 years: mean (SD) = 2.6 (NR) 2 years: Median (range) = 2 (NR)
	IFNβ-1a 44 mcg TIW	339	85 (25.1) 254 (74.9)	Mean (range) = 38.3 (18-55)	2.3 (NR) Median (range) = 2 (NR-NR)	6.5 (NR) Median (range) = 4 (NR-NR) (unclear)	2 years: mean (SD) = 2.6 (NR) 2 years: median (range) = 2 (NR)
GALA	GA 40 mg	943	302 (32) 641 (68)	37.4 (9.4)	2.8 (1.2)	7.7 (6.7) (1st MS symptoms)	1.3 (0.6)
	Placebo	461	148 (32.1) 313 (67.9)	38.1 (9.2)	2.7 (1.2)	7.6 (6.4) (first MS symptoms)	1.3 (0.6)
IFNB MS study	IFNβ-1b 50 mcg QAD	125	40 (32) 85 (68)	Mean (SE) = 35.3 (0.7)	Mean (SE) = 2.9 (0.1)	Mean (SE) = 4.7 (0.4) (MS diagnosis)	2 years: mean (SE) = 3.3 (0.1)
	IFNβ-1b 250 mcg QAD	124	38 (30.6) 86 (69.4)	Mean (SE) = 35.2 (0.6)	Mean (SE) = 3 (0.1)	Mean (SE) = 4.7 (0.4) (MS diagnosis)	2 years: mean (SE) = 3.4 (0.2)
	Placebo	123	35 (28.5) 88 (71.5)	Mean (SE) = 36 (0.6)	Mean (SE) = 2.8 (0.1)	Mean (SE) = 3.9 (0.3) (MS diagnosis)	2 years: mean (SE) = 3.6 (0.1)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
INCOMIN	IFNβ-1a 30 mcg QW	92	35 (38) 57 (62)	34.9 (7.9)	1.96 (0.7)	6.7 (5.4) (unclear)	NR
	IFNβ-1b 250 mcg QAD	96	30 (31) 66 (69)	38.8 (7.1)	1.97 (0.7)	5.9 (4.2) (unclear)	NR
MSCRG	IFNβ-1a 30 mcg QW	158	40 (25) 118 (75)	36.7 (7.16)	2.4 (0.75)	6.6 (NR) (MS diagnosis)	1.2 (0.63)
	Placebo	143	40 (28) 103 (72)	36.9 (7.65)	2.3 (0.84)	6.4 (NR) (MS diagnosis)	1.2 (0.6)
OPERA I	Ocrelizumab, 600 mg, Q24W	410	140 (34.1) 270 (65.9)	37.1 (9.3)	2.86 (1.24)	6.74 (6.37) (first MS symptoms)	1.31 (0.65)
	IFNβ-1a, 44 mcg, TIW	411	139 (33.8) 272 (66.2)	36.9 (9.3)	2.75 (1.29)	6.25 (5.98) (first MS symptoms)	1.33 (0.64)
OPERA II	Ocrelizumab, 600 mg, Q24W	417	146 (35.0) 271 (65.0)	37.2 (9.1)	2.78 (1.30)	6.72 (6.10) (first MS symptoms)	1.32 (0.69)
	IFNβ-1a, 44 mcg, TIW	418	138 (33.0) 280 (67.0)	37.4 (9.0)	2.84 (1.38)	6.68 (6.13) (first S symptoms)	1.34 (0.73)
PRISMS	IFNβ-1a 22 mcg TIW	189	62 (33) 127 (67)	Median (IQR) = 34.8 (29.3-39.8)	2.5 (1.2)	Median (IQR) = 5.4 (3-11.2) (unclear)	2 years: mean (SD) = 3 (1.1)
	IFNβ-1a 44 mcg TIW	184	63 (34) 121 (66)	Median (IQR) = 35.6 (28.4-41)	2.5 (1.3)	Median (IQR) = 6.4 (2.9-10.3) (unclear)	2 years: mean (SD) = 3 (1.1)
	Placebo	187	47 (25) 140 (75)	Median (IQR) = 34.6 (28.8-40.4)	2.4 (1.2)	Median (IQR) = 4.3 (2.4-8.4) (unclear)	2 years: mean (SD) = 3 (1.3)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
REGARD	GA 20 mg QD	378	106 (28) 272 (72)	36.8 (9.5)	2.33 (1.31) Median (range) = 2 (NR)	NR	NR
	IFNβ-1a 44 mcg TIW	386	119 (31) 267 (69)	36.7 (9.8)	2.35 (1.28) Median (range) = 2 (NR)	NR	NR
TEMSO	Teriflunomide 14 mg QD	359	104 (29) 255 (71)	37.8 (8.2)	2.67 (1.24)	8.7 (6.7) Median (range) = 7.2 (NR) (first MS symptoms)	1.3 (0.7) 2 years: median (range) = 2 (NR)
	Teriflunomide 7 mg QD	366	111 (30.3) 255 (69.7)	37.4 (9)	2.68 (1.34)	8.8 (6.8) Median (range) = 7 (NR) (first MS symptoms)	1.4 (0.7) 2 years: median (range) = 2 (NR)
	Placebo	363	88 (24.2) 275 (75.8)	38.4 (9)	2.68 (1.34)	8.6 (7.1) Median (range) = 6.3 (NR) (first MS symptoms)	1.4 (0.7) 2 years: median (range) = 2 (NR)
TENERE	Teriflunomide 14 mg QD	111	33 (29.7) 78 (70.3)	36.8 (10.3)	2.3 (1.4)	6.6 (7.6) (first MS symptoms)	1.4 (0.8)
	Teriflunomide 7 mg QD	109	39 (35.8) 70 (64.2)	35.2 (9.2)	2 (1.2)	7 (6.9) (first MS symptoms)	1.3 (0.8)
	IFNβ-1a 44 mcg TIW	104	33 (31.7) 71 (68.3)	37 (10.6)	2 (1.2)	7.7 (7.6) (first MS symptoms)	1.2 (1.0)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
TOWER	Teriflunomide 14 mg QD	372	114 (31) 258 (69)	38.2 (9.4)	2.71 (1.35)	8.18 (6.73) (first MS symptoms)	1.4 (0.7)
	Teriflunomide 7 mg QD	408	108 (26) 300 (74)	37.4 (9.4)	2.71 (1.39)	8.18 (6.75) (1st MS symptoms)	1.4 (0.7)
	Placebo	389	116 (30) 273 (70)	38.1 (9.1)	2.69 (1.36)	7.64 (6.7) (first MS symptoms)	1.4 (0.8)

BID = twice daily; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; IQR = interquartile range; IV = intravenous; MS = multiple sclerosis; NR = not reported; pegIFNβ-1a = pegylated interferon β-1a; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QAD = every other day; QD = once daily; Q24W = every 24 weeks; SD = standard deviation; SE = standard error; TID = 3 times a day; TIW = 3 times a week.

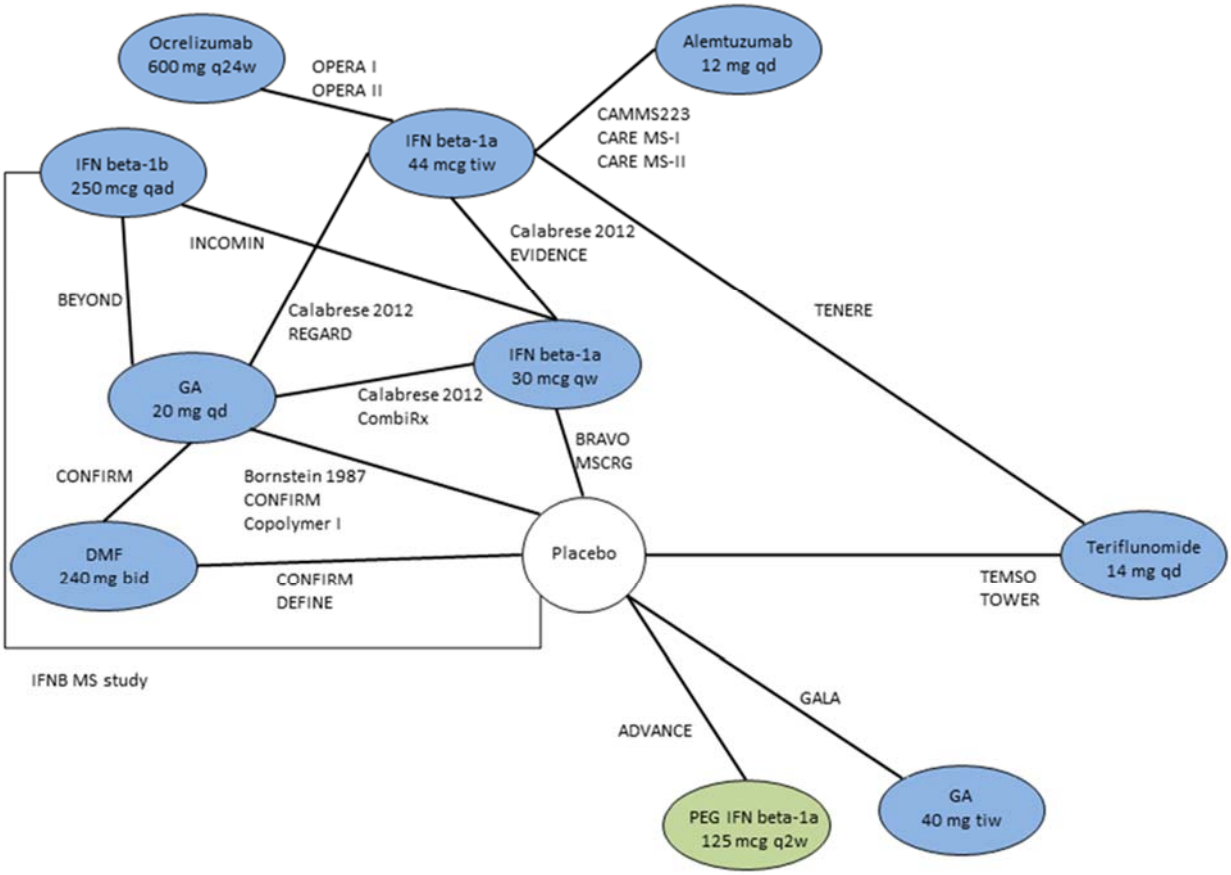
[a] The Boiko 2017 study also included a biosimilar GA drug arm (BCD-063, Biocad, Russia) (n = 61), which was not included in any analyses.

B.2.9.3.1 Annualised relapse rate

Studies that reported ARR at any time point ≥ 12 months were combined into an overall network based on the rationale that this represents an annualised rate (Figure 14). The Etemadifar et al. (2006)[141] study was not included in the network for the overall RRMS population as this study enrolled mostly RES-RRMS patients and the APEX, Boiko 2017 and PRISMS studies could not be included in the network as they did not report ARR (see Table 16).

The final network included 23 studies (ADVANCE, BEYOND, Bornstein 1987, BRAVO, Calabrese 2012, CAMMS223, CARE MS I, CARE MS II, CombiRx, CONFIRM, Copolymer I, DEFINE, EVIDENCE, GALA, IFNB MS, INCOMIN, MSCRG, OPERA I, OPERA II, REGARD, TEMSO, TENERE, TOWER). This included four studies that reported ARR after 12 months (ADVANCE, EVIDENCE, OPERA I, OPERA II) and 15 studies that reported ARR after 24 months (BEYOND, Bornstein 1987, BRAVO, Calabrese 2012, CARE MS I, CARE MS II, CONFIRM, Copolymer I, DEFINE, GALA, IFNB MS, INCOMIN, MSCRG, REGARD, TEMSO). There were four studies that reported ARR at follow-up times other than 12 or 24 months (CAMMS223, 36 months; CombiRx, 36 months; TENERE, ~14-15 months; TOWER, ~18-19 months).

Figure 14. Overall network for annualised relapse rate



DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly.

Mixed-treatment comparison analysis demonstrated that pegIFNβ-1a demonstrated a statistically significant decrease in RR relative to placebo (Figure 15). The MTC for ARR also demonstrated the following:

- The RR for pegIFNβ-1a was numerically decreased compared with IM IFNβ-1a 30 mcg once weekly (QW) or teriflunomide; however, these differences were not statistically significant.
- PegIFNβ-1a demonstrated a statistically significant increase in RR relative to alemtuzumab or ocrelizumab. The RR for pegIFNβ-1a was also numerically increased compared with DMF; however, these differences were not statistically significant.
- There was no difference in the RR (RR, ≥ 0.9 and ≤ 1.1) for patients receiving pegIFNβ-1a compared with IFNβ-1a 44 mcg, IFNβ-1b, GA 20 mg, or GA 40 mg. Indirect (Bucher) and direct meta-analyses are presented in Appendix L.

Figure 15. Annualised relapse rate of pegIFNβ-1a relative to all other treatments

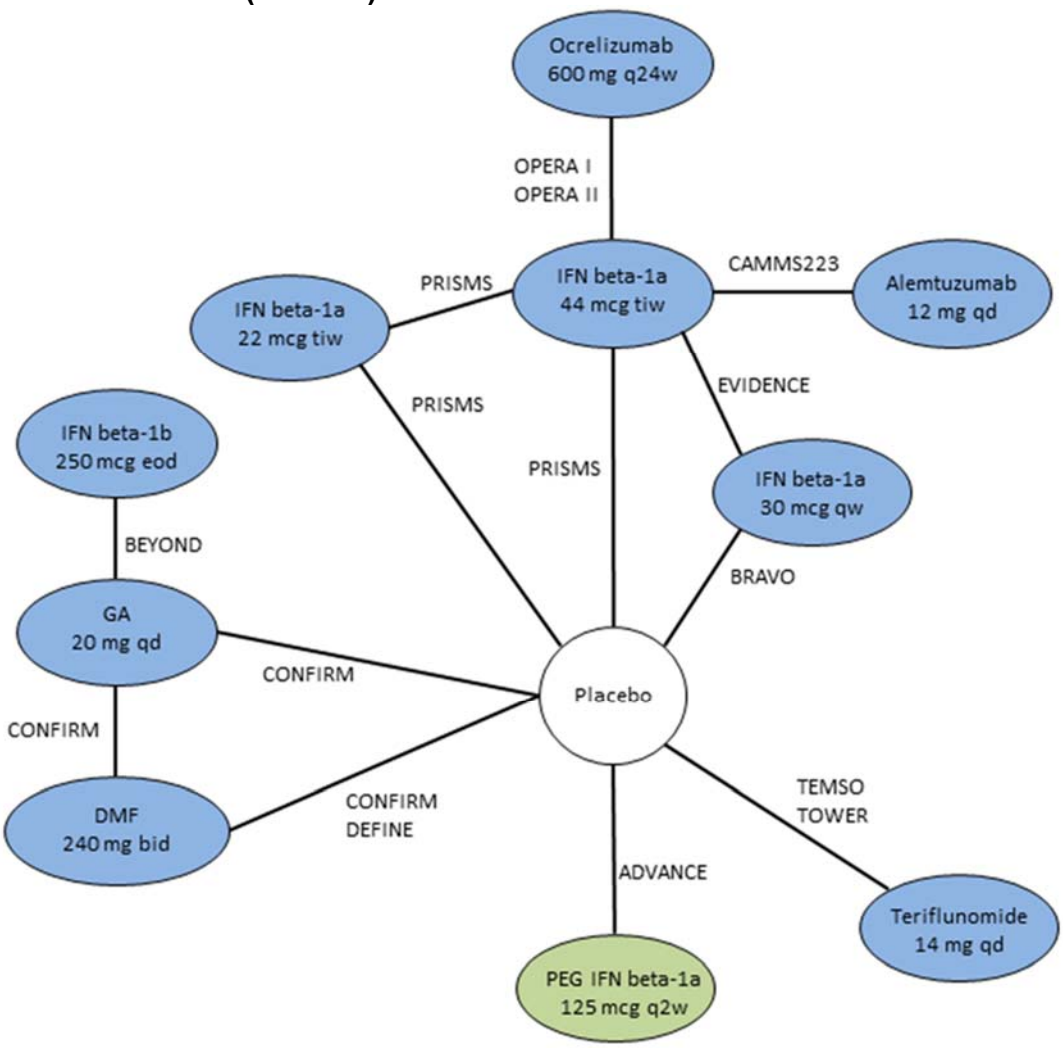
bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; tiw = three times weekly.

B.2.9.3.2 Disability progression confirmed after 3 months (CDP3M)

The final network for CDP3M and measured at 11, 18, or 24 months of follow-up included 12 studies (ADVANCE, BEYOND, BRAVO, CAMMS223, CONFIRM, DEFINE, EVIDENCE, OPERA I, OPERA II, PRISMS, TEMSO, TOWER) (Figure 16).

There were 15 studies that could not be included in the network because they did not report data for this outcome (APEX, Boiko 2017, Bornstein 1987, Calabrese 2012, CARE MS I, CARE MS II, CombiRx, Copolymer I, Etemadifar 2006, GALA, IFNB MS, INCOMIN, MSCRG, REGARD, TENERE) (Table 16).

Figure 16. Overall network for disability progression confirmed after three months (CDP3M)



bid = twice daily; DMF = dimethyl fumarate; eod = every other day; PEG IFN beta-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; tiw = three times weekly.

The ADVANCE study compared pegIFNβ-1a Q2W or Q4W versus placebo. After 12 months, the patients in the placebo arm were re-randomised to receive either pegIFNβ-1a Q2W or pegIFNβ-1a Q4W, and the study continued as a four-arm trial for an additional 12 months. These data are not directly comparable to studies that reported after 24 months of follow-up for patients who had remained on the same treatment for the full period. However, in order to link pegIFNβ-1a to the rest of the network, ADVANCE (12 months follow-up) was added to a network of studies with 24 months of follow-up. This limited the accuracy of the comparison but was the best method available for combining data from different time points to make

comparative effectiveness analysis possible. It should be acknowledged that despite limitations, this approach is also consistent with the MTC conducted by the assessment group for ID52.

Mixed-treatment comparison analysis demonstrated that there were no statistically significant differences in the risk of disability progression confirmed after 3 months for patients treated with pegIFNβ-1a compared with all other treatments in the network (Figure 17).

- The risk of CDP3M was numerically decreased in patients receiving pegIFNβ-1a compared with those receiving IM IFNβ-1a 30 mcg, IFNβ-1b, GA 20 mg, or placebo; however, these differences were not statistically significant.
- The risk of CDP3M was numerically increased for pegIFNβ-1a compared with either alemtuzumab or ocrelizumab; however, these differences were not statistically significant.
- There was no difference in the risk of CDP3M (HR ≥ 0.9 and ≤ 1.1) in patients receiving pegIFNβ-1a compared with IFNβ-1a 44 mcg, IFNβ-1a 22 mcg, teriflunomide, or DMF. Indirect (Bucher) and direct meta-analyses are presented in Appendix L.

Figure 17. Disability progression confirmed after 3 months (CDP3M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments

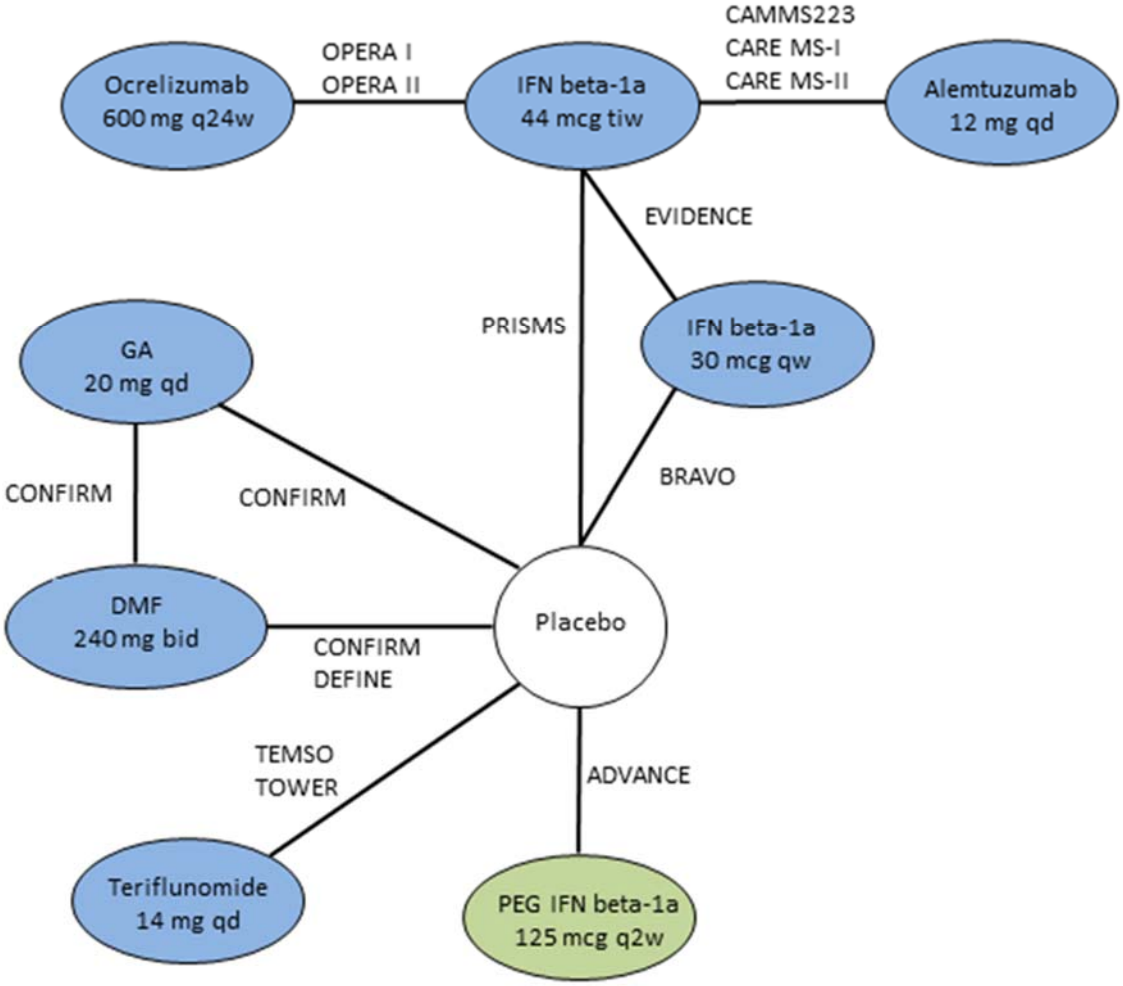
bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; qad = every other day; q24w = once every 24 weeks; qd = once daily; tiw = 3 times a week.

B.2.9.3.3 Disability progression after 6 months (CDP6M)

The overall network for CDP6M and measured after 11, 18, or 24 months of follow-up included 13 studies (ADVANCE, BRAVO, CAMMS223, CARE MS I, CARE MS II, CONFIRM, DEFINE, EVIDENCE, OPERA I, OPERA II, PRISMS, TEMSO, TOWER) (Figure 18).

There were 15 studies that could not be included in the network because they did not report data for this outcome (APEX, BEYOND, Boiko 2017, Bornstein 1987, Calabrese 2012, CombiRx, Copolymer I, Etemadifar 2006, GALA, IFNB MS, INCOMIN, MSCRG, REGARD, TEMSO, TENERE) (see Table 16).

Figure 18. Overall network for disability progression confirmed after 6 months (CDP6M)



bid = twice daily; DMF = dimethyl fumarate; PEG IFN = pegylated interferon; qad = every other day; q24w = once every 24 weeks; qd = once daily; tiw = 3 times a week.

Similar to the CDP3M network, 12-month placebo-controlled data from ADVANCE were combined with the comparator studies using 24-month data to allow for comparative effectiveness to be assessed.

There were no statistically significant differences in the risk of CDP6M for patients treated with pegIFNβ-1a compared with all other treatments in the network (Table 19; Figure 19).

- The risk of CDP6M was numerically decreased in patients receiving pegIFNβ-1a compared with those receiving IM IFNβ-1a 30 mcg, IFNβ-1a 44 mcg, GA 20 mg, DMF, teriflunomide, or placebo; however, this difference was only statistically significant against placebo.
- The risk of disability progression was numerically increased for pegIFNβ-1a compared with alemtuzumab and ocrelizumab; however, these differences were not statistically significant. Indirect (Bucher) and direct meta-analyses are presented in Appendix L.

Figure 19. Disability progression confirmed after 6 months (CDP6M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments

bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qad = every other day; qd = once daily; tiw = 3 times a week.

B.2.9.4 Additional comparator efficacy studies

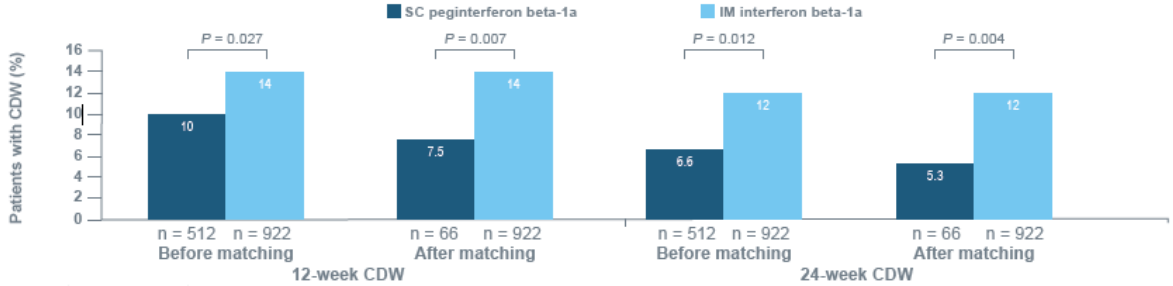
- Matching-adjusted indirect comparison of two phase III trials shows that, in patients with relapsing forms of MS, treatment with pegIFNβ-1a Q2W results in significantly lower numbers of patients with CDP3M and CDP6M, and significantly lower ARR compared with IM IFNβ-1a 30 mcg.
- Propensity score matching analysis of phase III trials ADVANCE and CONFIRM show that significantly lower ARRs and CDP are achieved with pegIFNβ-1a Q2W than with GA 20 mg in RRMS.
  - CDP3M: 10.0% v 14.6%; HR 0.625 (95% CI 0.393 – 0.995; P = 0.048)
  - CDP6M: 7.7% vs 10.6%; HR 0.684 (95% CI 0.398 – 1.178; P = 0.171)
  - Overall NEDA or MRI NEDA over 2 years was found to be significantly higher in patients treated with pegIFNβ-1a than GA.
- A matching-adjusted comparison of weighted individual patient data on pegIFNβ-1a, and aggregate data from 4 published phase 3 clinical trials of IFNβ-1a 44 mcg, was conducted and demonstrated that patients with RRMS receiving pegIFNβ-1a Q2W achieve better clinical outcomes than patients treated with IFNβ-1a 44 mcg.

B.2.9.4.1 PegIFNβ-1a Q2W vs. IM IFNβ-1a 30 mcg

A matching-adjusted indirect comparison of the clinical effectiveness of pegIFNβ-1a and IM IFNβ-1a in patients with RRMS was conducted to provide relevant information for clinicians on the comparative efficacy of these two agents. Data on patients receiving pegIFNβ-1a Q2W was taken from ADVANCE and data on patients receiving IM IFNβ-1a was taken from the DECIDE study. Using an indirect matching-adjusted comparison, the study aimed to analyse the proportion of patients with CDP3M, CDP6M, and confirmed relapse at 2 years, and ARR in patients with RRMS treated with pegIFNβ-1a or IM IFNβ-1a.[142]

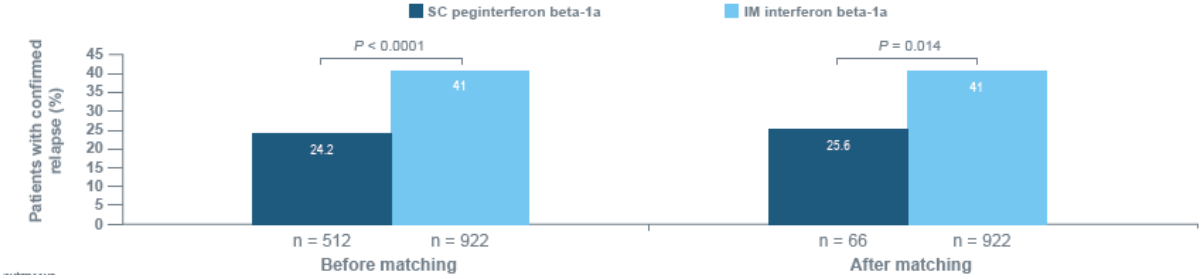
Before matching, patients randomised to SC pegIFNβ-1a Q2W (n = 512) had a lower proportion of previous IFNβ treatment and fewer Gd+ lesions compared with patients randomised to IM IFNβ-1a (n = 922). After matching, baseline characteristics were balanced across treatment groups. After 2 years of treatment, before and after matching, the percentage of patients with CDP3M or CDP6M (Figure 20) or confirmed relapse (Figure 21) were significantly lower in patients receiving pegIFNβ-1a compared with patients receiving IM IFNβ-1a. At 2 years, ARR after matching was also significantly lower in patients receiving pegIFNβ-1a compared with patients receiving IM IFNβ-1a (Figure 22).[142]

Figure 20. CDP3M or CDP6M at 2 years with SC pegIFNβ-1a and IM IFNβ-1a before and after matching baseline characteristics



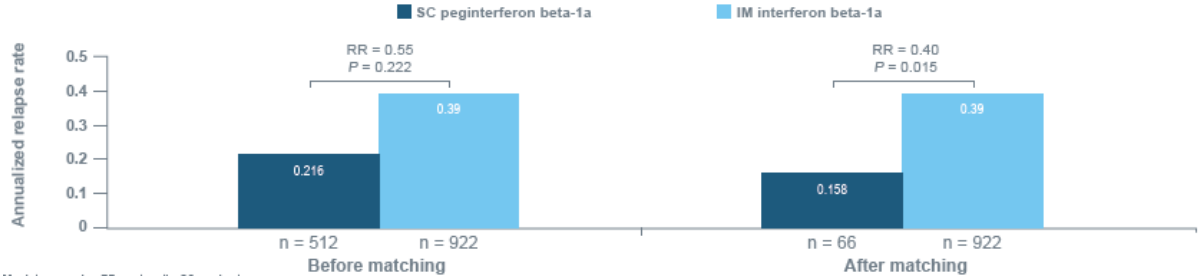
CDP = confirmed disability progression; CDW = confirmed disability worsening; IFNβ-1a = interferon β-1a; IM = intramuscular; pegIFNβ-1a = pegylated interferon β-1a; SC = subcutaneous.
Source: Scott et al. (2017)[142]

Figure 21. Confirmed relapse at 2 years with SC pegIFNβ-1a and IM IFNβ-1a before and after matching baseline characteristics



IFNβ-1a = interferon β-1a; IM = intramuscular; pegIFNβ-1a = pegylated interferon β-1a; SC = subcutaneous.
Source: Scott et al. (2017)[142]

Figure 22. ARR at 2 years with SC pegIFNβ-1a and IM IFNβ-1a before and after matching baseline characteristics



ARR = annualised relapse rate; IFNβ-1a = interferon β-1a; IM = intramuscular; pegIFNβ-1a = pegylated interferon β-1a; SC = subcutaneous.
Source: Scott et al. (2017)[142]

B.2.9.4.2 PegIFNβ-1a Q2W vs. GA 20 mg

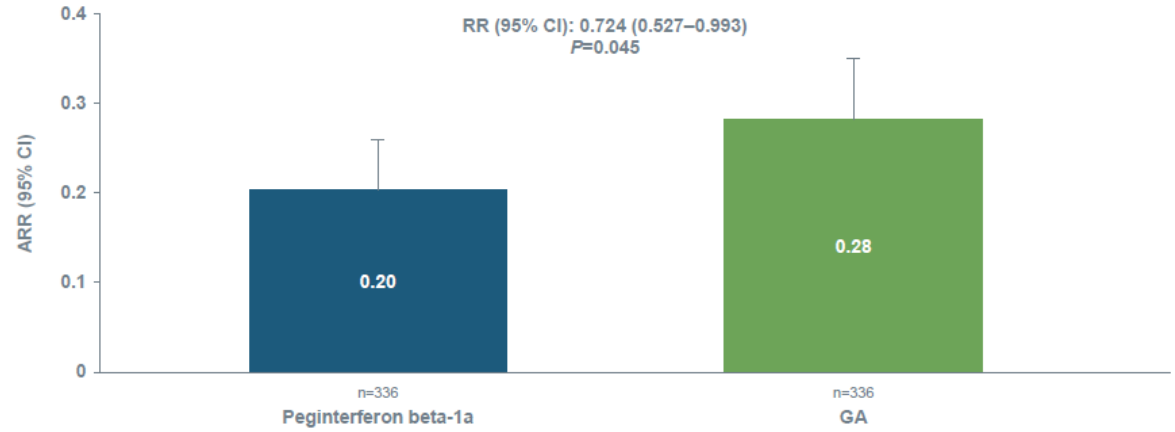
A second study compared data patients with RRMS receiving pegIFNβ-1a Q2W from ADVANCE (N = 512) and patients with RRMS receiving SC GA 20 mg/mL once daily from CONFIRM (N = 350) with 1:1 propensity score matching using key baseline characteristics (age, baseline EDSS score, years from onset of symptoms, number of relapses in prior year, and sex). The study aimed to compare these treatments across clinical efficacy end points over 2 years. The end points investigated were ARR, CDP3M, and CDP6M in addition to NEDA in the MRI sub-cohort.[143]

Propensity score matching was performed and 336 patients treated with pegIFNβ-1a and 336 patients treated with GA were matched and the treatment groups were balanced for each of the key baseline characteristics. For the NEDA analyses, 305 patients treated with pegIFNβ-1a and 165 patients treated with GA (from the CONFIRM MRI sub-cohort) were matched.

The results showed that at 2 years[143]:

- Patients treated with pegIFNβ-1a had a significantly lower ARR than GA-treated patients (Figure 23).
- Patients treated with pegIFNβ-1a had a significantly lower probability of CDP3M than GA-treated patients (10.0% vs. 14.6%), resulting in an HR of 0.625 (95% CI, 0.393-0.995; *P* = 0.048).
- Patients treated with pegIFNβ-1a had a numerically lower probability of CDP6M than GA-treated patients (7.7% vs. 10.6%; HR, 0.684; 95% CI, 0.398-1.178; *P* = 0.171).

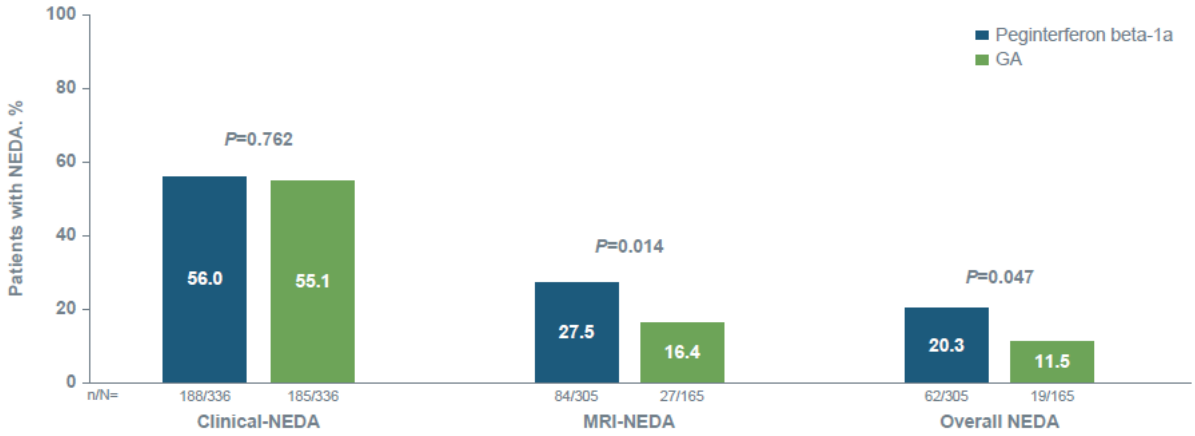
Figure 23. ARR in matched patients treated with pegIFNβ-1a or GA



ARR = annualised relapse rate; GA = glatiramer acetate; MRI = magnetic resonance imaging; IM = intramuscular; pegIFNβ-1a = pegylated interferon β-1a; SC = subcutaneous.
Source: Scott et al. (2018)[143]

Further analysis found that a significantly higher percentage of patients treated with pegIFNβ-1a achieved overall NEDA (20.3% vs. 11.5%; *P* = 0.047), MRI NEDA (27.5% vs. 16.4%; *P* = 0.014) and clinical NEDA (56.0% vs. 55.1%; *P* = 0.762) over 2 years than patients treated with GA (Figure 24).[143]

Figure 24. Clinical NEDA, MRI NEDA, and overall NEDA over 2 years in matched patients treated with pegIFNβ-1a or GA



GA = glatiramer acetate; MRI = magnetic resonance imaging; NEDA = no evidence of disease activity; IM = intramuscular; pegIFNβ-1a = pegylated interferon β-1a; SC = subcutaneous.
Source: Scott et al. (2018)[143]

B.2.9.4.3 PegIFNβ-1a Q2W vs. IFNβ-1a 44 mcg

Coyle et al. (2018)[144] conducted a matching-adjusted comparison of pegIFNβ-1a Q2W (using data from ADVANCE) versus IFNβ-1a (using pooled summary data from four published studies of IFNβ-1a 44 mcg) to evaluate the comparative efficacy of these two agents. A matching-adjusted comparison was conducted by weighting individual pegIFNβ-1a treated patients using estimated propensity of enrolling in IFNβ-1a 44 mcg treatment to match key aggregate baseline characteristics (e.g., age, sex, time since MS symptom onset, EDSS score prior to treatment initiation) of IFNβ-1a 44 mcg treated patients that may have an impact on response variables including ARR and CDP. After this matching process, weighted ARR and CDP6M for pegIFNβ-1a were compared with average outcomes from the four pooled IFNβ-1a 44 mcg studies (OPERA I and II, and CARE MS I and II). For pegIFNβ-1a, ARR was analysed with a negative binomial regression model adjusted for baseline

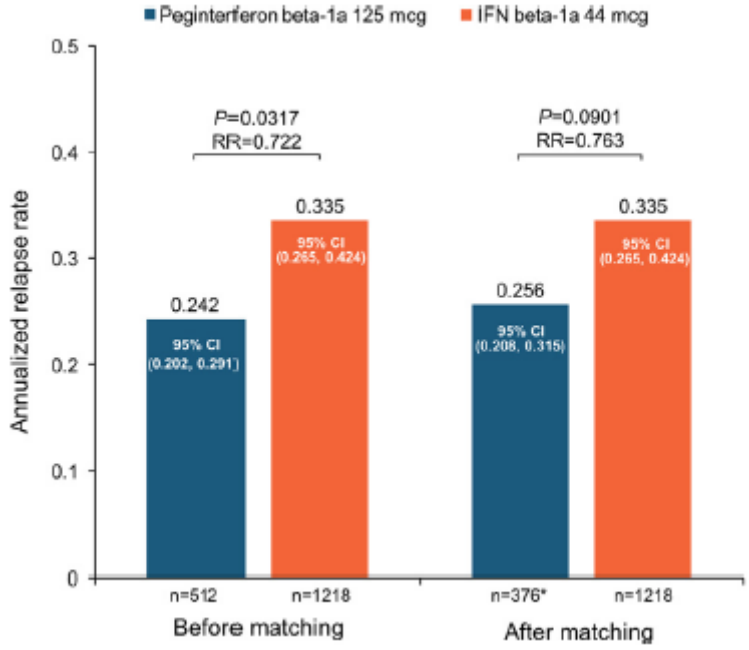
EDSS score, baseline ARR, and age. The proportion of patients who had CDP6M was compared using Rao-Scott chi-square test. Clinical NEDA was also analysed using the Rao-Scott method and was defined as no relapses and no onset of CDP6M and was compared with pooled data from the studies in which it was available. There was a sub-analysis that examined the outcomes with pegIFNβ-1a and IFNβ-1a 44 mcg in treatment-naive patients using individual patient data from ADVANCE and aggregate data from one of the studies included in the analysis that enrolled treatment-naive patients (CARE MS I trial). A matching-adjusted comparison was conducted and after matching for baseline characteristics, efficacy outcomes for pegIFNβ-1a treated patients were weighted based on the model that was used for IFNβ-1a 44 mcg in the CARE MS I trial.[144]

Baseline characteristics were well-balanced between treatment groups after weighting. Over 2 years of treatment, the results showed the following:

- ARR was significantly lower in patients treated with pegIFNβ-1a (before matching n = 512; after matching n = 376) compared with patients treated with IFNβ-1a 44 mcg (n = 1,218) before matching (0.24 vs. 0.34; *P* = 0.0317) but was not significantly lower after matching (0.256 vs. 0.335; *P* = 0.0901) (Figure 25).
- The percentage of patients who were relapse free over 2 years was significantly higher with pegIFNβ-1a treatment than with IFNβ-1a 44 mcg before matching (74.4% vs. 57.5%, *P* < 0.0001) and after matching (75.1% vs. 57.4%, *P* < 0.0001) (Figure 26).
- Patients treated with pegIFNβ-1a had significantly lower CDP6M compared with patients treated with IFNβ-1a 44 mcg (6.6% vs. 13.2%; *P* < 0.0001) before matching and after matching.
- Patients treated with pegIFNβ-1a also had a significantly lower proportion of patients with CDP6M compared with IFNβ-1a 44 mcg (6.5% vs. 13.2%; *P* = 0.0007) (Figure 27).

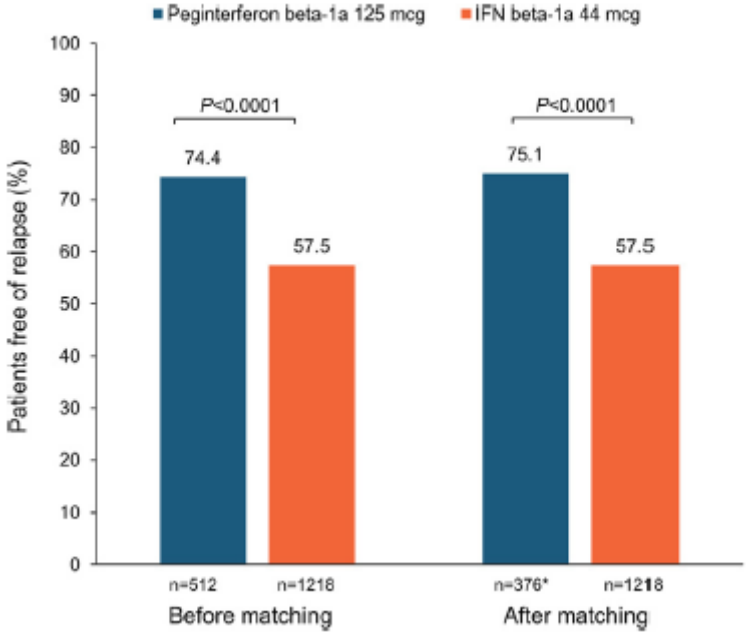
Data on clinical NEDA was only reported in two of the trials for IFNβ-1a 44 mcg, so only these trials were used in the analysis (CAR-MS I and II). Patients treated with pegIFNβ-1a were weighted to match the aggregate baseline characteristics of patients treated with IFNβ-1a 44 mcg in the CARE MS I and II studies. Clinical NEDA occurred in a statistically significantly higher proportion of patients treated with pegIFNβ-1a versus IFNβ-1a 44 mcg before matching (72.5% vs. 48.1%; *P* < 0.0001) and after matching (74.1% vs. 48.1%; *P* < 0.0001) (Figure 28).[144]

Figure 25. Comparison of ARR over 2 years with pegIFNβ-1a and IFNβ-1a 44 mcg before and after matching baseline characteristics.



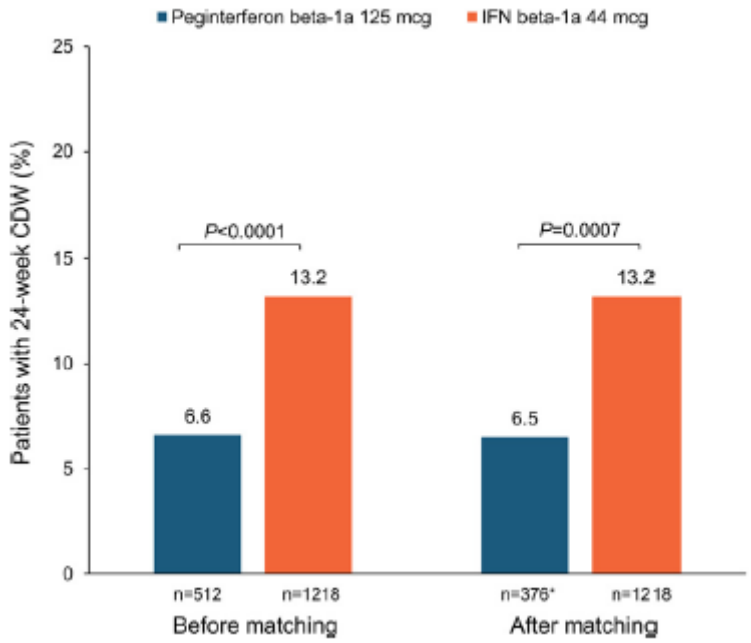
ARR = annualised relapse rate; CI = confidence interval; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MRI = magnetic resonance imaging; NEDA = no evidence of disease activity; pegIFNβ-1a = pegylated interferon β-1a; RR = rate ratio.
* Effective n.
Source: Coyle et al. (2018)[144]

Figure 26. Comparison of the percentages of patients who were relapse free over 2 years with pegIFNβ-1a and IFNβ-1a 44 mcg before and after matching baseline characteristics



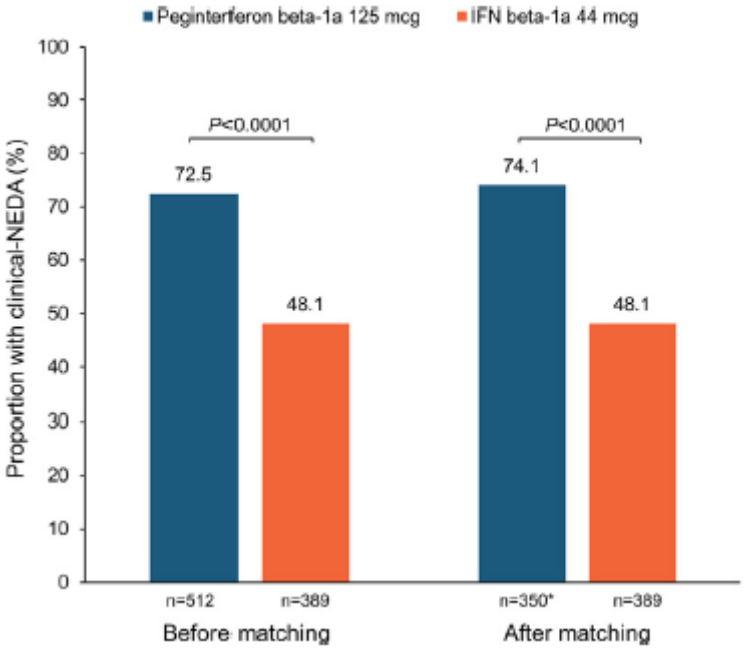
IFN = interferon; pegIFNβ-1a = pegylated interferon β-1a.
* Effective n.
Source: Coyle et al. (2018)[144]

Figure 27. Comparison of CDP6M over 2 years with pegIFNβ-1a and IFNβ-1a 44 mcg before and after matching baseline characteristics



CDP6M = confirmed disability progression at 6 months; IFN = interferon; pegIFNβ-1a = pegylated interferon β-1a.
* Effective n.
Source: Coyle et al. (2018)[144]

Figure 28. Summary of clinical NEDA analysis over 2 years' treatment with pegIFNβ-1a and IFNβ-1a 44 mcg



IFN = interferon; NEDA = no evidence of disease activity; pegIFNβ-1a = pegylated interferon β-1a.
* Effective n.
Source: Coyle et al. (2018)[144]

In the sub-analysis that evaluated only treatment-naive patients, there were some imbalances in baseline characteristics between patients, but after matching all baseline characteristics were balanced across the pegIFNβ-1a (effective sample size, n = 193) and IFNβ-1a 44 mcg (n = 187) treatment groups. In this population, the results at 2 years were as follows:

- ARR was significantly lower before matching for pegIFNβ-1a–treated patients than for patients treated with IFNβ-1a 44 mcg (0.21 vs. 0.39; *P* = 0.0013), and ARR remained significantly lower in pegIFNβ-1a–treated patients after matching (0.14 vs. 0.39; *P* < 0.0001).
- There were significant differences in favour of patients treated with SC pegIFNβ-1a versus patients treated with IFNβ-1a 44 mcg in the proportion of patients with CDP6M (4.9% vs. 10.7%; *P* = 0.030).
- Similarly, the proportion of patients with clinical NEDA was higher in the patients treated with pegIFNβ-1a versus patients treated with IFNβ-1a 44 mcg; 75.1% vs. 55.6% (*P* = 0.0001).[144]

B.2.9.5 Summary of comparative efficacy and safety profile

There were 23 studies that could be considered for inclusion in the analysis of ARR, and 27 studies that could be considered for inclusion in the analysis of other outcomes.

Outcomes assessed in the MTC included ARR, CDP3M, CDP6M, relapse severity, NEDA, and mortality in addition to AEs and SAEs.

B.2.9.5.1 Key results

Table 18. Key efficacy and safety outcomes of pegIFNβ-1a relative to all other treatments

Treatment	ARR (rate ratio)	CDP3M (HR)	CDP6M (HR)	Mortality	Any adverse event (odds ratio)	Any serious adverse event (odds ratio)	Treatment discontinuation due to any cause (odds ratio)
IM IFNβ-1a 30 mcg QW	[redacted]	[redacted]	[redacted]	-	-	-	-
IFNβ-1a 44 mcg TIW	[redacted]	[redacted]	[redacted]	-	-	-	-
IFNβ-1b 250 mcg QAD	[redacted]	[redacted]	[redacted]	-	-	-	-
GA 20 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA 40 mg TIW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-
DMF 240 mg BID	[redacted]	[redacted]	[redacted]	-	-	-	-
Alemtuzumab 12 mg QD	[redacted]	[redacted]	[redacted]	-	-	-	-
Ocrelizumab 600 mg Q24W	[redacted]	[redacted]	[redacted]	-	-	-	-
IFNβ-1a 22 mcg TIW	[redacted]	[redacted]	[redacted]	-	-	-	-
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ARR = absolute risk reduction; BID = twice daily; CDP3M = confirmed disability progression sustained for 3 months; CDP6M = confirmed disability progression at 6 months; DMF = dimethyl fumarate; GA = glatiramer acetate; HR = hazard ratio; IFNβ-1a = pegylated interferon β-1a; IFNβ-1b = pegylated interferon β-1b; IM = intramuscular; Q24W = every 24 weeks; QAD = every other day; QD = once daily; QW = once weekly; TIW = 3 times a week.

The results for the comparative efficacy showed that in terms of ARR:

- pegIFNβ-1a reduced the RR relative to IM IFNβ-1a 30 mcg, teriflunomide, and placebo; however, only the difference versus placebo was statistically significant.
- The RR for ARR was similar (RR, ≥ 0.9 and ≤ 1.1) for patients treated with pegIFNβ-1a relative to IFNβ-1a 44 mcg, IFNβ-1b, GA 20 mg, and GA 40 mg.
- There was a statistically significant increase in the RR for patients treated with pegIFNβ-1a compared with alemtuzumab and ocrelizumab. There was also an increase in RR when compared against DMF; however, this was not statistically significant.

The risk of CDP3M was not statistically different for patients treated with pegIFNβ-1a compared with all other treatments.

- The risk of CDP3M was numerically decreased in patients receiving pegIFNβ-1a compared with those receiving IM IFNβ-1a 30 mcg, IFNβ-1b 250 mcg, GA 20 mg, or placebo.
- The risk of CDP3M was numerically increased for pegIFNβ-1a compared with either alemtuzumab or ocrelizumab; however, these differences were not statistically significant.
- There was no difference in the risk of CDP3M (HR ≥ 0.9 and ≤ 1.1) in patients receiving pegIFNβ-1a compared with IFNβ-1a 44 mcg, IFNβ-1a 22 mcg, teriflunomide, or DMF

The risk of CDP6M was statistically significantly decreased in patients receiving pegIFNβ-1a compared with placebo.

- The risk of CDP6M was numerically decreased in patients receiving pegIFNβ-1a compared with those receiving IM IFNβ-1a 30 mcg, IFNβ-1a 44 mcg, GA 20 mg, DMF, or teriflunomide.
- The risk of CDP6M was numerically increased compared with alemtuzumab and ocrelizumab.

Indirect comparisons using matching-adjusted indirect comparisons also show the following:

- PegIFNβ-1a has relapse severity similar to IFNβ-1a.
- PegIFNβ-1a showed a statistically significant reduction in NEDA compared with GA 40 mg and no statistically significant differences regarding mortality compared with GA 20 mg, GA 40 mg, or placebo.
- Analysis of the relative safety profile of pegIFNβ-1a compared with other DMTs showed no statistically significant differences between pegIFNβ-1a, GA 20 mg, GA 40 mg, or placebo.

B.2.10 Adverse reactions

- PegIFNβ-1a is generally well tolerated, with manageable AEs that are consistent with the safety profile of non-pegylated interferons for MS.
- The most common AEs occurring in ≥ 10% of patients treated with pegIFNβ-1a Q2W at year 1 of the ADVANCE study were flu-like symptoms and injection-site reactions, which are the most common adverse effects of all types of IFNβ therapies. Most of these AEs were mild or moderate in severity and there are mitigation strategies in place to manage them; less than 1% of patients treated with pegIFNβ-1a Q2W discontinued treatment due to flu-like symptoms or injection-site reactions.
- Neutralising antibodies have the potential to reduce clinical efficacy. There was no significant difference in the incidence of neutralising antibodies between pegIFNβ-1a Q2W and placebo at year 1 (< 1% in both groups), demonstrating that pegIFNβ-1a provides a significant advantage over current IFNβ products.
- Over 1 year of treatment, pegIFNβ-1a Q2W compared with placebo did not increase the risk of other AEs of special interest, including patients' susceptibility to infection and depression/suicidal ideations.
- The safety profile of pegIFNβ-1a Q2W remained favourable for up to 6 years of continuous treatment.
  - The type and incidence of most AEs during the ATTAIN extension were similar to that of the ADVANCE study, except flu-like symptoms and injection-site reactions decreased beyond 2 years of treatment, suggesting improved tolerability of pegIFNβ-1a Q2W over time.

B.2.10.1 Introduction

The safety profile of pegIFNβ-1a was assessed in four studies, including the pivotal phase III study (ADVANCE), the long-term extension study (ATTAIN), a 1-year phase III study (ALLOW) and a pharmacokinetic study (COMPARE). The safety results from these studies are presented in this section.

B.2.10.2 ADVANCE

The safety profile of pegIFNβ-1a has been demonstrated in the randomised, double-blind, phase III study, ADVANCE, which was placebo-controlled in the first year, with a second year where all patients received pegIFNβ-1a. As all placebo patients switched to pegIFNβ-1a after 1 year, data are available for patients with 2 continuous years of pegIFNβ-1a treatment, and for patients with 1 year of placebo treatment followed by 1 year of pegIFNβ-1a treatment.

The overall incidence of AEs was numerically higher with pegIFNβ-1a Q2W group at 1 year, compared with placebo (94% vs. 83%). Treatment-related AEs were more common in the pegIFNβ-1a Q2W group than in the placebo group (90% vs. 53%). Most AEs were mild to moderate in intensity; the incidence of severe AEs was low in the pegIFNβ-1a Q2W group and in the placebo group (18% and 11%, respectively). Table 19 presents the summary of AEs.[7,11,145]

The incidence of SAEs was similar between groups, and there was no difference in the number of serious infections. More pegIFNβ-1a Q2W patients discontinued treatment due to AEs, compared with placebo; however, the proportion of discontinuations for both was low (5% vs. 1%). Adverse events resulting in discontinuation in > 1 patient were:

- PegIFNβ-1a Q2W: influenza-like illness (n = 4), injection-site erythema (n = 3), pyrexia (n = 4), suicidal ideation (n = 2), fatigue (n = 2), and increased transaminases (n = 2)
- Placebo: none

Table 19. Summary of adverse events in ADVANCE

AEs n (%)	pegIFNβ-1a Q2W		Placebo		pegIFNβ-1a Q4W	
	Year 1 (N = 512)	Year 2 (N = 740)	Year 1 (N = 500)	Year 2 (N = 0)	Year 1 (N = 500)	Year 2 (N = 728)
≥ 1 AE	481 (94)	699 (94)	417 (83)	-	472 (94)	687 (94)
≥ 1 moderate or severe AE	336 (66)	520 (70)	287 (57)	-	327 (65)	520 (71)
≥ 1 severe AE[a]	90 (18)	152 (21)	53 (11)	-	82 (16)	149 (20)
≥ 1 SAE	55 (11)	120 (16)	76 (15)	-	71 (14)	158 (22)
≥ 1 treatment-related AE	459 (90)	668 (90)	266 (53)	-	449 (90)	644 (88)
Discontinuation due to AEs	25 (5)	41 (6)	7 (1)	-	24 (5)	42 (6)
Withdrawal due to AEs	25 (5)	41 (6)	6 (1)	-	22 (4)	42 (6)

AE = adverse event; pegIFNβ-1a = pegylated interferon Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event.
Note: PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
[a] Defined as symptoms that cause severe discomfort, incapacitation, or significant effect on patient's daily life; severity could cause cessation of study treatment, treatment for symptoms, or admission to hospital.
Sources: Calabresi et al. (2014)[11]; Biogen Idec Inc (2013)[7]; Newsome et al. (2018)[124],Biogen Idec Inc (2014)[145]

The results at year 2 for all patients receiving pegIFNβ-1a Q2W or Q4W (i.e., patients with continuous treatment plus patients switched from placebo who had completed 1 year of treatment on either pegIFNβ-1a Q2W or Q4W) were similar to the year 1 results.

B.2.10.2.1 Neutralising antibodies

Neutralising antibodies against IFN can occur with IFN treatment and may reduce the efficacy of treatment.[12,13] PegIFNβ-1a was not associated with an increased risk of neutralising antibodies, compared with placebo, and the overall incidence over 2 years was < 1%. Anti-polyethylene glycol antibodies were observed in 7% of pegIFNβ-1a Q2W patients and 5% of placebo patients at 1 year but were not found to have any detrimental effect on efficacy (see Section B.3.3.3.2). A scenario with no treatment waning has also been explored as part of the cost-effectiveness analysis (Section B.3.8.3). Table 20 presents the results for patients positive for IFN–neutralising antibodies at 1 and 2 years in ADVANCE.[7,11,145]

Table 20. Patients positive for IFN-neutralising antibodies at 1 and 2 years in ADVANCE

n (%)	pegIFNβ-1a Q2W		Placebo		pegIFNβ-1a Q4W	
	Year 1 (N = 512)	Year 2 (N = 740)	Year 1 (N = 500)	Year 2 (N = 0)	Year 1 (N = 500)	Year 2 (N = 728)
Neutralising antibody positive	4 (< 1)	7 (< 1)	2 (< 1)	-	2 (< 1)	6 (< 1)

pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
Sources: Calabresi et al. (2014)[11]; [123]

B.2.10.2.2 Most common adverse events

The most common AEs with an incidence ≥ 10% in the pegIFNβ-1a Q2W group at 1 year, compared with placebo were injection-site erythema (62% vs. 7%); influenza-like illness (47% vs. 13%); pyrexia (45% vs. 15%); headache (44% vs. 33%); myalgia (19% vs. 6%), chills (17% vs. 5%); injection-site pain (15% vs. 3%); and injection-site pruritus (13% vs. 1%).[7,11,145]

Infections were similar across the groups. In year 1, the incidence of infections was similar across all treatment groups (39% in the placebo group vs. 33% and 37% in the pegIFNβ-1a Q2W and Q4W groups, respectively).[7] Nasopharyngitis, urinary tract infection, and upper respiratory tract infection were the most commonly reported infections (incidence of ≥ 5% total), with similar incidences in the placebo and pegIFNβ-1a treatment groups. In year 2, infections were reported in 23% of patients continuing pegIFNβ-1a Q2W and 19% of patients who switched from placebo to pegIFNβ-1a.[7]

B.2.10.2.3 Influenza-like symptoms and injection-site reactions

Flu-like symptoms are known to be associated with treatment with IFN. The incidence of flu-like symptoms using narrow and broad definitions in ADVANCE is shown in Table 21[7,11,145] and was consistent with the profile of other non-pegylated IFNs for MS.[146-148] The incidence of flu-like symptoms was highest at the initiation of treatment and generally decreased over the first 6 months. Of the patients who reported flu-like symptoms, 90% reported them as mild or moderate in severity.[1]

Injectable therapies for RRMS are also associated with injection-site reactions. Of the patients who experienced injection-site reactions, 95% reported them as mild or moderate in severity.[1,11]

Table 21. Summary of flu-like symptoms at 1 and 2 years in ADVANCE

Adverse event, n (%)	PegIFNβ-1a Q2W		Placebo		PegIFNβ-1a Q4W	
	Year 1 (N = 512)	Year 2* (N = 740)	Year 1 (N = 500)	Year 2 (N = 0)	Year 1 (N = 500)	Year 2 (N = 728)
Narrow definition						
Flu-like illness	239 (47)	377 (51)	63 (13)	-	234 (47)	365 (50)
Broad definition						
Myalgia	97 (19)	140 (19)	30 (6)	-	97 (19)	137 (19)
Musculoskeletal pain	12 (2)	20 (3)	16 (3)	-	11 (2)	21 (3)

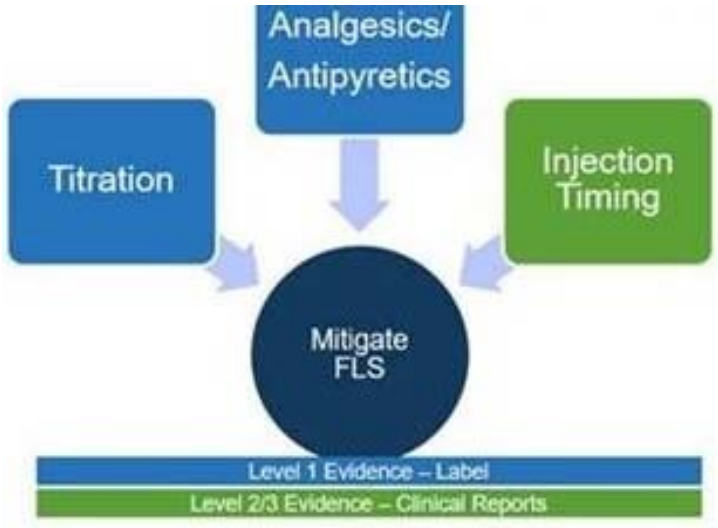
Pyrexia	228 (45)	320 (43)	76 (15)	-	218 (44)	298 (41)
Chills	88 (17)	124 (17)	23 (5)	-	92 (18)	123 (17)
Pain	25 (5)	40 (5)	16 (3)	-	29 (6)	42 (6)
Hyperpyrexia	-	1 (< 1)	-	-	-	1 (< 1)

pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: PegIFNβ-1a Q4W greyed out as pegIFNβ-1a Q2W is currently the only licensed dose and the focus of this submission.
Sources: Biogen Idec Inc (2013)[7]; Biogen Idec Inc (2014)[145]; Calabresi et al. (2014)[11]
*Includes all patients who received pegIFNβ-1a Q2W anytime over 2 years

A Delphi-consensus generating study of 374 patients treated by clinicians in ADVANCE found that both flu-like symptoms and injection-site reactions generally decreased in incidence and duration after 3 months of treatment and had a minimal impact on daily activities in their typical patient.[11,124]

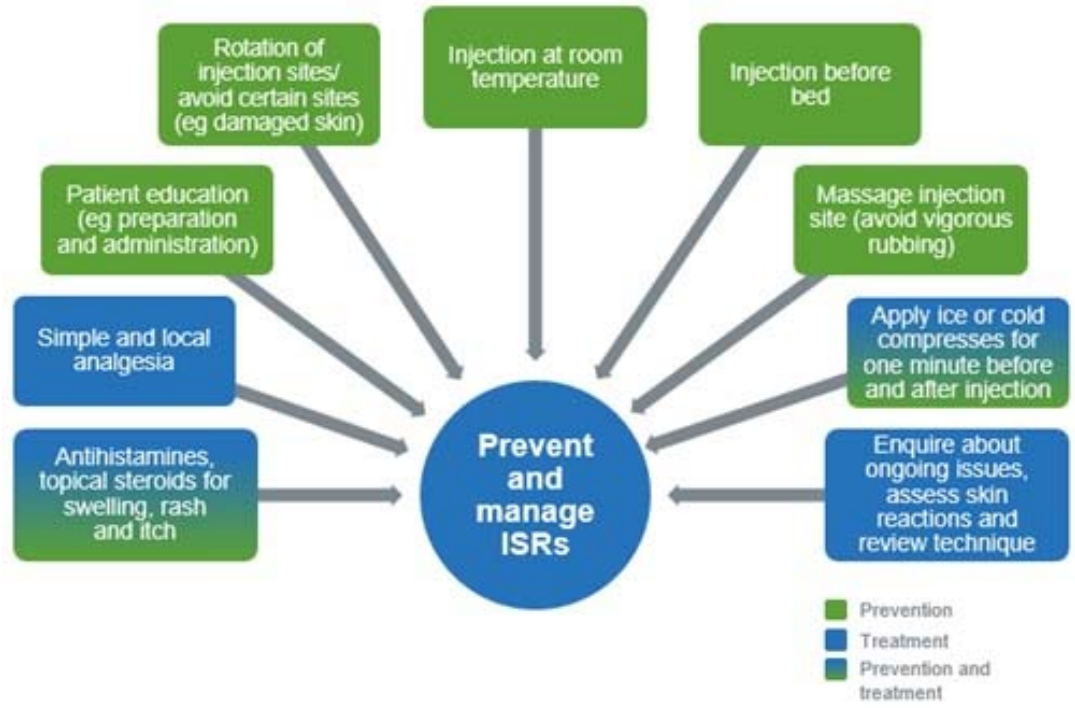
Several mitigating strategies are available to help minimise the effects of these AEs (Figure 29). Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with IFNs.

Figure 29. Mitigating flu-like symptoms



Prophylactic and concurrent use of anti-inflammatory, analgesic, and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during IFN treatment. The use of an aseptic injection technique may help to minimise the risk of injection-site reactions in patients.[1] This may be why < 1% of patients treated with pegIFNβ-1a Q2W discontinued treatment due to flu-like symptoms or injection-site reactions. Strategies suggested to prevent and manage injection-site reactions are outlined in Figure 30.

Figure 30. Strategies to prevent and manage injection-site reactions associated with self-injectable DMTs for MS



Source: Halper et al. (2016)[149]; McEwan et al. (2010)[150]

B.2.10.3 ATTAIN

The long-term tolerability of pegIFNβ-1a Q2W was demonstrated in the ATTAIN extension study.

During years 3 to 6 in the ATTAIN study, incidences of AEs and SAEs were similar to those reported over 2 years in ADVANCE (Table 22).[124] The most commonly reported AEs continued to be injection-site reactions and flu-like symptoms, with most reported as mild or moderate. The proportion of patients who discontinued treatment with pegIFNβ-1a Q2W remained low over 3 years of treatment. Subcutaneous pegIFNβ-1a 125 µg Q2W continued to be associated with low levels of immunogenicity and laboratory abnormalities over 3 years.[124] The incidence of any single AE that led to study discontinuation was < 1%.[124] The proportion of patients experiencing flu-like symptoms or injection-site reactions during each year of the study in each continuous treatment group decreased over time.[124] The incidence of flu-like symptoms was 77%, 61%, 51%, 44%, and 25% in year 1, 2, 3, 4, and 5 for patients treated with pegIFNβ-1a Q2W.[124]

Table 22. Adverse events in years 3 to 6 in patients in pegIFNβ-1a treatment groups[a]

Event, n (%)	PegIFNβ-1a Q2W (n = 547)	PegIFNβ-1a Q4W (n = 529)
Any AE	478 (87)	471 (89)
Most common AEs (≥ 5% of patients)		
Flu-like illness	234 (43)	232 (44)
Injection-site erythema	224 (41)	221 (42)
Headache	161 (29)	152 (29)
MS relapse	137 (25)	159 (30)
Pyrexia	131 (24)	146 (28)
Myalgia	67 (12)	65 (12)
Chills	58 (11)	69 (13)
Back pain	57 (10)	53 (10)
Fatigue	52 (10)	39 (7)
Nasopharyngitis	49 (9)	68 (13)
Asthenia	45 (8)	64 (12)
Injection-site pain	34 (6)	37 (7)
Injection-site pruritus	34 (6)	24 (5)
AEs related to study treatment	399 (73)	400 (76)
AEs leading to discontinuation	26 (5)	18 (3)
AEs leading to study withdrawal	22 (4)	13 (3)
Any SAE	90 (16)[b]	113 (21)[b]
Severe AEs	73 (13)	74 (14)

AE = adverse event; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; SC = subcutaneous.
[a] Duration of exposure ranges from 2 to 4 years in ATTAIN.
[b] Includes MS relapse, which was reported as an SAE for 57 patients (10%) in the Q2W group and 82 patients (16%) in the Q4W group.
Source: Newsome et al. (2018)[124]

B.2.10.4 ALLOW

In addition to ADVANCE and ATTAIN, a recently completed, 1-year, open-label, Phase IIIb trial (ALLOW) was conducted to assess the safety implications of switching patients from a non-pegylated IFNβ to pegIFNβ-1a, with focus on flu-like symptoms.[151]

For the primary end point, the majority of patients (89.6%) who switched to pegIFNβ-1a from their previous IFNβ therapy did not experience new/worsening flu-like symptoms over 8 weeks.[151] Of the 10.4% of patients who did experience new/worsening flu-like symptoms, patients receiving naproxen had a 44% lower incidence of new/worsening flu-like symptoms, compared with patients receiving the current flu-like symptoms regimen.[151] The safety profile of the two treatment regimens during ALLOW was consistent with ADVANCE.[151]

B.2.10.5 COMPARE

In addition, an open-label, crossover pharmacokinetic study (COMPARE), which also compares the incidence and frequency of AEs (particularly injection-site reactions and flu-like symptoms) was conducted in 30 healthy patients receiving pegIFNβ-1a or IFNβ-1a 44 mcg.[152]

Most treatment-emergent AEs were mild and overall incidence was similar between treatment groups.[152] Injection-site reactions were the most common AEs reported with both treatment arms. However, numerically lower frequencies and incidence rates of injection-site reactions were observed with pegIFNβ-1a compared with IFNβ-1a 44 mcg.[152] Numerically lower frequencies of headache, myalgia, and chills were also observed with pegIFNβ-1a compared with IFNβ-1a 44 mcg.[152]

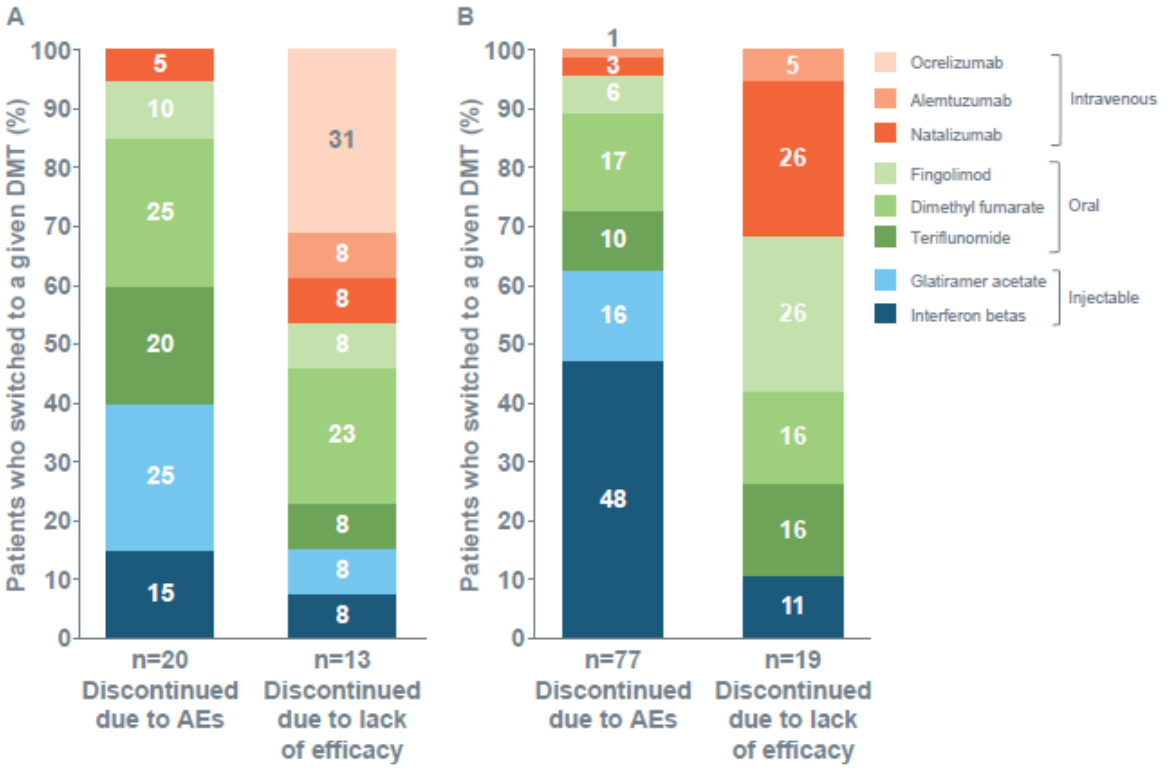
B.2.11 Ongoing studies

The Plegridy Observational Programme (POP) is an ongoing, 5-year phase IV study exploring the long-term safety profile and effectiveness of pegIFNβ-1a Q2W for patients with newly diagnosed and non-newly diagnosed relapsing MS in the real-world setting. Data from the second interim analysis as of September 2017 on safety profile, reasons for discontinuation, and number of relapses are available and were presented in October 2018.[153] Further interim analysis results from the POP study may be available in the next 6 to 12 months. At the time of this second interim analysis, 1,037 patients had enrolled in POP, of which 257 patients were newly diagnosed and 780 patients were non-newly diagnosed. Newly diagnosed patients were defined as patients who were diagnosed with relapsing forms of MS < 1 year prior to POP study consent and who were treatment-naive to prior MS DMT. Non-newly diagnosed patients were defined as those who were diagnosed ≥ 1 year prior to study consent and/or who had prior treatment with an MS DMT. Of these, 963 patients had received ≥ 1 dose of pegIFNβ-1a and were included in the study population. A total of 89% of patients had a treatment duration of ≥ 12 months; 38% had a treatment duration of ≥ 24 months. Newly diagnosed patients accounted for 25% of the study population. Overall baseline characteristics were well-balanced between the newly diagnosed and non-newly diagnosed subgroups.[153]

The incidence of treatment-emergent AEs and SAEs was similar in the two subgroups and the most commonly reported AEs in newly diagnosed and non-newly diagnosed patients were flu-like symptoms (seen in 43% and 38% of patients, respectively) and injection-site reactions (seen in 36% and 39% of patients, respectively). The incidence of SAEs was 14 (6%) and 37 (5%) in newly diagnosed and non-newly diagnosed populations, respectively. The incidence of any particular SAE in the study populations was ≤ 1%. At the time of this analysis, 33% of newly diagnosed patients and 35% of non-newly diagnosed patients in the study population had discontinued pegIFNβ-1a.[153]

Most newly diagnosed patients who discontinued pegIFNβ-1a due to AEs and started another DMT switched to an oral therapy (55%) or another injectable (40%) (Figure 31A) and most of the non-newly diagnosed patients who discontinued due to AEs and started another DMT switched to an injectable therapy (64%) (Figure 31B). In both subgroups, patients who discontinued due to lack of efficacy and started another DMT switched either to an oral therapy or an IV therapy.[153]

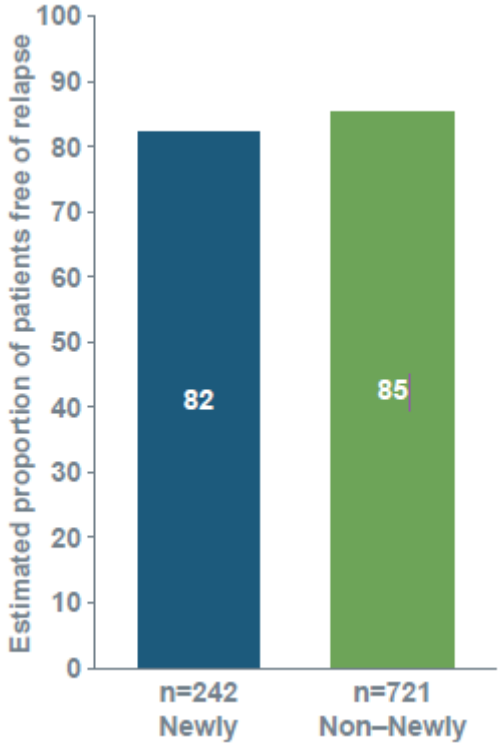
Figure 31. Switch DMT by reason for pegIFNβ-1a discontinuation in (A) newly diagnosed, and (B) non-newly diagnosed patients



AE = adverse event; DMT = disease-modifying therapy; pegIFNβ-1a = pegylated interferon β-1a.
Note: For each analysis, the n value below the bar represents the number of patients who discontinued pegIFNβ-1a for the indicated reason and started another DMT. Patients could switch to more than one DMT after pegIFNβ-1a discontinuation. Not all post-discontinuation DMTs are shown.
Source: Salvetti et al. (2018)[153]

This interim analysis found that a high proportion of both newly diagnosed patients (82%) and non-newly diagnosed patients (85%) were relapse free after 2 years of treatment with pegIFNβ-1a (Figure 32).[153]

Figure 32. Estimated proportions of newly diagnosed and non-newly diagnosed patients free of relapses at 2 years



Note: Proportions of patients in the study populations free of relapse based on Kaplan-Meier estimates.
Source: Salvetti et al. (2018)[153]

B.2.12 Innovation

PegIFNβ-1a is the first pegylated IFN for the treatment of RRMS. Interferons have a proven track record of efficacy and a favourable safety profile in the treatment of RRMS for over 16 years; pegylation of IFN creates a new molecular entity with increased biological half-life, allowing less frequent administration; pegIFNβ-1a is self-administered subcutaneously Q2W.

Interferons have been a mainstay of treatment for RRMS since their introduction; however, patients may develop neutralising antibodies against IFNs which are linked to treatment waning.[12,13,154,155] This issue is most significant with SC IFNβ-1a 22/44 µg (Rebif®) and SC IFNβ-1b 250 µg (Betaferon®/Extavia®), which were found to have rates of neutralising antibody formation of 22% to 35% (22 and 44 µg doses, respectively) and 22%, respectively, over 3 years.[154] In comparison, the rate with IM IFNβ-1a 30 µg (Avonex®) was 7.5% over 3 years.[154] In addition to the clinical impact of neutralising antibodies, there is also an economic impact, with patients generally stopping treatment with IFN and switching to more expensive drugs such as natalizumab or fingolimod.[156,157]

Pegylation can reduce the immunogenicity of therapeutic proteins with no detrimental effect on efficacy.[122] In the ADVANCE study, less than 1% of patients receiving pegIFNβ-1a subsequently developed neutralising antibodies against IFN over 2 years. Thus, pegIFNβ-1a offers the advantage of an extremely low rate of neutralising antibody formation (1%) over the IFN class, where rates of 7.5% to 35% have been reported.[7]

B.2.13 Interpretation of clinical efficacy and safety profile evidence

B.2.13.1 Efficacy

B.2.13.1.1 ADVANCE

The results from ADVANCE demonstrated the efficacy of pegIFNβ-1a for the treatment of RRMS by showing that pegIFNβ-1a Q2W was statistically significantly better than placebo in reducing ARR at year 1 (36% reduction, $P = 0.0007$) which was confirmed by sensitivity analysis. PegIFNβ-1a Q2W was also statistically significantly better than placebo in reducing the proportion of patients who relapsed (39% reduction, $P = 0.0383$), reducing EDSS disability progression sustained for 12 weeks at 1 year (38% reduction, $P < 0.0003$) and reducing the number of new or newly enlarging T2 lesions (67% reduction, $P < 0.0001$) active Gd+ lesions (86% reduction, $P < 0.0001$), and T1 lesions (53% reduction, $P < 0.0001$). PegIFNβ-1a Q2W had greater effects than pegIFNβ-1a Q4W at reducing ARR and several MRI measures, although there was no direct comparison performed. PegIFNβ-1a Q2W showed efficacy in patients who received it over 2 years, with patients showing significantly lower ARR ($P < 0.001$), significantly fewer relapses ($P < 0.0001$), and were significantly less likely to experience EDSS CDP3M ($P = 0.0257$) compared with patients who received placebo in year 1 and either Q2W or Q4W in year 2.[11,123]

A reduction of relapses is a very important treatment goal for patients with MS as relapses indicate an acute decline in neurological function that impairs a patient's QOL. T2-weighted lesions can accumulate over time in patients with MS and the number and volume of NET2 lesions is an important indicator of the accumulated burden of focal inflammatory disease.[11] This demonstrates the potential positive impact that treatment with pegIFNβ-1a Q2W can have in patients with RRMS.

Post hoc analyses presented in Section B.2.7.2 shows that patients receiving pegIFNβ-1a present with good MRI results as they develop fewer BHs and are more likely to achieve NEDA which may be prognostic for long-term clinical outcomes. BHs indicate the presence of severe tissue damage and NEDA indicates no disease progression and positive MRI effects of treatment. These analyses demonstrate that pegIFNβ-1a treatment can help patients with RRMS achieve positive MRI results and help prevent disease progression.[38,130]

B.2.13.1.2 ATTAIN

The ATTAIN study provided evidence to support the long-term clinical benefits associated with pegIFNβ-1a Q2W. The adjusted ARR was significantly improved in patients receiving continuous pegIFNβ-1a Q2W compared with patients receiving continuous Q4W for 0 to 6 years (0.188 vs. 0.263; $P = 0.0052$). Over the course of 5 years, continuous dosing Q2W significantly reduced the risk of relapse, from 49% to 36% ($P = 0.0018$), and patients showed a trend towards a reduced risk of 24-week confirmed disability worsening (15% vs. 20%, $P = 0.0526$) compared with continuous dosing Q4W. These results demonstrated the sustained and long-term efficacy of treatment with pegIFNβ-1a Q2W. Patients who received placebo in year 1 then pegIFNβ-1a Q2W from years 1 to 5 had a higher risk of relapse (47%) than patients who received continuous pegIFNβ-1a Q2W (36%). This supports the early use of the Q2W regimen as patients who receive placebo in year 1 have a higher risk of relapses than patients who received the continuous Q2W regimen.[124]

B.2.13.2 Safety profile

B.2.13.2.1 ADVANCE

In ADVANCE, the overall incidence of AEs was 94% in the pegIFNβ-1a group at 1 year, compared with 83% in the placebo group. The incidence of SAEs was similar for pegIFNβ-1a and placebo at 1 year (11% vs. 15%, respectively). The incidence of AEs leading to discontinuation was low at 1 and 2 years with pegIFNβ-1a (5% and 6%, respectively, vs. 1% for placebo at 1 year). The incidence of flu-like symptoms and injection-site reactions with pegIFNβ-1a was consistent with the safety profile of other non-pegylated IFNs for MS. PegIFNβ-1a was not associated with an increased risk of infections compared with placebo. Immunogenicity results for pegIFNβ-1a demonstrated a very low (< 1%) risk of developing neutralising antibodies, which can negatively affect the efficacy of non-pegylated IFNs for MS. The most common AEs associated with pegIFNβ-1a were injection-site reactions, flu-like symptoms, pyrexia, and headache.[7,11,145]

B.2.13.2.2 ATTAIN

The long-term tolerability of pegIFNβ-1a Q2W was demonstrated in the ATTAIN extension study. The overall incidence of AEs was 87%; the incidence of SAEs was 16%. The incidence of AEs leading to discontinuation was low with pegIFNβ-1a Q2W (5%). The most commonly reported AEs up to 6 years were flu-like symptoms and injection-site reactions, which were numerically decreased in later years of the study.[128]

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

The original SLR was conducted for publications between 2003 and 2014 and was part of NICE TA320 submission, which was subsequently updated in a SLR conducted between 2014 and 2016 for TA441 (further documentation for these can be provided by Biogen upon request). The current SLR covers the time period since the previous update and, therefore, was undertaken to identify all cost-effectiveness studies published between 1 February, 2016 and 30 November, 2018 that are relevant to the decision problem in this appraisal.

A total of 66 economic evaluation studies were identified in this update SLR. Of these, 12 economic evaluations were conducted in the UK, out of which only two were explicitly stated as having been conducted in England (Hettle et al., 2018[158]; Lambe et al., 2018[159]). Most of the remaining 54 studies were conducted in North America, Europe, and Asia, and are considered to have limited relevance for decision making in England. Therefore, only the studies in the UK are discussed in this document. Two of these 12 studies (Hernandez et al., 2017[160]; Melendez et al., 2017[161]), compared pegIFNβ-1a (Plegridy®) with other DMTs. In both of these studies, the pegIFNβ-1a dominated comparator DMTs in almost all comparisons over 30-year and 50-year time horizons in Markov models comprising health states defined by EDSS level. The only comparison where pegIFNβ-1a was not dominant was in the Hernandez et al. (2017)[160] study against GA, however, pegIFNβ-1a also would be considered cost-effective in that comparison using the conventional cost-effectiveness thresholds (ICER was £5,773). The full results of published economic evaluations that were included in this SLR, along with details of the search strategy and study selection process, are presented in Appendix G.

As the updated SLR was completed in November 2018, the EMBASE search strategy was re-run up to May 2019 to ensure no recent publications relevant to the decision problem were excluded. This search resulted in 123 hits; however, none of the studies were deemed relevant to this appraisal.

Table 23 presents the summary of the economic evaluations that are based in the UK and deemed to be more relevant for the submission.

Table 23. Summary list of published cost-effectiveness studies

Study (year)	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Maervoet et al. (2016)[162]	UK	Markov model, 21 health states, 20 defined by EDSS and death. 50-year time horizon.	RRMS, mean age = NR	QALY gains GA vs. IFN-1a 22 mcg = 0.226 GA vs. IFN-1a 30 mcg = 0.067 GA vs. BSC = NR	Costs, £ GA vs. IFN-1a 22 mcg = NR GA vs. IFN-1a 30 mcg = NR GA vs. BSC = NR	ICER (£) GA vs. IFN-1a 22 mcg = NR GA vs. IFN-1a 30 mcg = NR GA vs. BSC = 14,789/QALY
Hernandez et al. (2017)[160]	UK	Markov cohort model, 21 health states, 20 defined by EDSS, in RRMS and SPMS, and death. 30-year time horizon.	RRMS, mean age = 36.5 years	Total QALYs (patient + caregiver) PegIFNβ-1a = 7.32 IFNβ-1a 30 mcg = 6.88 IFNβ-1a 22 mcg = 6.99 IFNβ-1a 44 mcg = 7.01 IFNβ-1b = 6.88 GA = 6.90	Total direct costs, £ PegIFNβ-1a = 106,843 IFNβ-1a 30 mcg = 113,257 IFNβ-1a 22 mcg = 115,614 IFNβ-1a 44 mcg = 112,523 IFNβ-1b = 110,657 GA = 104,441	PegIFNβ-1a = reference IFNβ-1a 30 mcg = dominant IFNβ-1a 22 mcg = dominant IFNβ-1a 44 mcg = dominant IFNβ-1b = dominant GA = 5,773/QALY
Hettle et al. (2018)[158]	England	Markov model, 11 health states, 10 defined by EDSS and death. 50-year time horizon.	RRMS, mean age = 39.4 years	Total cost, £ Cladribine tablets = 92,484 ALZ = 104,136 NTZ = 212,969	Total QALYs Cladribine tablets = 9.45 ALZ = 8.482 NTZ = 7.739	ICER vs. cladribine ALZ = cladribine dominant NTZ = cladribine dominant

Study (year)	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Montgomery et al. (2017)[163]	UK	Discrete event simulation. Health states defined by EDSS and death. Lifetime (maximum age 100) time horizon	RRMS, mean age = 34.8 years	Total QALYs FNG = 6.18 NTZ = 6.35	Total costs, £ FNG = 334,897.93 NTZ = 337,501.15	ICER was not reported Net monetary benefit £20,000/QALY threshold, £ FNG vs. NTZ = −732.02 £30,000/QALY threshold, £ FNG vs. NTZ = −2,399.65
Melendez-Torres et al. (2017)[161]	UK	Cohort-based Markov model. Health states defined by EDSS and death. 50-year time horizon.	RRMS, starting age = 30 years	Total QALYs BSC = 8.664 DMT (pooled) = 9.607 PegIFNβ-1a = 11.223 GA = 10.012 IFNβ-1b = 9.934 IFNβ-1a (Rebif®) = 10.867 IFNβ-1a (Avonex®) = 10.348	Total costs, £ BSC = 362,100 DMT (pooled) = 394,000 PegIFNβ-1a = 379,900 GA = 381,400 IFNβ-1b = 392,400 IFNβ-1a (Rebif®) = 404,800 IFNβ-1a (Avonex®) = 406,400	ICER (£ per QALY) BSC = - DMT (pooled) = 33,800 PegIFNβ-1a = 7,000 GA = dominant IFNβ-1b = dominant IFNβ-1a (Rebif®) = dominant IFNβ-1a (Avonex®) = dominant

Study (year)	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Montgomery et al. (2017)[164]	UK	Discrete event simulation. Health states defined by EDSS and death. Lifetime time horizon.	RRMS, mean age = 38.2 years	Discounted QALY per person No AE incidence FNG = 4.44 ALZ = 4.64 Incremental (FNG vs. ALZ) = −0.20 AE incidence; AE length capped at 1 year FNG = 4.44 ALZ = 4.58 Incremental (FNG vs. ALZ) = −0.14 AE length greater than 1 year, where appropriate FNG = 4.44 ALZ = 4.48 Incremental (FNG vs. ALZ) = −0.04	Total costs at a Patient Access Scheme discount of 0%, £ FNG = 320,597 ALZ = 285,457	ICER was not reported as FNG price to the NHS is lower than that modelled

Study (year)	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Lambe et al. (2019)[159]	England	11 health states, 10 defined by EDSS and death. 50-year time horizon.	RES-MS and SOT-RRMS, mean age = NR	Incremental QALYs: RES-RRMS Cladribine vs. ALZ = Company: 0.182; ERG: − 1.541 Cladribine vs. NTZ = Company: 0.512; ERG: − 1.650 Cladribine vs. DCZ = Company: 0.924; ERG: − 1.362 SOT-RRMS Cladribine vs. ALZ = Company: 0.153; ERG: 0.004 Cladribine vs. NTZ = Company: 0.944; ERG: 0.013 Cladribine vs. DCZ = Company: 0.548; ERG: 0.010	Incremental costs: RES-RRMS Cladribine vs. ALZ = base case: −£19,134; ERG scenario: £38,423 Cladribine vs. NTZ = Company: −£130,676; ERG: −£133,754 Cladribine vs. DCZ = Company: −£89,182; ERG: −£87,566; SOT-RRMS Cladribine vs. ALZ = Company: −£17,549; ERG: −£8,711 Cladribine vs. NTZ = Company: −£72,065; ERG: −6,642 Cladribine vs. DCZ = Company: −£66,397; ERG: −£7,749	RES-RRMS Cladribine vs. ALZ = Company: dominant; ERG: dominated Cladribine vs. NTZ = Company: dominant; ERG: £81,050 Cladribine vs. DCZ = Company: dominant; ERG: £64,269 SOT-RRMS: Cladribine was dominant throughout
Tempest et al. (2017)[165]	Scotland	Markov model, Health states defined by EDSS and death, 50-year time horizon.	RRMS, mean age = NR	Incremental QALYs DCZ-beta vs. FNG = −0.206	Incremental costs DCZ-beta vs. FNG = −£4,441	DCZ-beta was cost-effective using a willingness-to-pay threshold of £20,000/QALY. This finding was consistent across scenario analyses

Study (year)	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Herring et al. (2018)[166]	Scotland	Markov model. Health states. defined by EDSS and death	RRMS, mean age = NR	Incremental QALYs NTZ vs. FNG = 0.393	Incremental costs NTZ vs. FNG = −£19,148	NTZ remained dominant across scenarios compared with fingolimod
Rog et al. (2017)[167]	UK	Model type not reported, 50-year time horizon.	≥ 80% RRMS, mean age = NR	Incremental QALYs for ALZ ranged from 1.26 (NTZ) to 2.12 (SC IFNβ-1a 44 mcg).	Total cost per person for ALZ was £276,188; total costs per person for comparators ranged from £274,401 (GA) to £343,790 (NTZ), giving incremental costs for ALZ vs. comparators ranging from −£67,602 (vs. NTZ) to + £1,787 (vs. GA).	ICER for ALZ vs. GA is £863 per QALY

Study (year)	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Noon et al. (2018)[168]	UK	A Markov model and a DES model. 21 health states, 20 defined by EDSS and death. Lifetime time horizon.	Highly active RRMS, mean age = 38.23 years; RES-RRMS, mean age = 34.85 years	Incremental QALYs: FNG vs. DMF; Markov = 0.86 DES = 0.86 FNG vs. NTZ; Markov = −0.27 DES (no AEs) = −0.27 DES (with AEs) = −0.22 QALYs FNG vs. ALZ; Markov = −0.18 DES (no AEs, no retreatment) = −0.18 DES (with AEs, no retreatment) = −0.08 QALYs DES (with AEs, with retreatment) = −0.08 QALYs	Incremental costs: FNG vs. DMF; Markov: £3,608 DES: £3,356 FNG vs. NTZ; Markov: −£6,790 DES (no AEs): −£7,249 DES (with AEs): −£7,404 FNG vs. ALZ Markov: £40,442 DES (no AEs, no retreatment): £37,524 DES (with AEs, no retreatment): £37,074 DES (with AEs, with retreatment): £5,302	ICER: FNG vs. DMF; Markov: £4,206/QALY DES: £3,910/QALY FNG vs. NTZ: Markov: £25,412 cost saving per QALY lost DES: £34,209 cost saving per QALY lost FNG vs. ALZ: NR
Versteegh (2016)[169]	UK	Markov model 7 health states, 2 are based on relapses (mild and severe), 4 on EDSS levels and death. Lifetime time horizon.	RRMS, mean age = NR	Symptom management vs. GA Using EQ-5D-3L utilities Incremental QALYs = 0.16	Symptom management vs. GA, US $ Incremental costs = 25,277	Deterministic ICER (US $) = 153,476/QALY Probabilistic ICER (US $) = 140,735/QALY

AE = adverse event; ALZ = alemtuzumab; BSC = best supportive care; DCZ = daclizumab; DES = discrete event simulation; DMF = dimethyl fumarate; DMT = disease-modifying therapy; EDSS = expanded disability status scale; ERG = evidence review group; FNG = fingolimod; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFNβ-1a = interferon β-1a; IFNβ-1b = interferon β-1b; NHS = National Health Service; NR = not reported; NTZ = natalizumab; PegIFNβ-1a = pegylated interferon β-1a QALY = quality-adjusted life-year; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SOT = suboptimally treated; SPMS = secondary-progressive multiple sclerosis; UK = United Kingdom; US = United States.

B.3.2 Economic analysis

The previous NICE appraisals and combined literature on economic analyses in patients with RRMS informed the development of economic analysis for this submission.

B.3.2.1 Patient population

Data from the ADVANCE study were used in the base case to inform patient characteristics at baseline.[11] The population for this economic evaluation included adult patients (i.e., age 18 and older) with RRMS. The average age was 36 years and 29% of patients were male.[11]

As a scenario analysis, data from the UK RSS MTA assessment group report were used.[170] The mean age for the RSS population at baseline was 30 years, and 25% of patients were male.

In comparison with the UK RSS, ADVANCE is a recent trial where people with RRMS are treated earlier in their disease course. Therefore, ADVANCE is expected to have a higher proportion of patients with lower disease activity at baseline (EDSS < 4). This is confirmed by the baseline EDSS distribution, which was used as the starting distribution for the transition matrices (Table 24).

Table 24. Baseline EDSS distribution

EDSS	ADVANCE study – base case (cumulative %)	RSS MTA Assessment Group (cumulative %)
0	5.6% (5.6%)	3.2% (3.2%)
1-1.5	25.9% (31.5%)	16.3% (19.5%)
2-2.5	28.1% (59.6%)	25.8% (45.3%)
3-3.5	24.3% (83.9%)	23.0% (68.3%)
4-4.5	12.3% (96.2%)	15.5% (83.8%)
5-5.5	3.8% (100.0%)	10.5% (94.3%)
6-6.5	0.0% (100.0%)	5.7% (100.0%)
7-7.5	0.0% (100.0%)	0.0% (100.0%)
8-8.5	0.0% (100.0%)	0.0% (100.0%)
9-9.5	0.0% (100.0%)	0.0% (100.0%)

EDSS = Expanded Disability Status Scale; MTA = multiple technology appraisal; RSS = Risk Sharing Scheme.

B.3.2.2 Model structure

A Markov cohort model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA) to track the cohort's disease progression and costs throughout the time horizon. Main features of the model are provided in Figure 33. Every year (the cycle length), the model predicts disability progression (measured by EDSS and progression from RRMS to SPMS), the occurrence of relapses and other AEs according to the treatment received. The model then translates these predictions into QALYs and costs accumulated over the model time horizon (50 years). Health outcomes included life-years, QALYs, EDSS changes (CDP), RRs, disease progression rates from RRMS to SPMS, and treatment discontinuation. Cost outcomes included those for disease management, drug acquisition, administration and monitoring, relapses, and AE management pertinent to the NHS and PSS perspective. The incremental cost-effectiveness ratios (ICERs) for pegIFNβ-1a compared with other DMTs are reported.

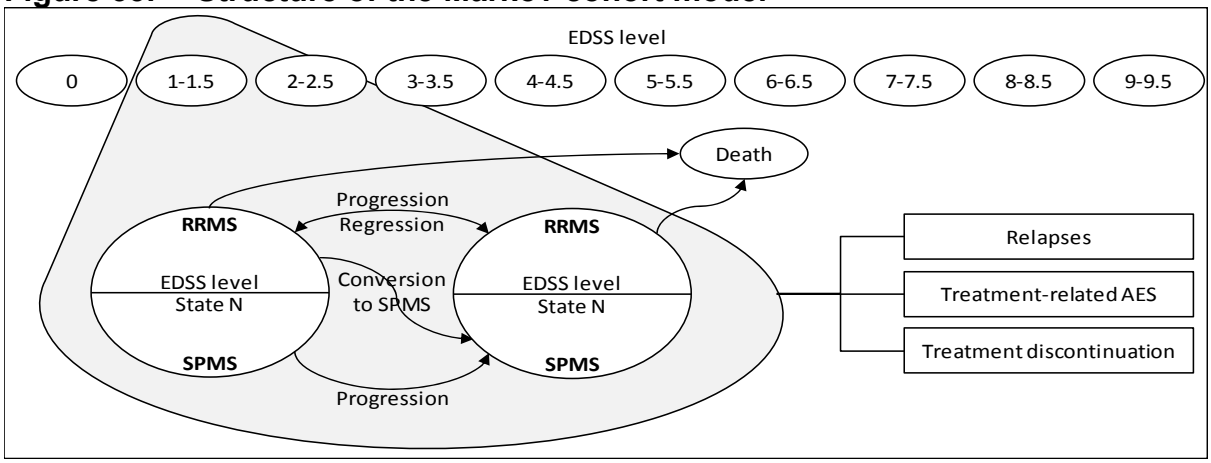
Figure 33 illustrates the model structure. The model includes 21 health states: RRMS EDSS levels 0, 1-1.5, 2-2.5, …, 9-9.5; SPMS EDSS levels 0, 1-1.5, 2-2.5, …, 9-9.5; and death (absorbing state). The cohort of patients, all with RRMS, starts with an initial EDSS distribution. Every year (model cycle length), patients with RRMS may:

- Remain at the same EDSS level with RRMS
- Progress to a higher EDSS level with RRMS (increasing disability)
- Improve to a lower EDSS level with RRMS (decreasing disability)
- Progress to the next EDSS level and to SPMS
- Die

Once patients progress to SPMS, they cannot return to a lower EDSS level or to RRMS; they can only stay at the same EDSS level, move to a higher EDSS level, or die. Patients can experience relapses at any time, with the risk of relapse based on disease phase (i.e., RRMS vs. SPMS) and EDSS level.

Treatment acts to delay disability (i.e., delay transitions to a higher EDSS level) and reduce the frequency of relapses. Patients receiving treatment can experience treatment-related AEs at any time, and can discontinue treatment due to various predefined rules (see Sections B.3.3.2.1 and B.3.3.2.4). After treatment discontinuation, patients are assumed to follow the natural disease progression course.

Figure 33. Structure of the Markov cohort model



AE = adverse event; EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; State N = current EDSS state.
Note; ovals represent health states. Rectangles represent events that patients could experience at any time. Treatment-related AEs and treatment discontinuation could only occur for patients receiving treatment.

Once the dispositions over time of both “on treatment” and “off-treatment” sub-cohorts are calculated, a half-cycle correction is applied to ensure that outcomes are neither under- nor overestimated. The half-cycle-corrected cohort dispositions are used to calculate life-years, costs, and QALYs. This is done by averaging the number of patients in each health state at the beginning and the end of the year each year.[171] Note however that the half-cycle correction was not implemented for the calculation of these outcomes for alemtuzumab and ocrelizumab, due to the particular dosing schedule of these DMTs. Alemtuzumab is administered during 5 consecutive days at the beginning of year 1 of treatment, and 3 consecutive days 1 year after; while ocrelizumab is administered as 600 mg every 6 months after two initial 300 mg doses at day 0 and day 14.

Table 25. Features of the economic analysis in this submission

Factor	Chosen values	Justification
Time horizon	50 years (lifetime)	NICE Reference Case,[172] ISPOR Good Practice Guidelines[173]
Cycle length	Annual	In line with the transition matrices for disease progression
Half-cycle correction	Yes	Mitigate bias due to cycle length
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE Reference Case[172]
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case[172]
Perspective (NHS/PSS)	Yes	NICE Reference Case[172]

ISPOR = International Society of Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life-year.

All life-years, QALYs, and costs are discounted by a user-specified discount rate (costs and health benefits: 3.5% in the base case).[172] Each cycle, these outcomes are multiplied by the discount factor calculated using the following formula: $(1 + r)^{-t}$, where *r* is the annual discount rate (for either health or cost outcomes) and *t* is the time from time zero in years.

Table 26 provides the main features of the economic analysis conducted in this dossier and in the recent relevant technology appraisals to NICE.

Table 26. Features of the economic analysis in this submission versus the previous NICE technology appraisals

	Previous appraisals*										Current appraisal	
Factor	**TA32**	**TA127**	**TA254**	**TA303**	**TA312**	**TA320**	**TA441**	**TA493**	**TA527**	**TA533**	**Chosen values**	**Justification**
Source of natural history EDSS	London, Ontario	Trial placebo arm for EDSS 0-6 - London, Ontario, for EDSS 7-9	London, Ontario	Trial placebo arm for EDSS 0-6 - London, Ontario, for EDSS 7-9 Committee considered EDSS improvements more appropriate	Trial placebo arm for EDSS 0-6 - London, Ontario, for EDSS 7-9 Committee considered EDSS improvements more appropriate	Trial placebo arm for EDSS 0-7 - London, Ontario, for EDSS 8-9	Trial placebo arm for EDSS 0-7 - British Columbia for EDSS 8-9 - placebo arm from different trials for highly active subgroup - as per TA127 for RES subgroup	BCMS[174]	BCMS[174]	BCMS[174]	BCMS for transitions across EDSS levels for patients with RRMS. London, Ontario, for transitions from RRMS to SPMS and during SPMS	In line with the majority of previous submissions
Source of natural history relapse	Patzold et al. (1982)[175], adjusted for EDSS distribution	Patzold et al. (1982)[175], combined with UK MS survey data - adjusted for RES using trial data	Patzold et al. (1982)[175], combined with UK MS survey data	Held (2005)[176], combined with Orme et al. (2007) data, divided by assumption about hospitalised vs. non-hospitalised	Held (2005)[176], combined with Orme et al. (2007) data, divided by assumption about hospitalised vs. non-hospitalised	Patzold et al. (1982)[175], combined with UK MS survey data	Trial data for EDSS 0-5 Patzold et al. (2005), combined with UK MS survey data for EDSS 6-9	CLARITY trial[41] and Tremlett et al. (2010)[177]	UK MS survey	Patzold et al. (1982)[175], combined with UK MS survey data	Patzold et al. (1982)[175], combined with UK MS survey data	In line with the majority of previous submissions
Source of MS mortality multiplier	Not applied	Pokorski (1997)[178]	Pokorski (1997)[178]	Pokorski (1997)[178], extrapolated for EDSS states	Pokorski (1997)[178], extrapolated for EDSS states	Pokorski (1997)[178], extrapolated for EDSS states	Pokorski (1997)[178], extrapolated for EDSS states	Jick et al. (2014)[77]	Not applied	Pokorski (1997), extrapolated for EDSS states	Pokorski (1997), extrapolated for EDSS states	In line with the majority of previous submissions
Application of treatment effect	Not reported	- ARR - CDP6M - SPMS transition	- ARR - CDP6M	- ARR - CDP6M - SPMS transition	- ARR - CDP6M - SPMS transition	- ARR - CDP6M	- ARR - CDP6M (if available, otherwise CDP3M)	- ARR - CDP6M	- ARR - CDP6M - SPMS transition	- ARR - CDP3M - SPMS transition	- ARR - CDP6M - SPMS transition	In line with the majority of previous submissions
Model structure	Unknown	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	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 health states (31 when RRMS DMT and RRMS BSC health states are considered separately) based on 10 EDSS states for each of RRMS DMT, RRMS BSC and SPMS BSC, and death	21 health states (the same as TA527 submissions)	In line with the majority of previous submissions

	Previous appraisals*										Current appraisal	
Factor	**TA32**	**TA127**	**TA254**	**TA303**	**TA312**	**TA320**	**TA441**	**TA493**	**TA527**	**TA533**	**Chosen values**	**Justification**
Time horizon	20 years	20 years, but committee considered longer time horizon more appropriate	50 years	50 years	50 years	30 years	50 years	50 years	50 years	50 years	50 years	In effect, a lifetime horizon, in line with the majority of previous relevant TAs, NICE Reference Case[172], ISPOR Good Practice Guidelines[173]
Treatment waning effect	Not applied	Not applied	50% waning after 5 years	25% waning after 2 years and 50% after 5 years	25% waning after 2 years and 50% after 5 years, time-dependent rate of retreatment	25% waning after 2 years and 50% after 5 years	25% waning after 2 years and 50% after 5 years	25% waning after 2 years and 50% after 5 years	25% waning after 2 years and 50% after 5 years	25% waning after 2 years and 50% after 5 years	25% waning after 2 years and 50% after 5 years	In line with the majority of previous submissions
Application of treatment withdrawal	Trial data, assumed higher for years 1-2 than years 2+	Trial data, constant annualised rates for 10 years	Trial data (discontinuation due to AEs), constant annualised rates	Trial data (all-cause discontinuation), constant annualised rates for year 1-2, 50% applied for year 2+	Trial data (all-cause discontinuation), constant annualised rates for year 1-2, 50% applied for year 2+	Trial data (all-cause discontinuation), constant annualised rates	Trial data (all-cause discontinuation rates year 1, 2, 3), year 3+ based on year 3 rate	Trial data (all-cause discontinuation), constant annualised rates	UK MS survey, Tappenden et al. (2001)	Trial data (all-cause discontinuation), constant annualised rates	Trial data (all-cause discontinuation), constant annualised rates	In line with the majority of previous submissions
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)	- 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	In line with the majority of previous submissions
Source of patient utilities	Kobelt et al. (2000)	UK MS survey (2005) (later published by Orme et al., 2007)[78]	UK MS survey (2005) (later published by Orme et al., 2007)[78]	Trial data and Orme et al. (2007)[78]	Trial data and Orme et al. (2007)[78]	Trial data and Orme et al. (2007)[78]	BOI study, 2015 (not published)	Trial data, Hawton et al. (2016a)[179] and Orme et al. (2007)[78]	Orme et al. (2007)[78]	Trial data and Orme et al. (2007)[78]	Trial data and Orme et al. (2007)[78]	In line with the majority of previous submissions

	Previous appraisals*										Current appraisal	
Factor	**TA32**	**TA127**	**TA254**	**TA303**	**TA312**	**TA320**	**TA441**	**TA493**	**TA527**	**TA533**	**Chosen values**	**Justification**
Source of relapse disutilities	Parkin et al. (2000)	UK MS survey (2005) (published by Orme et al., 2007)[78], adjusted with trial data for EDSS specific disutilities	Orme et al. (2007)[78]	Orme et al. (2007)[78] (non-hospitalised), Prosser et al. (2003) (hospitalised)	Orme et al. (2007)[78] (non-hospitalised), Prosser et al. (2003) (hospitalised)	UK MS survey, 2005 (published by Orme et al., 2007)[78]	BOI study, 2015 (not published)	Orme et al. (2007)[78]	Not applied	Orme et al. (2007)[78]	Orme et al. (2007)[78]	In line with the majority of previous submissions
Source of caregiver disutilities	Not applied	Loveman et al. (2006) and UK MS survey data	Loveman et al. (2006) and UK MS survey data	Loveman et al. (2006) and UK MS survey data	Loveman et al. (2006) and UK MS survey data	Loveman et al. (2006) and UK MS survey data	Maximum disutility reduced	No caregiver disutilities	Acaster et al. (2013)[180]	Loveman et al. (2006) and UK MS survey data	Acaster et al. (2013)[180]	In line with TA527 that provides the most up-to-date relevant source
Source of EDSS costs	Kobelt et al. (2000), direct costs for EDSS 0-7, direct + indirect costs for EDSS 8-9	UK MS survey (2005), direct medical and non-medical (NHS & PSS) (later published by Tyas et al., 2007)[83]	UK MS survey (2005), direct medical and non-medical (NHS & PSS) (later published by Tyas et al., 2007)[83]	Tyas et al. (2007)[83] (direct medical and midpoint of non-medical)	Tyas et al. (2007)[83] (direct medical only)	UK MS survey (2005) (NHS & PSS)	BOI study, 2015 (not published), direct medical and partial non-medical)	TA32	Tyas et al. (2007)[83]	Tyas et al. (2007)[83]	UK MS survey (2005) (direct medical only), inflated to 2019	In line with the latest submissions
Source of relapse costs	Not reported	UK MS survey (2005), (later published by Tyas et al., 2007)[83]	Tyas et al. (2007)[83]	Dee et al. (2012)	Dee et al. (2012)	UK MS survey (2005)	BOI study, 2015	Not reported	Tyas et al. (2007)[83]	Tyas et al. (2007)	Tyas et al. (2007)[83]	In line with the majority of previous submissions

AE = adverse event; ARR = annualised relapse rate; BCMS = British Columbia Multiple Sclerosis; BOI = burden of illness; BSC = best supportive care; CDP3M = confirmed disability progression sustained for 3 months; CDP6M = confirmed disability progression sustained for 6 months; DMT = disease-modifying therapy; 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; pegIFN = pegylated interferon; PSS = personal social services; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis TA = technology appraisal.
* The values for TA32, TA127, TA254, TA303, TA312, TA320, and TA441 are based on the committee papers of TA493 (Table 59) and TA533 (Table 25). The values for TA493, TA527, and TA533 reflect the preferences of the assessment groups and are based on the committee papers for each submission.

B.3.2.3 Intervention technology and comparators

As per the NICE scope, the cost-effectiveness analysis estimates the cost-effectiveness of pegIFNβ-1a compared with other DMTs available in the UK. The list of comparators are listed with the dosing schedules below:

- PegIFNβ-1a (Plegridy®): 125 µg Q2W, Biogen Idec
- IM IFNβ-1a 30 (Avonex®): 30 µg QW, Biogen Idec
- IFNβ-1a 22 (Rebif®): 22 µg TIW, EMD Serono Inc
- IFNβ-1a 44 (Rebif®): 44 µg TIW, EMD Serono Inc
- IFNβ-1b (Extavia®): 250 µg every other day, Novartis Pharmaceuticals Corporation
- GA 20 mg (Copaxone®): 20 mg once daily, Teva Pharmaceutical Industries Ltd
- GA 40 mg (Copaxone®): 40 mg once daily, Teva Pharmaceutical Industries Ltd
- Generic glatiramer acetate (genGA) 20 (Brabio®): 20 mg once daily, Generics [UK] Limited t/a Mylan
- genGA 40 (Brabio®): 40 mg once daily, Generics [UK] Limited t/a Mylan
- teriflunomide (Aubagio®): 14 mg once daily, Genzyme Corporation
- DMF (Tecfidera®): 240 mg twice daily, Biogen Idec
- alemtuzumab (Lemtrada®): 12 mg once daily, 5-days year 1, 3 days year 2, Genzyme Corp
- Ocrelizumab (Ocrevus®): 600 mg, every 6 months, Genentech

Comparators that are recommended for highly active RRMS (fingolimod [Gilenya®] and cladribine [Mavenclad®]) and RES-RRMS (natalizumab [Tysabri®]) only have not been included in the cost-effectiveness analyses because pegIFNβ-1a is not used in this population in clinical practice.

B.3.3 Clinical parameters and variables

B.3.3.1 Derivation of clinical outcomes

B.3.3.1.1 Transition probabilities within RRMS

The transition of patients between each RRMS EDSS state was modelled using a Markov state transition matrix. The dimension of the transition matrix was 10 × 10 (EDSS 0-9) with death accounted for separately (equivalent to EDSS 10).

Transition matrices for the natural history were identified from, and are aligned with, recent previous NICE appraisals (see Table 26).

The scientific advisory group (SAG) to the UK RSS scheme conducted a critical appraisal of natural history data sets within MS. Literature reviews and clinical expert opinion were implemented to examine available patient registries that considered the availability of EDSS score measurements, the use of data smoothing or manipulation, the size of the database, and applicability to the UK health system to determine a preferred data set. Table 27 below outlines key characteristics of the two largest natural history data sets available.

Table 27. Comparison of London, Ontario, and British Columbia[174] data sets

London, Ontario	British Columbia
Widely used in previous models	Recent publication
N = 345	N = 898
Longitudinal data set from MS clinic in Canada	Longitudinal data set from MS clinic in Canada
Patients followed up 1972-1989	Patients followed up 1980-1995
Smoothed disability data censored improvements in EDSS	Improvement in EDSS allowed
No transitions from EDSS 0 or EDSS 9	Contains transitions from all states
May have more rapid progression than clinical trials	May be subject to same limitations as London, Ontario
Separate transition matrices for RRMS and SPMS	Contains RRMS and SPMS patients (SPMS 15.7% at baseline)

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

Comparison of the transition matrices demonstrates that:

- The probability of remaining in the same EDSS state in each cycle is between 0.1 and 0.3 higher in London, Ontario, than British Columbia (for all EDSS states). This difference is likely to be partially because British Columbia allows for patients to transition to a lower EDSS state (improvement in disability).
- The probability of changing by one EDSS state is similar for London, Ontario, and British Columbia (magnitude of difference is up to 0.1, direction varies).
- In both data sets, the probability of staying in the same EDSS state is higher in EDSS states between 5.5 and 9.5 than in the lower EDSS states. This is likely to be due to the non-linearity of the EDSS scale.

The RSS SAG scored the British Columbia Multiple Sclerosis (BCMS) data set highly in terms of the methodology used to capture EDSS score (EDSS prospectively captured) and registry completeness (an estimated 80% coverage of the BCMS population). The SAG concluded that the BCMS data set was the best natural history Markov state transition matrix for untreated patients who could be used as a historical control in the economic model, relevant to the UK context, and was therefore considered the preferred data set for this appraisal.

Cleaning procedures were applied to ensure disability progression or regression were independent of relapses in the untreated natural history and reflective of the UK context. Patients were eligible for inclusion in the data set if they met the ABN criteria for treatment with IFN or GA, i.e., adult with an EDSS score no worse than 6.5 and at least two relapses in the previous two calendar years. Data were truncated at the end of 1995, this being the last year when DMTs were not widely available in British Columbia. Data were also excluded if EDSS scores were collected at the time of relapses or disability levels could have been affected by confounding factors (e.g., fractures). Finally, data underlying the transition matrix probabilities were not truncated if a patient moved into SPMS.

Two models (discrete and continuous time multi-state methods, with and without baseline covariates [e.g., sex, age at MS onset, and disease duration]) were implemented to derived transition probabilities. Ultimately the continuous time model was used in this appraisal due to the poor fit of the discrete model (underestimating EDSS in earlier years vs.

overestimation in later years). Moreover, the model containing onset age as a binary covariate was deemed the most suitable model for the RSS analysis. This led to two matrices conditional on median age of onset of < 28 years of age (data not shown) or ≥ 28 years of age. Given the mean age of the patients simulated in the model (36 years), the transition matrices used for patients ≥ 28 years of age on RRMS EDSS levels were from the BCMS data set.[195] The resulting natural history matrix has non-zero elements below its diagonal, reflecting the assumption that patients can improve to a lower EDSS level within the RRMS phase of the disease (Table 28).

Table 28. British Columbia transition probability matrix (≥ 28 years)

	EDSS at year x+1										
	0	**1-1.5**	**2-2.5**	**3-3.5**	**4-4.5**	**5-5.5**	**6-6.5**	**7-7.5**	**8-8.5**	**9-9.5**	**Total**
0	0.6954	0.2029	0.0725	0.0217	0.0042	0.0014	0.0018	0.0001	0.0000	0.0000	1.0000
1-1.5	0.0583	0.6950	0.1578	0.0609	0.0164	0.0046	0.0064	0.0005	0.0001	0.0000	1.0000
2-2.5	0.0159	0.1213	0.6079	0.1680	0.0446	0.0185	0.0216	0.0017	0.0005	0.0000	1.0000
3-3.5	0.0059	0.0496	0.1201	0.5442	0.0911	0.0585	0.1165	0.0103	0.0036	0.0003	1.0000
4-4.5	0.0017	0.0221	0.0666	0.1152	0.4894	0.1039	0.1681	0.0258	0.0067	0.0006	1.0000
5-5.5	0.0005	0.0053	0.0294	0.0587	0.0874	0.4870	0.2731	0.0388	0.0188	0.0010	1.0000
6-6.5	0.0001	0.0013	0.0044	0.0250	0.0307	0.0408	0.7407	0.1090	0.0438	0.0042	1.0000
7-7.5	0.0000	0.0002	0.0005	0.0025	0.0073	0.0039	0.1168	0.6927	0.1606	0.0156	1.0000
8-8.5	0.0000	0.0000	0.0000	0.0003	0.0006	0.0005	0.0188	0.0557	0.9034	0.0207	1.0000
9-9.5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0018	0.0057	0.1741	0.8183	1.0000

EDSS = Expanded Disability Status Scale.

B.3.3.1.2 Transition probabilities from RRMS to SPMS

Transition probabilities describing the probability of progressing from RRMS to SPMS health states are detailed in Table 29. These probabilities are applied to the RRMS population in order to estimate the proportion of patients who are expected to progress to SPMS for each annual cycle. Upon progression, the EDSS state is assumed to increase by 1 during the given cycle (e.g., from EDSS 5 to EDSS 6) consistent with prior technology appraisals. The RRMS to SPMS transition probabilities are estimated from hazards presented in the appendix to the original 2002 MTA report (extracted from the Evidence Review Group [ERG] report for daclizumab [TA441] which was based on the London, Ontario, data set). The hazards were converted to probabilities using:

$$p = 1 - exp(-h).$$

Corresponding values are not available in BCMS. Despite the transition matrix probabilities reported in Palace et al. (2014)[174] considering a range of covariates (as described in Section B.3.3.1.1), it does not appear that transition into SPMS was included in these covariates. Furthermore, their baseline population included 15.7% patients with SPMS. Therefore, an argument could be made that efforts to delineate between RRMS and SPMS in a model based on these transition probabilities matrices may not be warranted and EDSS progression could be exaggerated by assuming a worsening by one EDSS upon SPMS transition. Although Biogen believes the approach taken in the base case is valid and consistent with prior technology appraisals, a key scenario analysis where the probability of conversion from RRMS to SPMS is set to zero for all EDSS states has been provided (in essence collapsing the 21-health state model into an 11-health state model).

Table 29. London, Ontario natural history transition probabilities from RRMS to SPMS

EDSS[a]	Hazards	Probability
0	0.004	0.004
1-1.5	0.002	0.002
2-2.5	0.030	0.029
3-3.5	0.103	0.097
4-4.5	0.199	0.181
5-5.5	0.256	0.225
6-6.5	0.184	0.168
7-7.5	0.237	0.211
8-8.5	0.066	0.064
9-9.5	0.167	0.154

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
[a] EDSS level goes up by one for each transition.

B.3.3.1.3 Transition probabilities within SPMS

When patients move to SPMS, their transitions are governed by a natural history transition probability matrix between EDSS levels within SPMS. This matrix is upper-triangular (i.e., with zero elements below the diagonal), reflecting the assumption that patients cannot improve to a lower EDSS level while in the SPMS phase as per the clinical definition. These transition probabilities are shown in Table 30, were obtained from the London, Ontario, data set, and are consistent with previous technology appraisals where SPMS has been modelled separately to RRMS.[181]

Table 30. London, Ontario SPMS natural history transition probability matrix

EDSS at year x	EDSS at year x+1										Total
	0	1-1.5	2-2.5	3-3.5	4-4.5	5-5.5	6-6.5	7-7.5	8-8.5	9-9.5	
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	N/A
1-1.5	0.0000	0.7692	0.1538	0.0769	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
2-2.5	0.0000	0.0000	0.6357	0.2713	0.0620	0.0233	0.0078	0.0000	0.0000	0.0000	1.0000
3-3.5	0.0000	0.0000	0.0000	0.6291	0.2527	0.0769	0.0330	0.0027	0.0055	0.0000	1.0000
4-4.5	0.0000	0.0000	0.0000	0.0000	0.4854	0.3504	0.1387	0.0073	0.0182	0.0000	1.0000
5-5.5	0.0000	0.0000	0.0000	0.0000	0.0000	0.6325	0.3173	0.0221	0.0261	0.0020	1.0000
6-6.5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.7631	0.1903	0.0446	0.0020	1.0000
7-7.5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8046	0.1891	0.0062	1.0000
8-8.5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9258	0.0742	1.0000
9-9.5	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	1.0000

EDSS = Expanded Disability Status Scale; N/A = not applicable; SPMS = secondary-progressive multiple sclerosis.

B.3.3.1.4 Relapse rates

The natural history ARRs are specific to each EDSS level and to whether a patient is in the RRMS or SPMS phase. For the off-treatment sub-cohort (those who discontinue treatment due to any reason, including AEs, lack of efficacy, or clinical trial protocol discontinuation rules [i.e., overall discontinuation]), the natural history ARRs are applied to the number of patients who are alive and who have discontinued treatment at each cycle. For the on-treatment sub-cohort (patients who remain on treatment), a rate ratio relative to placebo is applied to the natural history ARRs, which is then applied to the number of patients alive and on treatment at each cycle.

The UK MS Survey[78,83] provides the total number of patients who experienced a relapse by EDSS health state by years since diagnosis. Patzold (1982)[175] conducted a regression analysis to investigate the relationship between the mean annual ARRs and the number of years since diagnosis. The annualised natural history ARRs by EDSS level are shown below (Table 31) and are consistent with approaches in prior technology appraisals.

Table 31. RRMS and SPMS natural history ARRs: UK MS survey and Patzold (1982)

EDSS	ARRs RRMS	ARRs SPMS
0	0.709	0.000
1-1.5	0.729	0.000
2-2.5	0.676	0.465
3-3.5	0.720	0.875
4-4.5	0.705	0.545
5-5.5	0.591	0.524
6-6.5	0.490	0.453
7-7.5	0.508	0.340
8-8.5	0.508	0.340
9-9.5	0.508	0.340

ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; UK = United Kingdom.

B.3.3.2 Calculation of patient disposition over time

The disposition of the cohort (i.e., distribution of patients throughout the health states of the model) must be calculated over time to calculate the costs, life-years, and QALYs. The cohort of patients is divided into two sub-cohorts:

- On-treatment sub-cohort
- Off-treatment sub-cohort

Each cycle, the disposition for the on-treatment sub-cohort is recalculated using the following steps:

1. Patients who have discontinued treatment are moved to the off-treatment sub-cohort.
2. Patients who die are taken out of the cohort.
3. Relapses are calculated.
4. The transition probability matrix is applied.

5. Patients who discontinued due to progression to an EDSS level higher than a user-specified threshold (e.g., EDSS ≥ 7) were moved to the off-treatment sub-cohort.
6. Patients who discontinued due to progression to SPMS are moved to the off-treatment sub-cohort.

The disposition for the sub-cohort of patients who discontinued treatment is recalculated similarly:

1. Patients who discontinued treatment each year are added to the off-treatment sub-cohort from the on-treatment sub-cohort.
2. Patients who died are taken out of the cohort.
3. Relapses are calculated.
4. The transition probability matrix is applied (the natural history transition probability matrix).
5. Patients who discontinued due to progression to an EDSS level higher than a user-specified threshold were added to the off-treatment sub-cohort from the on-treatment sub-cohort.
6. Patients who discontinued due to progression to SPMS are added to the off-treatment sub-cohort from the on-treatment sub-cohort.

B.3.3.2.1 Treatment discontinuation

The model considers an annual risk of treatment discontinuation for each comparator. The probability of discontinuation was derived from the all-cause discontinuation rates reported in trials used in the network meta-analysis for ARR (Section B.2.6).

It should be noted that the all-cause discontinuations used in the economic model included the proportion of patients who discontinued the study drug for any reason such as AEs, lost to follow-up, investigator decision, or withdrew consent. With pegIFNβ-1a, 65% of the patients who discontinued did so due to non–AE-related reasons (50/74), of which 47% were due to withdrawn consent. As a result, a scenario analysis is presented that included annual risk of discontinuation due to adverse drug reactions only.

Of the 23 studies included in the network, only 18 reported outcome data for all-cause discontinuation. The probabilities reported in the individual studies were converted to annualised probabilities (aligned with the model cycle length) using the following equation:

$$P = 1 - (1 - \mathrm{p})\text{^}\mathrm{t}$$

where *t* is study follow-up time in weeks and *P* is the probability of discontinuation. The weights used to derive the treatment discontinuation for each DMT were based on sample size from each trial included in the analysis. The weights used for each study in the derivation of the discontinuation risk are shown in Appendix M. In addition, the annual discontinuation risk for each treatment option based on studies being included in ARR MTC network (as this is the most complete network) and are provided in Appendix M. To assess the impact of discontinuation rates on cost-effectiveness estimates, a scenario analysis using a parity rate of 5% per annum for all treatments is considered aligned with the assessment group report for TA527; however, as acknowledged within that report, there is little evidence to support this assumption.

The proportion of patients who discontinue each year is calculated by applying the risk of discontinuation directly to the number of patients on treatment at the beginning of that year. The patients who discontinue are then shifted from the on-treatment sub-cohort to the off-treatment sub-cohort for the next year onward.

Table 32 shows the annual risk of overall treatment discontinuation for each treatment.

Table 32. Annual risk of treatment discontinuation (all-cause discontinuation)

Treatment	Annual risk (all-cause discontinuation)	Annual risk due to ADRs	Sources
PegIFNβ-1a	15.56%	5.28%	ADVANCE[182]
IM IFNβ-1a 30	7.88%	3.07%	Calabrese (2012)[183], CombiRx,[184] EVIDENCE[185], BRAVO[186], INCOMIN[187]
IFNβ-1a 22	6.00%	1.60%	PRISMS[188]
IFNβ-1a 44	10.85%	3.81%	Calabrese (2012)[183], EVIDENCE[185], OPERA I & II[189], CARE MS I[190], CARE MS II[191], REGARD[192]
IFNβ-1b	6.87%	1.27%	IFNB MS Study[155], BEYOND[193], INCOMIN[187]
GA 20	9.72%	2.48%	BEYOND[193], CONFIRM[125], Copolymer 1 Study[194], REGARD[192], Bornstein[195]
GA 40	8.91%	3.08%	GALA[196]
genGA 20	9.72%	2.48%	Assumed equivalent to Copaxone® 20
genGA 40	8.91%	3.08%	Assumed equivalent to Copaxone® 40
teriflunomide	18.57%	7.84%	TOWER[140], TEMSO[197]
DMF	18.01%	7.95%	CONFIRM[125], DEFINE[127]
alemtuzumab	2.46%	1.19%	CARE MS I[190], CARE MS II[191]
ocrelizumab	6.69%	1.92%	OPERA I & II[189]

ADR = adverse drug reaction; GA = glatiramer acetate; genGA = generic glatiramer acetate; IFNβ-1a = interferon β-1a, IFNβ-1b = interferon β-1b; IM = intramuscular; PegIFNβ-1a = pegylated interferon β-1a; SC = subcutaneous.

B.3.3.2.2 Mortality

Mortality is accounted for using all-cause mortality risks, specific to age and gender[198] and adjusted with different relative risks (for each EDSS level independent of RRMS versus SPMS due to lack of evidence suggesting a differential mortality risk). First, the model derives a weighted mortality risk for each age from the male and female mortality risks by age. This is weighted according to the proportion of males and females in the model cohort (a user input). At the beginning of the model, the mortality risk corresponding to the baseline age of the cohort (also a user input) is adjusted by relative risks for MS. Either the overall relative risk for all patients with MS (scenario analysis) or individual relative risks for each EDSS (irrespective of RRMS versus SPMS) are applied to the all-cause mortality risk. This is then applied to the number of patients alive at the beginning of the year. This calculation is carried out for the on- and off-treatment sub-cohorts. Once patients die, they accrue no more costs, utilities, or life-years in the model.

Age- and gender-specific all-cause mortality risks for the general population were obtained from the Office for National Statistics UK (2016).[198] The all-cause mortality risk is adjusted by applying a disease-specific relative risk.

The relative risks are from Pokorski (1997)[178], a Canadian study including 2,348 patients followed in MS specialty clinics between 1972 and 1985. Pokorski reports a standardised mortality ratio (SMR) by EDSS level, which were used in the base case to adjust the all-cause mortality risks in the general population where the SMR increases with increases in EDSS states, which aligns with the natural history of MS (Table 33). Use of Pokorski has

been previously critiqued as potentially overestimating mortality for the following key reasons: (1) the study is dated and there are large difference in smoking prevalence rates versus the present day and (2) there is now improved care for MS with a relatively high uptake of DMTs, which manage MS more effectively. Despite these limitations, it has been the preferred committee assumption for mortality in prior technology appraisals.

Other sources considered included a study by Jick et al. (2014)[77], who reported mortality for the largest sample of people with MS (N = 1,822) covering mortality across multiple regions of the UK and had a good follow-up (14,295 person-years), with a total number of deaths of 130, resulting in a mortality ratio of 1.68 (95% CI, 1.38-2.05). Another study by Kingwell et al. (2012)[76] reported mortality of 6,917 patients (89% relapsing onset) with MS from the BCMS data set between 1980 and 2004. The total number of deaths were 1,025, which resulted in an overall SMR of 2.89 (95% CI, 2.71-3.07). Use of single SMRs has been previously critiqued for underestimating mortality, most notably in the higher EDSS state where patients typically accrue higher health state costs. To assess the impact of varying SMRs, the values from Kingwell et al. (2012)[76] were used in scenario analyses as this more aligned with the natural history transition matrices and had a larger population and a higher SMR than Jick et al. (2014)[77].

Table 33. Relative risks for MS mortality

EDSS	Relative risk
1-3.5	1.6000
4-6.5	1.8400
7+	4.4400

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

B.3.3.2.3 Transitions between Health States

After mortality is applied and patients who discontinue treatment are moved to the off-treatment sub-cohort, the transition probabilities are applied to derive:

- The number of patients in each EDSS level who move within RRMS
- The disposition of patients who move to SPMS (no patients can regress from SPMS to RRMS)
- The number of patients in each EDSS level within SPMS

B.3.3.2.4 Stopping rules

Patients stop treatment when they reach EDSS level ≥ 7 and/or progress to SPMS. After the transition probabilities are applied, any patients in the on-treatment sub-cohort who transition to an EDSS level ≥ 7 are moved to the off-treatment sub-cohort. Similarly, any patients in the on-treatment sub-cohort who progress to SPMS are also moved to the off-treatment sub-cohort. The natural history ARRs and BCMS data set are applied to off-treatment sub-cohorts aligned with prior technology appraisals. Treatment sequencing has not been considered as this would favour DMTs with higher discontinuation rates that would transition to higher efficacy treatments in subsequent treatment lines and demonstrate more favourable cost-effectiveness outcomes.

B.3.3.2.5 End of year

After applying each of the changes listed above (in the listed order), the model arrives at the disposition at the end of the year for both sub-cohorts. The disposition (i.e., distribution of patients across the health states) for the beginning of the next year is then set equal to the

end-of-year disposition of the previous year, and the model moves through the transitions explained above until the end of the user-specified model time horizon (maximum: 50 years).

B.3.3.3 Treatment effects on disability progression and relapse frequency

B.3.3.3.1 Disability progression

The model includes an HR comparing the CDP of a specific treatment to progression with no treatment. To derive the transition probability matrices for the active treatments, the MTC treatment-specific HR for CDP3M or CDP6M is applied to the best supportive care transition probability matrix probabilities of worsening; i.e., to all the probabilities above the principal diagonal. The probabilities of remaining in the same health state, are then increased so as to make the rows sum to unity. The probabilities of improving are assumed to be the same for the active treatment as for the natural history (i.e., no treatment).

Once patients discontinue treatment, they are no longer exposed to any treatment effect and follow the BCMS transition probabilities.

Data from the MTC informed the relative efficacy (Section B.2.9.3). The median HRs for CDP relative to placebo at 3 and 6 months are shown in Table 34. For the base case, CDP6M was implemented as this is considered a more robust outcome (indicative of permanent disability progression) than CDP3M (which can be influenced by relapse activity) by regulatory bodies and is also the preference for committee assumptions in prior technology appraisals. Scenario analyses are also presented for CDP3M to allow for comparisons against technologies excluded using CDP6M.

Table 34. MTC: CDP HR versus placebo at 3 and 6 months

Treatment	3 months	3-month 95% CI	6 months (base case)	6-month 95% CrI
PegIFNβ-1a	[redacted]	[redacted]	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]	[redacted]
GA 40	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 20	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 40	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

CDP = confirmed disability progression; CrI = credible interval; HR = hazard ratio; MTC = mixed-treatment comparison; NA = not available.
* Assumed equivalent to GA 20 due to the absence of disability progression data.
Note: values that are less than 1 indicate favourable efficacy for treatment versus placebo.

B.3.3.3.2 Treatment waning

Despite no published literature supporting the waning of treatment effect over the long-term and clinical consensus that perceived lack of efficacy is highly likely to be a reflection of underlying disease progression, all previous appraisals since TA254 have included this feature to reflect uncertainty in the long-term benefits of DMTs upon request of the committee.

Consistent with these prior appraisals, the waning effect has been included in the base-case analysis and is applied by adjusting the HR for CDP in a step-wise manner using the following equation and proportions in Table 35.

$$CDP\ HR\ waning\ =\ 1-\ (1-\ CDPHR\ mtc)\ \times\ proportion\ of\ effect\ remaining$$

Table 35. Treatment waning - proportion of CDP treatment effect by year

Year	Proportion of treatment effect
0-2	100%
2-5	75%
5+	50%

Scenario analyses excluding treatment waning are also presented.

B.3.3.3.3 Relapses

The number of relapses is calculated during each cycle. The natural history (i.e., no treatment) ARRs are adjusted by a treatment-specific rate ratio to derive the rate of relapse for patients on treatment; this is done similar to the way that the natural history transition rates between EDSS levels are adjusted during RRMS.

A median rate ratio comparing the ARRs of each treatment relative to placebo is used to adjust the RR for the treatment effect using data from the MTC (Table 36). Consistent with prior technology appraisal, treatment waning is not assumed to impact the treatment effect on RRs.

Table 36. Rate ratio on ARRs versus placebo

Treatment	Rate ratio on ARR	95% CrI
PegIFNβ-1a	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]
GA 20	[redacted]	[redacted]
GA 40	[redacted]	[redacted]
GenGA 20	[redacted]	[redacted]
GenGA 40	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
DMF	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]

ARR = annualised relapse rate; CrI = credible interval; NA = not available; SC = subcutaneous.
Note: values that are less than 1 indicate favourable efficacy for treatment vs. placebo.

B.3.4 Measurement and valuation of health effects

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

The relevant model parameters for the cost-effectiveness analysis conducted relied on the information from the relevant literature.

B.3.4.2 Mapping

Utility values used to inform the cost-effectiveness analyses were based on two studies[78,180] that used EQ-5D instrument to elicit the utility values directly, which aligns with the NICE reference case and negates the need for mapping.[172]

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

An SLR to identify health-related QOL studies (Appendix H) was performed as part of the SLR described in Section B.3.1 using the inclusion and exclusion criteria and the search strategy presented in Appendix H.

A total of 29 studies were identified that met the eligibility criteria for the review. Of these, 11 presented utilities by EDSS score. Two publications specified UK studies (Kobelt et al., 2017[71]; Thompson et al., 2017[199]); however, as both had the same population samples and mean EDSS scores, it was deemed that the relevant information reported should be based on the same sample (Table 37). In line with the previous NICE technology appraisals, utility data from Orme et al.'s (2007)[78] study has been used to inform the patient utility values and data from Acaster et al. (2013)[180] were used to inform caregiver disutility values in the model in this submission.

Table 37. Summary list of published HRQOL studies

Study (ID)	Country	Study details[a]	Methods of elicitation and valuation[b]	Health state description	Mean (SD) utility estimate
Daigl et al. (2016)[200] Value in Health Ref ID 425	US populations	Evaluates health utilities at different stages of RRMS by studying the relationship between EDSS and EQ-5D using data from OPERA I and II	EQ-5D administered at baseline, 48 and 96 weeks, value set not reported	EDSS states from 0-7 representing different stages of RRMS	EDSS 0: 0.88 (95% CI, 0.85-0.91) EDSS 1: 0.84 (95% CI, 0.83-0.86) EDSS 2: 0.77 (95% CI, 0.76-0.78) EDSS 3: 0.70 (95% CI, 0.69-0.72) EDSS 4: 0.64 (95% CI, 0.63-0.66) EDSS 5: 0.60 (95% CI, 0.57-0.63) EDSS 6: 0.49 (95% CI, 0.45-0.53) EDSS 7: 0.44 (95% CI, 0.24-0.63) Authors state, "these results are comparable with previous published data" (Orme et al., 2007)[78].
Brola et al. (2017)[201] Poland Ref ID 365	Poland	765 MS patients with average EDSS score of 3.8 +/- 2.3. Proportions of patients with RRMS were 65.2%, SPMS were 26.6%, and PPMS were 8.3%	Polish version of the EQ-5D, standardised for the general Polish population.	EDSS (mild = 0.0-3.5, moderate or severe = ≥ 4)	EDSS 0.0-3.5: 0.72 (0.36) EDSS ≥ 4.0: 0.54 (0.16)

Study (ID)	Country	Study details[a]	Methods of elicitation and valuation[b]	Health state description	Mean (SD) utility estimate
Gyllentsen et al. (2018)[202] Ref ID = 43	Sweden	To estimate the HRQOL, by disability levels, among MS patients	EQ-5D-3L direct measurement. UK tariff and Swedish tariff used.	EDSS categorised into ≤ 3.5, 4-5.5, 6-6.5, and ≥ 7, representing different disability levels	EDSS 0-3.5: Swedish experience-based index value: 0.867 (95% CI, 0.860-0.873); UK general population-based index values: 0.766 (0.753-0.778); EDSS 4-5.5: Swedish: 0.752 (95% CI, 0.735-0.768); UK: 0.579 (0.541-0.616); EDSS 6-6.5: Swedish: 0.724 (95% CI, 0.704-0.745); UK: 0.526 (0.476-0.576); EDSS 7-9.5: Swedish: 0.626 (95% CI, 0.584-0.668); UK: 0.141 (0.019-0.264); All MS patients with EQ-5D responses = Swedish: 0.836 (95% CI, 0.830-0.842); UK: 0.709 (0.697-0.722);
Flachenecker et al. (2017)[203] Ref ID: 375.	Germany	5,475 MS patients with phenotypes including RRMS, SPMS, and PPMS. Mean EDSS (SD) of 4.0 (2.5)	Utility by EDSS level estimated with the EQ-5D using both the UK and German value set.	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	EDSS 0: German value set 0.974; UK values set 0.922 EDSS 1: German 0.939; UK 0.852 EDSS 2: German 0.872; UK 0.748 EDSS 3: German 0.806; UK 0.676 EDSS 4: German 0.77; UK 0.637 EDSS 5: German 0.728; UK 0.591 EDSS 6: German 0.695; UK 0.555 EDSS 6.5: German 0.662; UK 0.521 EDSS 7: German 0.554; UK 0.393 EDSS 8: German 0.321; UK 0.146 EDSS 9: German 0.012; UK −0.237

Study (ID)	Country	Study details[a]	Methods of elicitation and valuation[b]	Health state description	Mean (SD) utility estimate
Calabrese et al. (2017)[204] Ref ID: 376.	Switzerland	The proportion of 721 MS patients with RRMS was 61%, with SPMS was 18%, and with PPMS was 17% (5% missing). Mean EDSS (SD) of 3.1 (2.5)	Utility by EDSS level estimated with the EQ-5D using the UK value sets	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	EDSS 0:0.918 EDSS 1:0.835 EDSS 2:0.746 EDSS 3:0.641 EDSS 4:0.643 EDSS 5:0.64 EDSS 6:0.619 EDSS 6.5:0.508 EDSS 7:0.494 EDSS 8:0.283 EDSS 9:-0.075
Dubois et al. (2017)[205] Ref ID: 378.	Belgium	The proportion of 1,856 MS patients with RRMS was 43%, with SPMS was 24%, and with PPMS was 22% (10% missing). Mean EDSS (SD) of 4.6 (2.5)	Utility by EDSS level estimated with the EQ-5D using the UK value sets and Belgium VAS value set	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	EDSS 0: UK 0.862; Belgian VAS value set 0.764 EDSS 1: UK 0.752; Belgian 0.693 EDSS 2: UK 0.687; Belgian 0.642 EDSS 3: UK 0.607; Belgian 0.576 EDSS 4: UK 0.535; Belgian 0.516 EDSS 5: UK 0.508; Belgian 0.492 EDSS 6: UK 0.442; Belgian 0.438 EDSS 6.5: UK 0.409; Belgian 0.426 EDSS 7: UK 0.341; Belgian 0.363 EDSS 8: UK 0.092; Belgian 0.198 EDSS 9: UK −0.237; Belgian 0.044

Study (ID)	Country	Study details[a]	Methods of elicitation and valuation[b]	Health state description	Mean (SD) utility estimate
Lebrun-Frenay et al. (2017)[206] Ref ID: 379	France	The proportion of 491 MS patients with RRMS was 61%, with SPMS was 22%, and with PPMS was 11%. Mean EDSS (SD) of 3.6 (2.3)	Utility by EDSS level estimated with the EQ-5D using both the UK and France value sets	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	EDSS 0: UK tariff 0.924; French tariff 0.896 EDSS 1: UK 0.806; French 0.76 EDSS 2: UK 0.735; French 0.709 EDSS 3: UK 0.647; French 0.632 EDSS 4: UK 0.586; French 0.521 EDSS 5: UK 0.555; French 0.473 EDSS 6: UK 0.437; French 0.335 EDSS 6.5: UK 0.516; French 0.392 EDSS 7: UK 0.419; French 0.261 EDSS 8: UK 0.231; French 0.169
Berger et al. (2017)[207] Ref ID: 394.	Austria	The proportion of 516 MS patients with RRMS was 42%, with SPMS was 25%, and with PPMS was 23% (2% missing). Mean EDSS (SD) of 4.4 (2.5)	Utility by EDSS level estimated with the EQ-5D using the UK value sets	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	EDSS 0: 0.887 EDSS 1: 0.829 EDSS 2: 0.751 EDSS 3: 0.706 EDSS 4: 0.666 EDSS 5: 0.54 EDSS 6: 0.606 EDSS 6.5: 0.553 EDSS 7: 0.371 EDSS 8: 0.194 EDSS 9: −0.303

Study (ID)	Country	Study details[a]	Methods of elicitation and valuation[b]	Health state description	Mean (SD) utility estimate
Kobelt et al. (2017)[71] Ref ID: HS3	Multiple European countries (includes the UK among 16 countries)	MS phenotype and mean EDSS score reported for each country. Only data for the UK is presented here. The proportion of 779 MS patients with RRMS was 37%, with SPMS was 38%, and with PPMS was 24%. Mean EDSS (SD) of 5.5 (2.2)	Utility by EDSS level estimated with the EQ-5D using the UK value sets	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	Based on the sample populations and mean EDSS, the UK study in this study is the same as Thompson et al. (2017)[199]. Only figure is provided for utility estimates, therefore see Thompson et al. (2017)[199] for these estimates
Thompson et al. (2017)[199] Ref ID: HS4	UK	The proportion of 779 MS patients with RRMS was 37%, with SPMS was 38%, and with PPMS was 24%. Mean EDSS (SD) of 5.5 (2.2)	Utility by EDSS level estimated with the EQ-5D using the UK value sets	EDSS 0-3 = Mild MS EDSS 4-6.5 = Moderate MS EDSS 7-9 = Severe MS	EDSS 0: 0.898 EDSS 1: 0.787 EDSS 2: 0.695 EDSS 3: 0.573 EDSS 4: 0.605 EDSS 5: 0.569 EDSS 6: 0.480 EDSS 6.5: 0.431 EDSS 7: 0.373 EDSS 8: 0.157 EDSS 9: −0.111

Study (ID)	Country	Study details[a]	Methods of elicitation and valuation[b]	Health state description	Mean (SD) utility estimate
Maurer, (2016)[208] Ref ID: 567	Country: Multinational	A post hoc analysis of two phase III randomised controlled trials (TEMSO and TOWER), with patients defined by severity of relapse with sequelae – EDSS/FS Number of patients with sequelae-EDSS/FS (non-severe relapse) were 146, sequelae-EDSS/FS (severe relapse) were 274, with mean (SD) EDSS scores of 2.8 (1.3) and 2.7 (1.3) respectively	Preference based SF-6D administered on patients. Valuation method was not reported but refers to Brazier et al. (2002)[209]	Severity of relapse with sequelae - EDSS/FS was defined by an increase in EDSS/FS score ≥ 30 days post-relapse	No relapse = 0.7 (0.1), *Patients with relapse(s);* Sequelae-EDSS/FS (non-severe relapse) = 0.7 (0.1), Sequelae-EDSS/FS (severe relapse) = 0.7 (0.1)

EDSS = expanded disability status scale; FS = functional system; HRQOL = health-related quality-of-life; MS = multiple sclerosis; PPMS = primary-progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SF-6D = SF-6D Health Survey; SPMS = secondary-progressive multiple sclerosis; UK = United Kingdom; US = United States; VAS = visual analogue scale.

B.3.4.4 Adverse Events

For each AE included in the model, several treatment-dependent inputs are used to calculate the associated utility decrement: the annual incidence for each AE, the proportion of AEs that are serious events, the durations of serious and non-serious events, and the utility decrements for serious and non-serious events.

The annual utility decrement for each AE is calculated by weighting the utility decrement for a serious and a non-serious event by the proportion of serious events. Then, the incidence and duration of the event (in years) is applied. This weighted annual utility decrement is calculated for all AEs and summed to give an annual AE-associated utility decrement for each treatment. This decrement was only added to the utility for patients on treatment.

Disutility and duration associated with each AE (both serious and non-serious) is shown in Table 38.

Table 38. Disutility and duration associated with serious adverse events and non-serious adverse events

Adverse event	Disutility of non-serious event	Disutility of serious event	Source	Duration of non-serious event (days)	Duration of serious event (days)	Source
Arthralgia	−0.25	−0.25	Retrieved from NICE TA441, Table 91	10.50	24.50	Retrieved from NICE TA441, Table 91
Back pain	−0.25	−0.50	Retrieved from NICE TA441 Table 91	10.50	24.50	Retrieved from NICE TA441 Table 91
Fatigue	0.00	0.00	Assumption	182.50	182.50	Assumption
Gastroenteritis	−0.07	−0.07	Retrieved from Swedish adaptation 2016	10.50	24.50	Retrieved from Swedish adaptation 2016
Headache	−0.14	−0.49	Retrieved from NICE TA533 Table 42	10.50	24.50	Retrieved from NICE TA533 Table 42
Immune thrombocytopenic purpura	−0.09	−0.09	Retrieved from NICE TA312 Table B7.4.4	15.00	81.00	Retrieved from NICE TA312 Table B7.4.4
Influenza-like illness	−0.08	−0.08	Retrieved from NICE TA441 Table 91	1.00	1.00	Retrieved from NICE TA441 Table 91
Injection-site reaction - erythema	0.00	0.00	Assumption	0.00	0.00	Assumption
Injection-site reaction - pain	0.00	0.00	Assumption	0.00	0.00	Assumption
Injection-site reaction - pruritus	0.00	0.00	Assumption	0.00	0.00	Assumption
Meningitis listeria	−0.02	−0.61	Bennett (2000)[210]	365.00	365.00	Assumption
Nasopharyngitis	0.00	0.00	Retrieved from Swedish adaptation from 2016	7.00	14.00	Retrieved from Swedish adaptation from 2016

Adverse event	Disutility of non-serious event	Disutility of serious event	Source	Duration of non-serious event (days)	Duration of serious event (days)	Source
Progressive multifocal leukoencephalopathy	−0.30	−0.30	Retrieved from NICE TA533 Table 42	365.00	365.00	Retrieved from NICE TA533 Table 42
Pneumonia / urinary tract infection	−0.20	−0.20	Retrieved from NICE TA533 Table 42	7.00	14.00	Retrieved from NICE TA533 Table 42
Pyrexia	−0.11	−0.11	Retrieved from NICE TA441 Table 91	7.00	14.00	Retrieved from NICE TA441 Table 91

NICE = National Institute for Health and Care Excellence; Pneumonia = upper respiratory tract infection; TA = technology appraisal.

The annual incidence of AEs for each treatment is shown in Appendix M. These figures were obtained from the following trials:

- PegIFNβ-1a: ADVANCE[182]
- IM IFNβ-1a: Calabrese (2012)[183], CombiRx[184], EVIDENCE[185], BRAVO[186], INCOMIN[187]
- IFNβ-1a 22: PRISMS
- IFNβ-1a 44: Calabrese (2012)[183], EVIDENCE[185], OPERA I & II[189], CARE MS I[190], CARE MS II[191], REGARD[192]
- IFNβ-1b: IFNB MS study[155], BEYOND[193], INCOMIN[187]
- GA20 (and genGA 20): BEYOND[193], CONFIRM[125], Copolymer 1 study[194], REGARD[192], Bornstein[195]
- GA40 (and genGA 40): GALA[196]
- teriflunomide: TOWER[140], TEMSO[197]
- DMF: CONFIRM[125], DEFINE[127]
- alemtuzumab: CARE MS I[190], CARE MS II[191]
- ocrelizumab: OPERA I & II[189]

The annual incidence rate of each AE for each treatment and study is calculated as the proportion of patients experiencing each AE over the study duration, scaling the study duration to 1 year. The annual incidences for each AE are assumed to apply throughout the model time horizon for patients receiving treatment. When more than one study is used for a specific treatment, the annual incidence of each AE is calculated as a weighted average of the annual incidence rates using the number of patients observed in each study as weights. The proportion of SAEs for each treatment is shown in Appendix M.

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

Since patient utilities depend on a patient's health state and whether a patient has had a relapse, the risk of relapse over time for each health state needs to be calculated. This will give the number of patients experiencing a relapse in each health state over time, which will allow the utility to be weighted. The ARR for patients on treatment is adjusted by a rate ratio, then converted into a probability. The same is done for patients off treatment, except no treatment effect (i.e., the rate ratio) is needed. Once the probability of relapse is calculated for each health state for both sub-cohorts over time, the utilities for each health state are weighted by these probabilities.

The mean utility scores for RRMS by EDSS level without relapse were extracted from the study by Orme et al. (2007)[78] and are shown in Table 39. The derivation of the utility decrements by EDSS level for RRMS and SPMS patients with and without relapse are described below (and are consistent with preferred committee assumptions from prior technology appraisals):

- To obtain the utilities for SPMS patients with no relapse, a decrement of 0.045 was applied to the mean utility scores for RRMS patients with no relapse
- To obtain the utilities for RRMS patients with relapse, a decrement of 0.071 was applied to the mean utility scores for RRMS patients with no relapse
- To obtain the utilities for SPMS patients with relapse, a decrement of 0.071 was applied to the mean utility scores for SPMS patients with no relapse

Table 39. Utility by EDSS level stratified by relapse versus no relapse and RRMS versus SPMS

EDSS	No relapse		Relapse	
	RRMS	SPMS	RRMS	SPMS
0	0.8700	0.8250	0.799	0.7540
1-1.5	0.7990	0.7540	0.728	0.6830
2-2.5	0.7050	0.6600	0.634	0.5890
3-3.5	0.5740	0.5290	0.503	0.4580
4-4.5	0.6100	0.5650	0.539	0.4940
5-5.5	0.5180	0.4730	0.447	0.4020
6-6.5	0.4600	0.4150	0.389	0.3440
7-7.5	0.2970	0.2520	0.226	0.1810
8-8.5	-0.0490	-0.0940	-0.120	-0.1650
9-9.5	-0.1950	-0.2400	-0.266	-0.3110

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

Alternative values used in scenario analyses were derived based on pooled data sets from the original 2002 MTA ScHARR model[5], which relied on information from a two-stage survey of 1,554 respondents from the MS Trust database, and the UK MS RSS cohort as described in the assessment group report for TA527.

NICE accepts the effect of a treatment on the utility of caregivers as a valid benefit of treatment.[94,170,211] Caregiver disutility values by EDSS and disease phase (i.e., RRMS vs. SPMS) were derived from a study by Acaster et al. (2013).[180] Alternative caregiver disutility values are taken from Gani et al. (2008).[212] Both sets of disutilities are shown in Table 40, where the same disutility is assumed to be valid for both disease phases.

Table 40. Caregiver utility decrements by EDSS level stratified by RRMS versus SPMS

	Acaster et al. (2013)[180] (base case)		Gani et al. (2008)[212] (scenario)	
EDSS	RRMS	SPMS	RRMS	SPMS
0	−0.0020	−0.0020	0.0000	0.0000
1-1.5	−0.0020	−0.0020	−0.0014	0.0000
2-2.5	−0.0020	−0.0020	−0.0032	−0.0032
3-3.5	−0.0020	−0.0020	−0.0091	−0.0091
4-4.5	−0.0450	−0.0450	−0.0090	−0.0090
5-5.5	−0.1420	−0.1420	−0.0199	−0.0199
6-6.5	−0.1670	−0.1670	−0.0272	−0.0272
7-7.5	−0.0630	−0.0630	−0.0534	−0.0534
8-8.5	−0.0950	−0.0950	−0.1070	−0.1070
9-9.5	−0.0950	−0.0950	−0.1400	−0.1400

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

After the patient utilities are calculated, they are multiplied by the number of patients in each health state at each cycle. These values are added up across the health states for each cycle to obtain the patient QALYs of both sub-cohorts over time. For reporting purposes, the patient QALYs of both sub-cohorts are added each year. This is done with the caregiver QALY decrements as well.

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

An SLR was conducted to identify costs and resource use in the treatment and ongoing management of adult patients with MS from a UK perspective as described in Appendix I. A total of 114 costs and healthcare resource use studies were identified. Five of these studies were (at least partly) captured costs and/or resource use in the UK (Adlard et al., 2017[213]; Kobelt et al., 2017[71]; Thompson et al., 2017[199]; Hawton et al., 2016[214], and Zarkali et al., 2017[215]) out of which only one was explicitly stated as having been conducted in England (Zarkali et al., 2017[215]). Costs and healthcare resource use were presented by EDSS score in three studies (Kobelt et al., 2017[71]; Thompson et al., 2017[199], and Hawton et al., 2016[214]). Most of the remaining studies were conducted in North America, Europe, and Asia and are considered less relevant for decision making in England, therefore only the UK studies were included in this submission.

In the same manner as the health outcomes, cost outcomes are also calculated during each cycle. The individual components of the overall cost are calculated. From the payer's perspective, these components include direct disease management, drug acquisition, administration, monitoring, relapse, and AE management costs. Indirect costs include the relapse and disease management costs. All costs are multiplied by the half-cycle corrected patient numbers (except for the DMTs for which the half-cycle correction does not apply).

B.3.5.1 Intervention and comparators' costs and resource use

Annual treatment acquisition costs are considered in the model for each treatment and are only applied while patients are on treatment (Table 41). Costs are sourced from the British National Formulary (BNF). Disease management costs by the EDSS level are provided in Table 43.

There are no administration costs associated with teriflunomide and DMF (oral DMTs). For pegIFNβ-1a, IM IFNβ-1a, IFNβ-1a 22, IFNβ-1a 44, IFNβ-1b and the GAs 20/40, genGA 20/40, the administration cost is the same (cost of teaching the patients to self-administer the DMT) and applies only for the first year. For alemtuzumab and ocrelizumab, there is a differential administration cost between first and subsequent years (Table 41). The resource use associated with the administration costs are provided in Appendix M.

The annual cost of routine monitoring while patients are on treatment is considered separately for the first year of treatment and subsequent years and is calculated from the expected resource use per patient per year on treatment. Details on the unit costs and frequencies of the resources used are provided in Table 41.

Table 41. Annual Treatment-related costs for each treatment (2018 values)

Treatment	Drug acquisition		Administration cost		monitoring cost	
	First year	Subsequent years	First year	Subsequent years	First year	Subsequent years
PegIFNβ-1a	£8,502	£8,502	£159.00	£0.00	£238.07	£207.45
IM IFNβ-1a 30*	£8,502	£8,502	£159.00	£0.00	£238.07	£207.45
IFNβ-1a 22*	£7,976	£7,976	£159.00	£0.00	£271.94	£207.45
IFNβ-1a 44 *	£10,572	£10,572	£159.00	£0.00	£271.94	£207.45
IFNβ-1b*	£7,239	£7,239	£159.00	£0.00	£238.07	£207.45
GA 20*	£6,681	£6,681	£159.00	£0.00	£171.00	£171.00
GA 40*	£6,681	£6,681	£159.00	£0.00	£171.00	£171.00
GenGA 20*	£6,013	£6,013	£159.00	£0.00	£171.00	£171.00
GenGA 40*	£6,013	£6,013	£159.00	£0.00	£171.00	£171.00
Teriflunomide*	£13,529	£13,529	£0.00	£0.00	£618.08	£345.78
DMF*	£17,849	£17,849	£0.00	£0.00	£441.42	£266.47
Alemtuzumab	£35,225	£21,135	£2,742.10	£1,674.10	£653.08	£580.80
Ocrelizumab*	£19,160	£19,160	£1,633.49	£1,088.99	£229.98	£203.02

DMF = dimethyl fumarate; GA = glatiramer acetate; genGA = generic glatiramer acetate; IM = intramuscular; pegIFNβ-1a = pegylated interferon.
* comparator associated with confidential commercial agreements that has not been accounted for.

B.3.5.1.1 Alemtuzumab re-treatment rates

Five-year follow up data of the pivotal phase 3 studies for alemtuzumab have shown that a considerable proportion of patients need require re-treatment with alemtuzumab in years 3-5 (beyond the licensed posology of 5 infusions in year 1, followed by 3 infusions in year 2) or need to switch to other DMTs predominantly due to recurring disease activity. It is currently unclear how many of these additional cycles of treatment are commissioned by NHS England.

In TA303, the need for re-treatment with alemtuzumab was taken into consideration by the committee in decision making; all subsequent appraisals have also included including re-treatment up to and including year 5. For this appraisal, average re-treatment rates for years 3-5 from the CARE MS I and II follow up data were applied (19%, 16%, and 14% respectively)[216,217]. Switching to other DMTs after failure on alemtuzumab has not been accounted for with patients following the natural history disease progression following any discontinuation (all-cause, SPMS conversion or progression > EDSS 7), consistent for all comparators.

B.3.5.1.2 Administration costs – resource use

For teaching the patients to self-administer the DMT, 3 hours of a nurse's time has been assumed, with the unit cost sourced from the PSSRU for a a band 7 community nurse.[218] The cost per hour of advanced community nurse was included.

For alemtuzumab and ocrelizumab, the resource used for treatment administration varies across the first and second years alligned with the dosing schedule, and presented in Appendix M.

B.3.5.2 Costs and resource use associated with the health states

B.3.5.2.1 Disease management costs

The systematic review conducted in accordance with the NICE methods guide identified three studies that reported resource use and costs by EDSS health state for the UK (Kobelt et al., 2017[71]; Thompson et al., 2017[199]; and Hawton et al., 2016[214]). We have also considered the three additional studies (Karampampa et al., 2012[60]; Kobelt et al., 2006[80]; Tyas et al., 2007[83]) that have been frequently discussed in the previous technology appraisals (Table 26). These six studies are outlined in Table 42.

The study sample of Kobelt et al. (2017)[71] and Thomson et al. (2017)[199] was based on 779 respondents. The proportions of these subgroups compared with the overall study population are unknown for the Hawton et al. (2016)[214] study, which is about "people with MS."

The publication by Tyas et al. (2007)[83] uses the same resource data as the UK MS Survey (2005), with unit costs applied from the PSSRU and NHS reference costs. The Tyas et al. publication also separates costs into medical, non-medical, out of pocket, and indirect costs.

In general, a clear trend was observed in all studies from the literature correlating increased costs with increasing disability, in particular with severe disability (EDSS 7-9). The type of MS (RRMS or SPMS) also has an impact on resource use, with more progressive disease associated with higher cost.

Table 42. Annual disease management costs by EDSS level

	Kobelt et al. (2017)[71] Mean total annual cost per patient[a]	Kobelt et al. (2017) [199] Total mean annual cost per patient[b]	Hawton et al. (2016)[179] (Annualised) mean (SD) 2016[c]	Kobelt et al. (2006) [80] UK MS Survey 2005 Total mean annual cost per patient[d]	Karampampa et al. (2012a)[60] (Excluding DMT costs) Mean[c]	Tyas et al. (2007)[83] Mean (SD)[c]
Sample size	779 (UK sample)	779	289 (with EDSS)	2,048 (UK sample)	119	2,048
Cost year	2015	2015	2012	2004	2009	2005
EDSS score 0	€2,140	£425	£1,020 (281)	€7,260	£1,345	£250 (1,975)
EDSS score 1		£499	£910 (168)			£85 (899)
EDSS score 2		£2,840	£716 (92)			£213 (868)
EDSS score 3		£2,450	£668 (81)			£850 (1,237)
EDSS score 4	€4,060	£1,470	£1,002 (110)	€9,060	£2,602	£806 (884)
EDSS score 5		£1,350	£1,006 (120)			£1,419 (823)
EDSS score 6		£1,990	£1,304 (94)			£2,162 (851)

	Kobelt et al. (2017)[71] Mean total annual cost per patient[a]	Kobelt et al. (2017) [199] Total mean annual cost per patient[b]	Hawton et al. (2016)[179] (Annualised) mean (SD) 2016[c]	Kobelt et al. (2006) [80] UK MS Survey 2005 Total mean annual cost per patient[d]	Karampampa et al. (2012a)[60] (Excluding DMT costs) Mean[c]	Tyas et al. (2007)[83] Mean (SD)[c]
EDSS score 6.5		£2,960	-			-
EDSS score 7	€7,040	£2,960	£1,316 (180)	€10,300		£6,583 (995)
EDSS score 8		£4,330	£3,320 (395)		£3,961	£10,761 (1,069)
EDSS score 9		£8,160	Not reported			£15,121 (2,656)

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale.

[a] UK-specific values were digitised based on Figure 6 – "Direct healthcare" costs.

[b] Values were digitised based on Figure 6 – "Direct healthcare" costs – the total of "Hospital care" and "Outpatient Care" costs.

[c] Values are obtained from NICE TA533 (Table 87).

[d] UK-specific values were digitised based on Figure 3 – "Direct healthcare" costs.

Disease management costs in the economic model are separated into two types:

- Costs of disease management by EDSS states and disease phase (excluding costs of DMTs, informal care, social security, and assistance, as well as relapses)
- Costs of treating MS relapses

The health states used in the base case have been summarised in Table 43, and were obtained from TA320 inflated 7% from 2011/12 to 2017/18 values using the HCHS index from the PSSRU 2018. Use of the TA320 values were preferred by the assessment group in TA527 following a critical appraisal of available sources.

Values from TA320 were based on a Seemingly Unrelated Regression (SUR) analysis of the UK MS Survey 2005 resource use data used in TA127, with updated unit costs applied to the the resource use estimates. The SUR estimated the impact of various covariates upon the likelihood of resource use compared to a reference patient of 0 years, female, RRMS, EDSS 0, no relapse and no DMT.

The UK MS survey 2005 is a UK specific cross-sectional postal survey. The sample size was large at n=2,048 (response rate 16%) using patients in the MS Trust database, which may introduce selection bias. No data is presented on the characteristics of non-responders. The majority of respondents (60%), were between EDSS 4.0 and EDSS 6.5, with few responses for EDSS states 0, 3 and 9.

Resource use data is collected over 115 different resource use items. The NHS&PSS analysis includes:

- Direct NHS medical costs
- Direct non-medical social care costs
- Aids and appliances costs

The cost of treating MS relapses (NHS and PSS perspective: £2,168 [2017/2018], inflated 7% from 2011/2012 values using the HCHS index from PSSRU 2018[219]) and the disease management costs by EDSS level from the NHS and PSS perspective were also obtained from TA320 (which were derived using a seemingly unrelated regression using data from the UK MS survey 2005[83] inflated to 2017/2018 values by 7% from 2012 values). At each cycle, the disposition (the number of patients in each EDSS state in RRMS and SPMS) is multiplied by the annual management cost and summed across EDSS states. This is done for both sub-cohorts to give the direct disease management costs every year.

Table 43. Disease management costs by EDSS level (2016/2017 values)

EDSS	NHS and PSS perspective (£, base case)	
	RRMS	SPMS
0	£965	£1,301
1-1.5	£1,004	£1,340
2-2.5	£735	£1,071
3-3.5	£4,025	£4,360
4-4.5	£1,950	£2,285
5-5.5	£3,307	£3,644
6-6.5	£4,415	£4,750
7-7.5	£11,621	£11,956
8-8.5	£28,304	£28,640
9-9.5	£22,648	£22,985
Cost of relapse	£2,168	—

EDSS = Expanded Disability Status Scale; NHS = National Health Service; PSS = personal social services; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.

B.3.5.2.2 Monitoring costs – resource use

Unit costs of the resources are provided in Appendix M. The annual cost of routine monitoring while patients are on treatment is considered separately for the first year of treatment and subsequent years and is calculated from the expected resource use per patient per year on treatment (Appendix M).

B.3.5.3 Adverse reaction unit costs and resource use

The model requires five types of inputs related to AEs:

1. Annualised incidence of each AE
2. Proportion of AEs reported as non-serious and serious
3. Unit cost of each AE (serious and non-serious)
4. Disutility of each AE (serious and non-serious)
5. Duration of each AE (serious and non-serious)

The derivation of the AE annual unit cost is similar to the derivation of the AE annual disutility. It is calculated for each AE by weighting the cost for a serious and a non-serious event by the proportion of serious events. Then, the incidence of the event is applied. This weighted annual cost is calculated for all AEs and then summed to give an annual AE-associated cost for each treatment. All costs above were summed each year to give the total direct cost each year.

The cost of managing each AE that was considered in the model is presented in Appendix M.

The duration of each AE (both serious and non-serious) is shown in Table 38. Details on resource use and resource unit costs are provided in Appendix M, respectively.

B.3.5.4 Miscellaneous unit costs and resource use

There are no additional costs included in the model apart from those outlined in the previous sections.

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

B.3.6.1 Summary of base-case analysis inputs

Main inputs and the data sources for the based case are as follows:

- Natural history transitions:
  - Data from the University of British Columbia for the natural history transitions across EDSS levels for patients with RRMS
  - Data from the London, Ontario database were used to model the natural history transitions from RRMS to SPMS and during SPMS
  - Annual RRs by EDSS level were obtained from the UK MS survey 2005 and Patzold (1982)[175]
- The comparative efficacy of treatments versus placebo were obtained from the network meta-analysis and MTC analysis
- Patients stopped treatment after progression to an EDSS level ≥ 7 or upon conversion to SPMS. An overall discontinuation risk was applied for each comparator over the time horizon of the model
- Utility scores by EDSS level came from a study by Orme et al. (2007)[78] based on the UK MS Survey 2005
- Health state costs by EDSS level were derived from a Tyas et al. (2007)[83], based on the UK MS Survey 2005.

Further details of the input values or the relevant sections of this dossier where these values are provided are reported in Table 44.

Table 44. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section
Patient demographics			
Age	36 years	Scenario analysis	B.3.2.1
Gender (Male)	29.0%	Scenario analysis	B.3.2.1
Baseline EDSS distribution	Table 24	Scenario analysis	B.3.2.1
Model structure			
Time horizon	50 years	Fixed (Consistent with previous appraisals - Table 26)	B.3.2.2
Cycle length	1 year		B.3.2.2
Discount rate for costs and outcomes	3.5%		B.3.2.2
Half cycle correction	Yes		B.3.2.2

Transition probabilities			
EDSS Relapse rate	Table 31	Lognormal	B.3.3.1.4
RRMS to RRMS transition matrix	Table 28	Beta	B.3.3.1.1
RRMS to SPMS	Table 29	Dirichlet	B.3.3.1.2
Treatment effect			
Relapse rate	Table 36	Lognormal	B.2.9.3
Disability progression	Table 34	Lognormal	B.2.9.3
All-cause discontinuation	Table 32	Beta	B.3.3.2.1
Utilities			
Patient utility by EDSS	Table 39	Beta	B.3.4.5
Caregiver utility decrement	Table 40	Beta	B.3.4.5
AE disutility	Table 38	Beta	B.3.4.4
Costs			
Drug acquisition	Table 41	Fixed	B.3.5.1
Drug administration	Table 41	Fixed	B.3.5.1
Monitoring	Table 41	Fixed	B.3.5.1
AE costs and management	Appendix M	Gamma	B.3.5.3
Cost per EDSS health state	Table 43	Gamma	B.3.5.2.1
Cost of relapse	Table 43	Gamma	B.3.5.2.1

AE = adverse event; EDSS = Expanded Disability Status Scale; MTC = mixed-treatment comparison; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.

B.3.6.2 Assumptions

Table 45 presents a list of the main parameters and assumptions used in the economic analysis.

Table 45. Key assumptions within the economic model

Parameter	Base-case assumption	Justification
Disability progression	Disability progression and relapses were modelled independently, with independent treatment effects applied to each.	In line with previous NICE TAs (Table 26). EDSS progression is a key driver of cost-effectiveness. A number of studies have shown a strong correlation between EDSS, resource consumption, and HRQOL. EDSS is the preferred tool for measuring disability in people with MS as recommended by the EMA. This approach avoids any potential double counting. In

Parameter	Base-case assumption	Justification
		addition, it is a pragmatic approach, as modelling relapses as independent health states would significantly increase size and complexity of the model. However, this approach could have overestimated the effect of treatment on the ARRs, as they depended on the EDSS level. However, as the natural history ARRs were lower at higher levels of EDSS during the RRMS phase and during SPMS, the possible overestimated effect of treatment in the ARRs for pegIFNβ-1a could have been offset.
	Treatments had an indirect effect on the risk of progression to SPMS and mortality.	Delaying progression to higher EDSS levels avoids higher mortality multipliers associated with risk of mortality from MS and avoids higher probabilities of progression to SPMS.
	Transition probabilities within RRMS: "The resulting natural history matrix has non-zero elements below its diagonal, reflecting the assumption that patients can improve to a lower EDSS level within the RRMS phase of the disease". Transition probabilities within SPMS: This matrix is upper-triangular (i.e., with zero elements below the diagonal), reflecting the assumption that patients cannot improve to a lower EDSS level while in the SPMS phase.	As per the definition of RRMS, patients can regress (demonstrated in the BCMS data set), as per the definition of SPMS patients cannot regress – aligned with the London, Ontario, data set.
	After treatment discontinuation, patients are assumed to follow the natural disease progression course.	In line with previous NICE TAs (Table 26). An escalation of treatment (such as to fingolimod/ ocrelizumab, and alemtuzumab) would be likely in clinical practice. This approach would make treatments with the highest discontinuation rates most cost-effective ones, as they transition to higher efficacy drugs.
Mortality	The same RRs were assumed for the RRMS and SPMS phases.	Due to lack of data (conservative assumption)
Treatment waning	The treatment effect assumed to wane over time, with the same decline applying to all DMTs. ▪ Year 1-2: 100% of the treatment benefit	In line with previous NICE TAs (Table 26).

Parameter	Base-case assumption	Justification
	▪ Years 3-5: 75% of the full treatment effect ▪ Year 6 onwards: 50% of the full treatment effect This assumption was applied equally to all comparators.	
Time horizon	50 years	Lifetime equivalent consistent with NICE reference case.
HRQOL	Fatigue, injection-site reaction – erythema, injection-site reaction – pain, and injection-site reaction – pruritus assumed not be associated with a disutility.	Due to lack of data.
	It was assumed that a patient who received treatment would incur the risk of disutility and costs associated with AEs for each year in the model. This may have overestimated the impact of AEs, as patients with severe/frequent AEs may have withdrawn from treatment during the first few years.	Due to lack of data.
	Caregiver disutility values by EDSS and disease phase (i.e., RRMS vs. SPMS) were assumed to be the same for both disease phases.	Due to lack of data (conservative assumption)
Costs	Non-serious type of fatigue, injection-site reaction – erythema, injection-site reaction – pain, injection-site reaction – pruritus, and nasopharyngitis are assumed to have no costs associated with them.	Injection-site reactions often do not lead to any resource use, particularly not ones relevant as part of a payer perspective.

AE = adverse event; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; EMA = European Medicines Agency; HRQOL = health-related quality-of-life; MS = multiple sclerosis; NICE = National Institute for Health and Care Excellence; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; TA = technology assessment.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Base-case analyses have been conducted using list prices only. Results should be interpreted with caution for comparisons against technologies that are recommended contingent upon commercial agreements.

For the base case using it was not possible to obtain results for IFNβ-1a 22 (Rebif® 22) and IFNβ-1b (Extavia®), due to the lack of relative efficacy estimates for these comparators (CDP6M HR vs. placebo was not available from the network meta-analysis for any of these comparators, and for SC IFNβ-1a 22 there was no estimate for the ARR ratio vs. placebo). For GA 40 (Copaxone® 40), genGA 20 (Brabio® 20) and genGA 40 (Brabio® 40) CDP estimates were assumed at parity to GA20 (Copaxone® 20), due to lack of outcome reporting.

Full incremental analyses using all comparators for which there was relative efficacy available are presented. The comparators are ordered using their total cost in ascending order (i.e., pegIFNβ-1a had the lowest total cost and ocrelizumab the highest).

Results for the base case indicate that pegIFNβ-1a was a dominant treatment (i.e., cost saving and with higher QALYs) compared with teriflunomide, IFNβ-1a (Avonex®, Rebif® 44), all doses of GA (including genGA), and DMF. Compared with alemtuzumab, pegIFNβ-1a had a lower total cost and lower QALYs, hence pegIFNβ-1a was a less costly and less effective; alemtuzumab could be considered highly cost-effective versus pegIFNβ-1a with an ICER of £1,155 per QALY gained. Compared with ocrelizumab, pegIFNβ-1a was less costly and less effective; using ocrelizumab as the reference comparator the ICER versus pegIFNβ-1a will be £131,776, hence ocrelizumab will not be cost-effective when using a willingness-to-pay threshold of £20,000 per QALY gained.

Patients receiving pegIFNβ-1a spent more time (undiscounted years) with an EDSS score < 7 than patients receiving all other DMTs except alemtuzumab and ocrelizumab; the EDSS level of patients receiving all DMTs other than alemtuzumab and ocrelizumab was predicted to have a similar increase from baseline after 50 years (5.9 points on average, vs. 5.0 and 5.6 point increase on average, for alemtuzumab and ocrelizumab, respectively). Patients receiving pegIFNβ-1a spent the third largest amount of years (undiscounted) over lifetime free of SPMS; pegIFNβ-1a was associated with higher QALYs than IFNβ-1a 30, IFNβ-1a 44 GA and genGA 20/40, teriflunomide and DMF. PegIFNβ-1a and alemtuzumab had the highest life years.

Over 50 years, the total discounted cost of pegIFNβ-1a was the lowest. Alemtuzumab had a slightly lower total cost, which was about 0.5% more costly than pegIFNβ-1a. The total cost for pegIFNβ-1a is low due to 1) the savings on disease management costs, where pegIFNβ-1a ranks as the DMT with the third lowest behind alemtuzumab and ocrelizumab, and 2) pegIFNβ-1a also ranks as the fifth lowest DMT in total drug acquisition cost, behind GA and genGA by a small margin, largely driven by higher discontinuation rates.

A summary of the analysis results comparing pegIFNβ-1a with other DMTs is shown in Table 46.

Table 46. Base-case results – deterministic analysis – full incremental analysis

	Total			Incremental			ICER
Treatment	**Costs**	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**£/QALY**
pegIFNβ-1a	£ 273,641	19.275	4.393				*
alemtuzumab	£ 274,892	19.281	5.475	£ 1,250	0.006	1.082	£1,155
genGA 20	£ 282,343	19.194	3.646	£ 7,451	-0.087	-1.829	dominated
genGA 40	£ 284,674	19.195	3.658	£ 9,783	-0.086	-1.818	dominated
GA 20	£ 285,064	19.194	3.646	£ 10,173	-0.087	-1.829	dominated
GA 40	£ 287,676	19.195	3.658	£ 12,784	-0.086	-1.818	dominated
SC IFNβ-1a 44	£ 292,969	19.258	4.224	£ 18,077	-0.024	-1.251	dominated
IM IFNβ-1a 30	£ 294,199	19.228	3.929	£ 19,307	-0.053	-1.547	dominated
teriflunomide	£ 297,437	19.211	3.796	£ 22,545	-0.070	-1.679	dominated
DMF	£ 308,506	19.224	3.949	£ 33,614	-0.057	-1.526	dominated
ocrelizumab	£ 339,668	19.201	4.894	£ 64,776	-0.080	-0.581	dominated

DMF = dimethyl fumarate; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LY = life-year; pegIFNβ-1a = pegylated interferon; QALY = quality-adjusted life-year SC = subcutaneous.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the model was run for 5,000 simulations to generate scatter plots of incremental QALYs versus incremental cost (discounted per patient over 50 years), and to generate cost-effectiveness acceptability curves (Figure 34 to Figure 53). To account for statistical uncertainties of multiple key parameters, PSAs were performed by simultaneously varying the following parameters:

- **Log-normal distribution:** rate ratios for the ARRs and CDP HRs relative to placebo, ARRs by EDSS level, incidence of AEs, RR for MS mortality
- **Beta distribution:** transition probabilities from RRMS to SPMS, annual treatment discontinuation risk, proportion of AEs reported as serious, disutility for SAEs and non-SAEs, and patient utilities
- **Gamma distribution:** SAE and non-SAE management costs and duration, cost of relapse, and disease management costs
- **Dirichlet distribution:** transition probabilities between RRMS and SPMS EDSS levels

Where a standard error or CI was not available for a selected parameter, a ± 25% variation from the mean was assumed, which is a common approach used in economic models.[220,221]

Mean PSA results based on 5,000 simulations are presented in Table 47, which demonstrates that alemtuzumab dominates all other comparators. Compared to the deterministic results, alemtuzumab is 0.25% less costly than pegIFNβ-1a, hence the change from the deterministic results.

Based on the results of 5,000 simulations, the probability of pegIFNβ-1a being cost-effective compared with genGA 20 is 85%; with genGA 40 is 87%; with GA 20 is 89%; with GA 40 is 90%; with IFNβ-1a 44 is 92%; with IM IFNβ-1a 30 is 95%; with teriflunomide is 98%; with DMF is 99%; with ocrelizumab is 100%; and with alemtuzumab is 17%. These results are aligned with those in the base case.

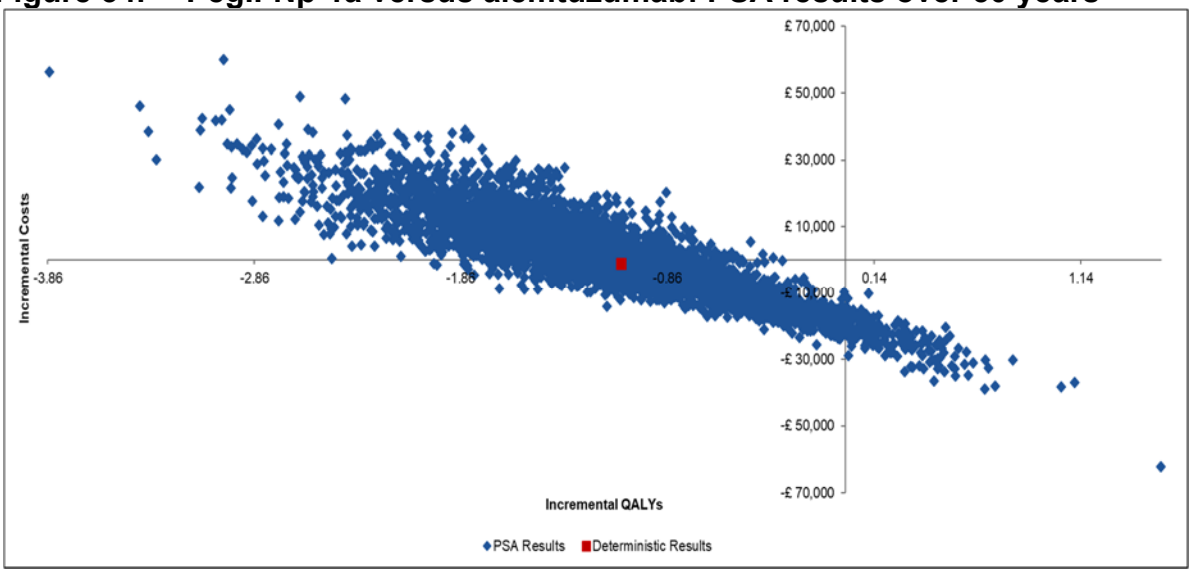
The cost-effectiveness acceptability curves highlight that at any willingness-to-pay threshold, pegIFNβ-1a has a higher probability of being the most cost-effective treatment option, except for the comparison with alemtuzumab, where alemtuzumab has a higher probability of being cost-effective. It should be noted that all analyses are conducted using list prices for comparators and should therefore be interpreted with caution for comparators where commercial agreements are in place.

Table 47. Base-case results – probabilistic analysis

	Total			Incremental			ICER
Treatment	Costs	LYs	QALYs	Costs	LYs	QALYs	£/QALY
alemtuzumab	£ 255,439	19.298	6.378				
pegIFNβ-1a	£ 256,067	19.350	5.259	£ 628	0.052	-1.119	dominated
genGA 20	£ 263,692	19.267	4.575	£ 8,253	-0.031	-1.802	dominated
genGA 40	£ 266,683	19.264	4.571	£ 11,244	-0.034	-1.807	dominated
GA 20	£ 266,761	19.253	4.560	£ 11,322	-0.045	-1.818	dominated
GA 40	£ 269,683	19.267	4.581	£ 14,244	-0.031	-1.797	dominated
IFNβ-1a 44	£ 276,057	19.335	5.125	£ 20,618	0.037	-1.252	dominated
IM IFNβ-1a 30	£ 277,288	19.305	4.851	£ 21,849	0.007	-1.527	dominated
teriflunomide	£ 279,016	19.264	4.721	£ 23,576	-0.034	-1.657	dominated
DMF	£ 290,828	19.298	4.863	£ 35,389	0.000	-1.515	dominated
ocrelizumab	£ 329,231	19.292	5.780	£ 73,792	-0.006	-0.598	dominated

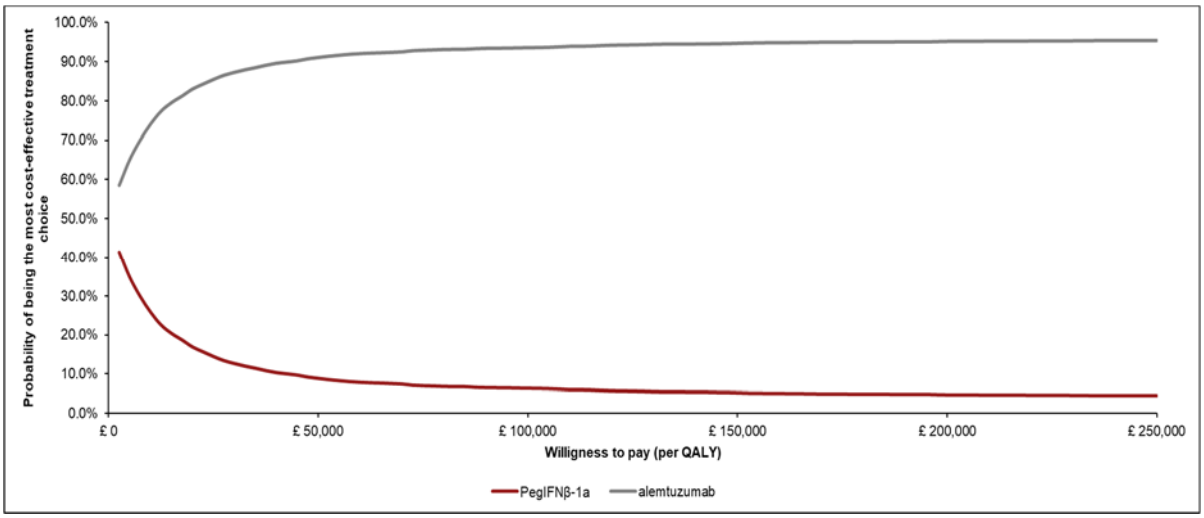
DMF = dimethyl fumarate; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LY = life-year; pegIFNβ-1a = pegylated interferon; QALY = quality-adjusted life-year SC = subcutaneous.

Figure 34. PeglFNβ-1a versus alemtuzumab: PSA results over 50 years



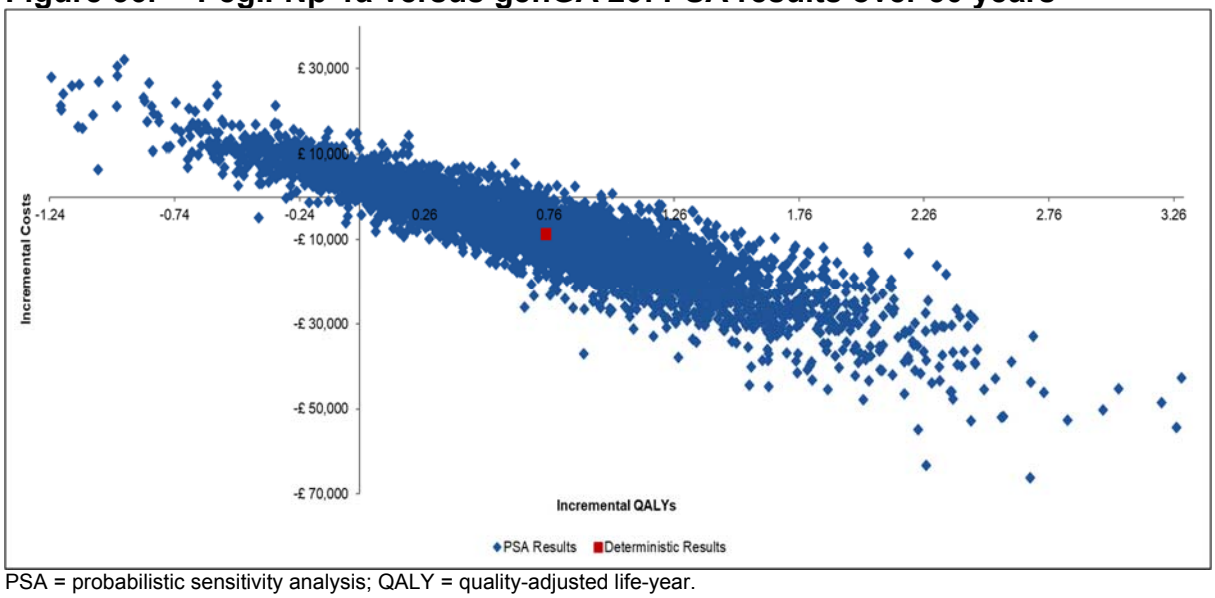
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 35. PeglFNβ-1a versus alemtuzumab: cost-effectiveness acceptability curve



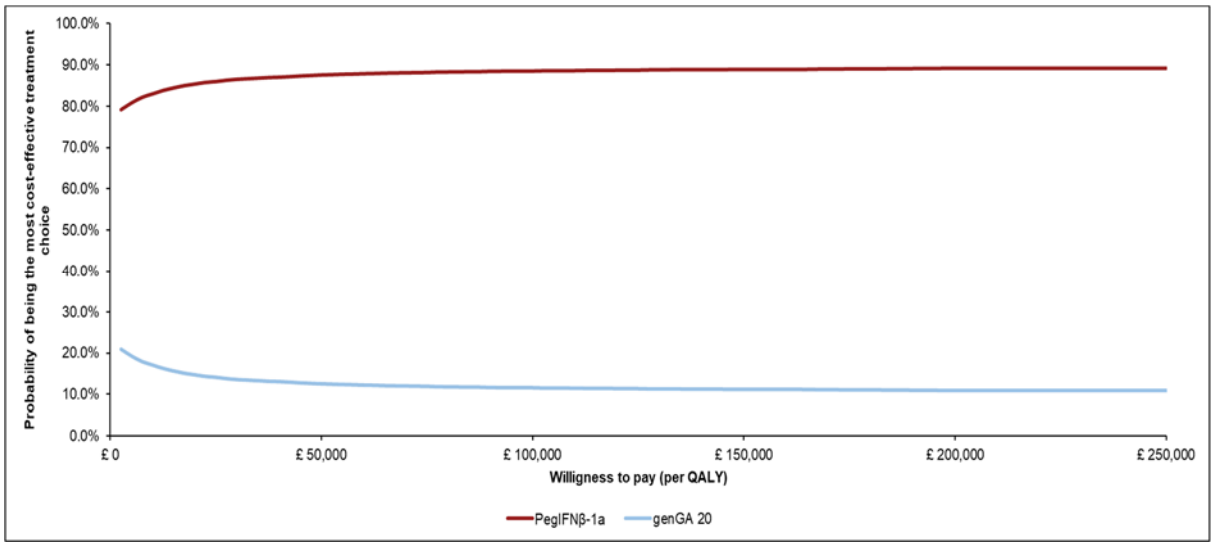
QALY = quality-adjusted life-year.

Figure 36. PeglFNβ-1a versus genGA 20: PSA results over 50 years



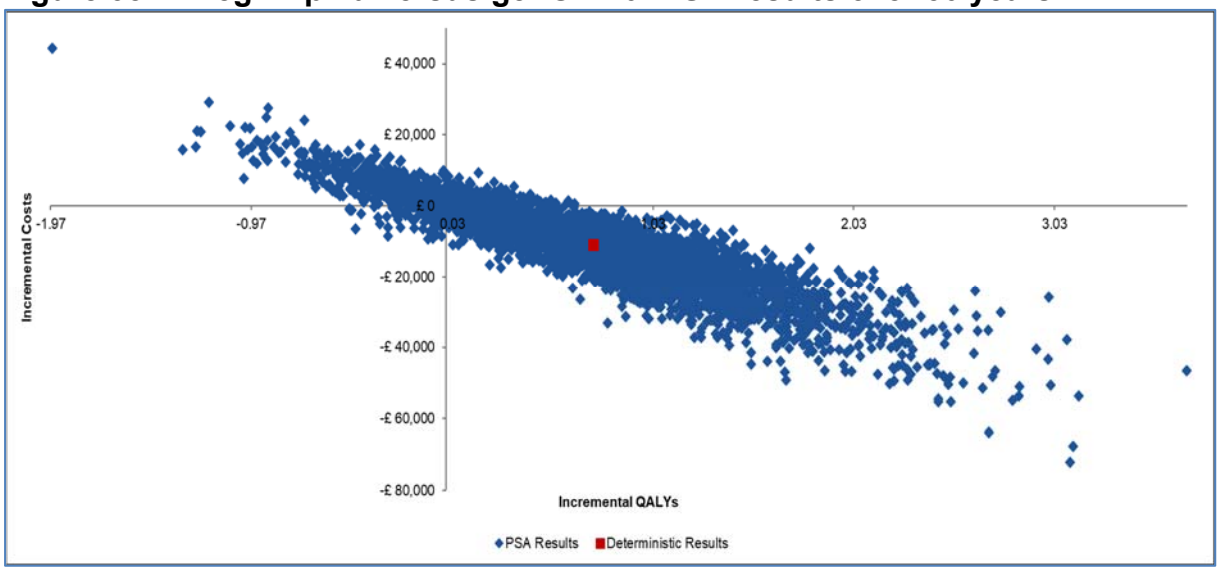
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 37. PeglFNβ-1a versus genGA 20: cost-effectiveness acceptability curve



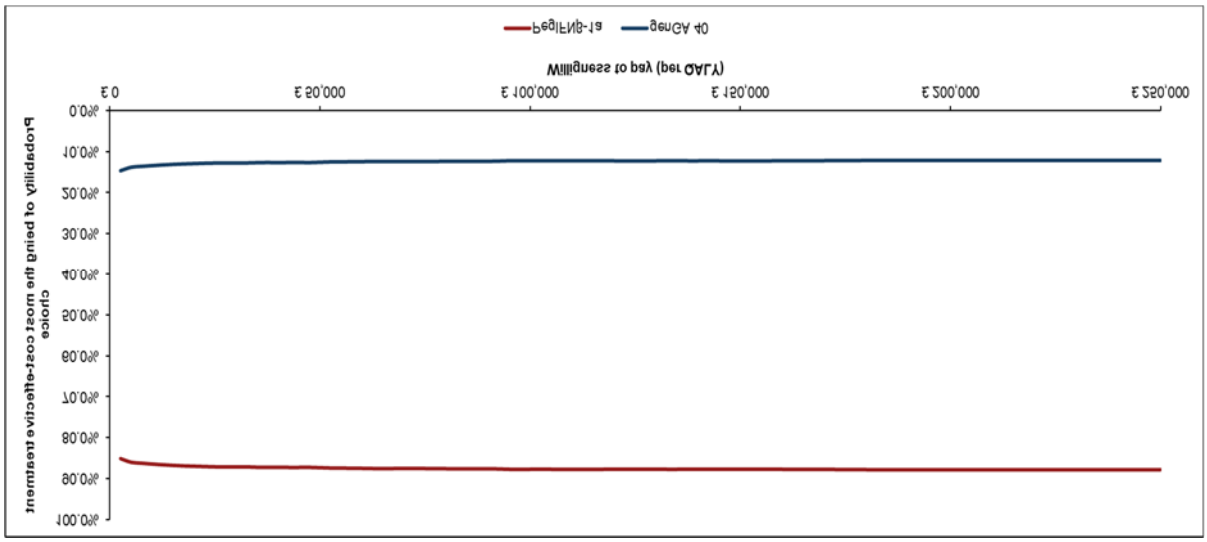
QALY = quality-adjusted life-year.

Figure 38. PegIFNβ-1a versus genGA 40: PSA results over 50 years



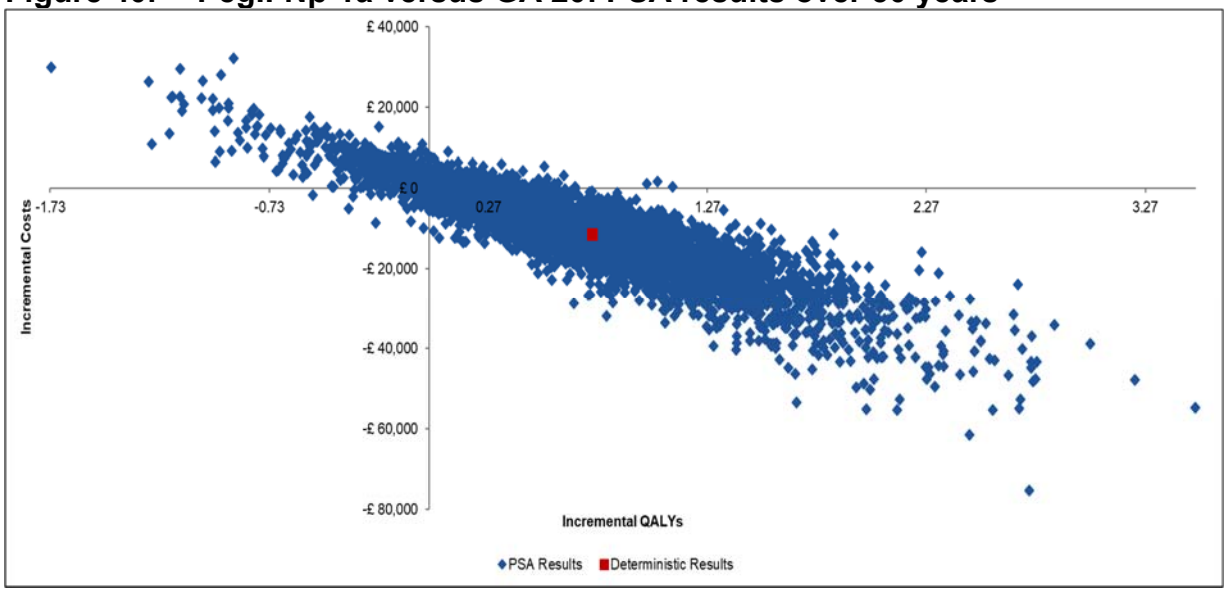
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 39. PegIFNβ-1a versus genGA 40: cost-effectiveness acceptability curve



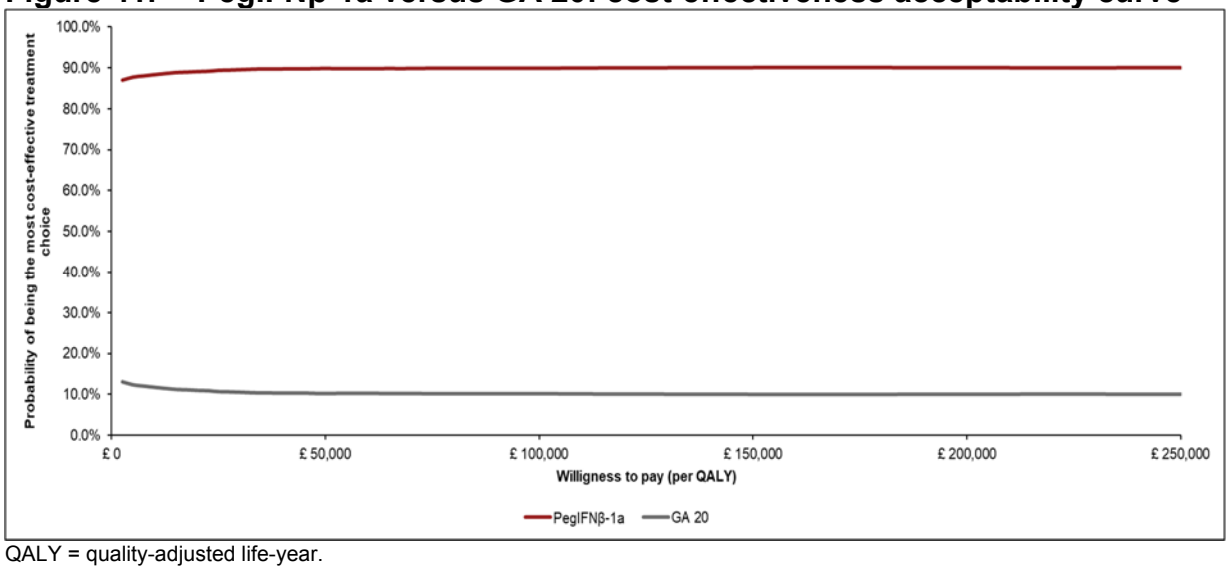
QALY = quality-adjusted life-year.

Figure 40. PegIFNβ-1a versus GA 20: PSA results over 50 years



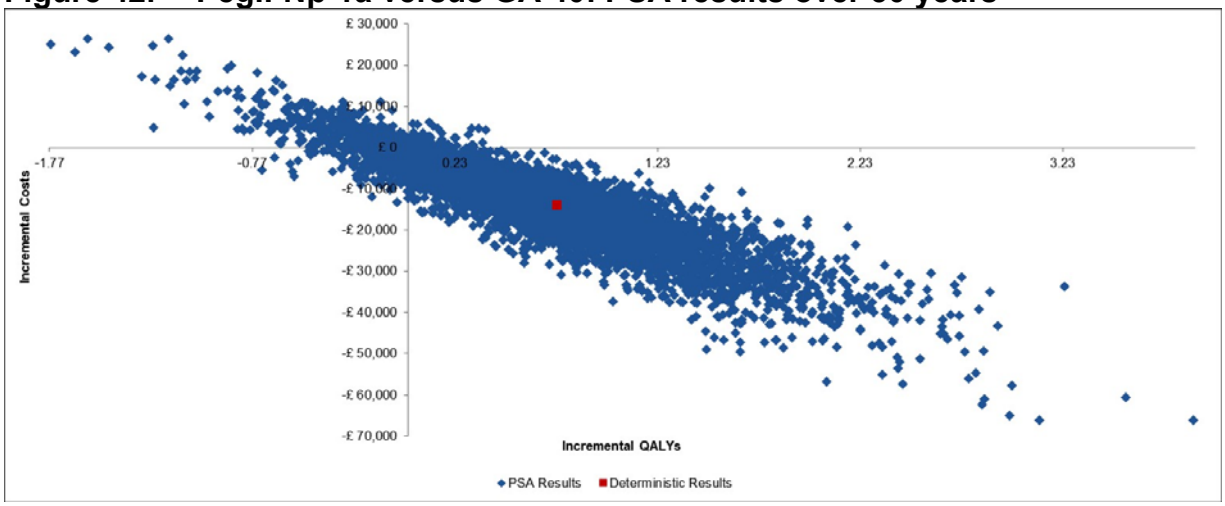
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 41. PegIFNβ-1a versus GA 20: cost-effectiveness acceptability curve



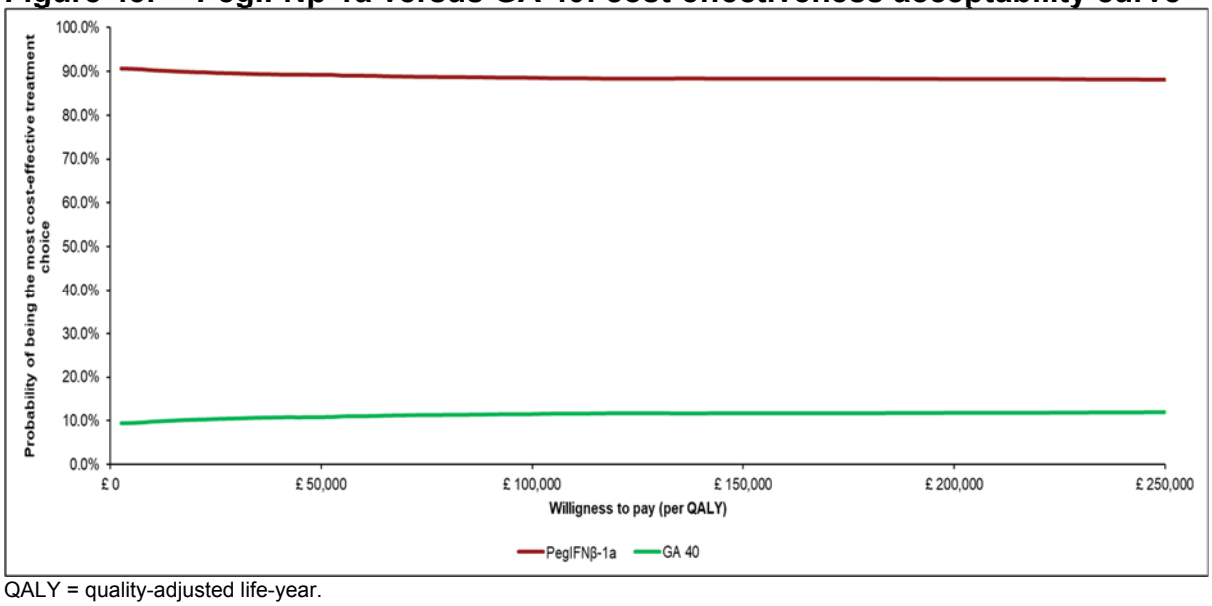
QALY = quality-adjusted life-year.

Figure 42. PegIFNβ-1a versus GA 40: PSA results over 50 years



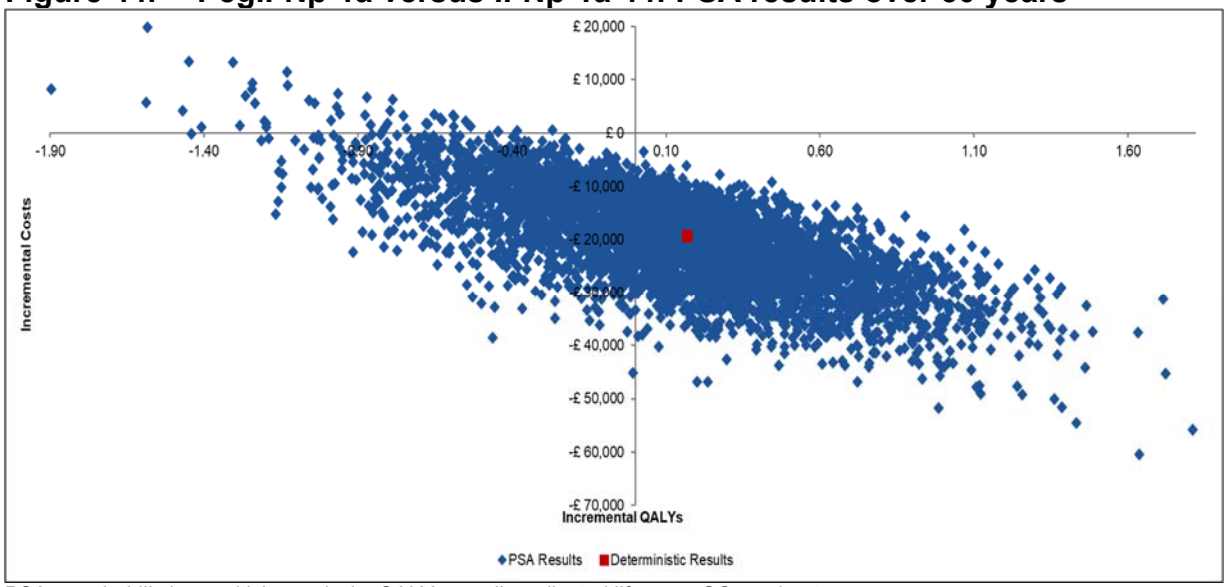
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 43. PegIFNβ-1a versus GA 40: cost-effectiveness acceptability curve



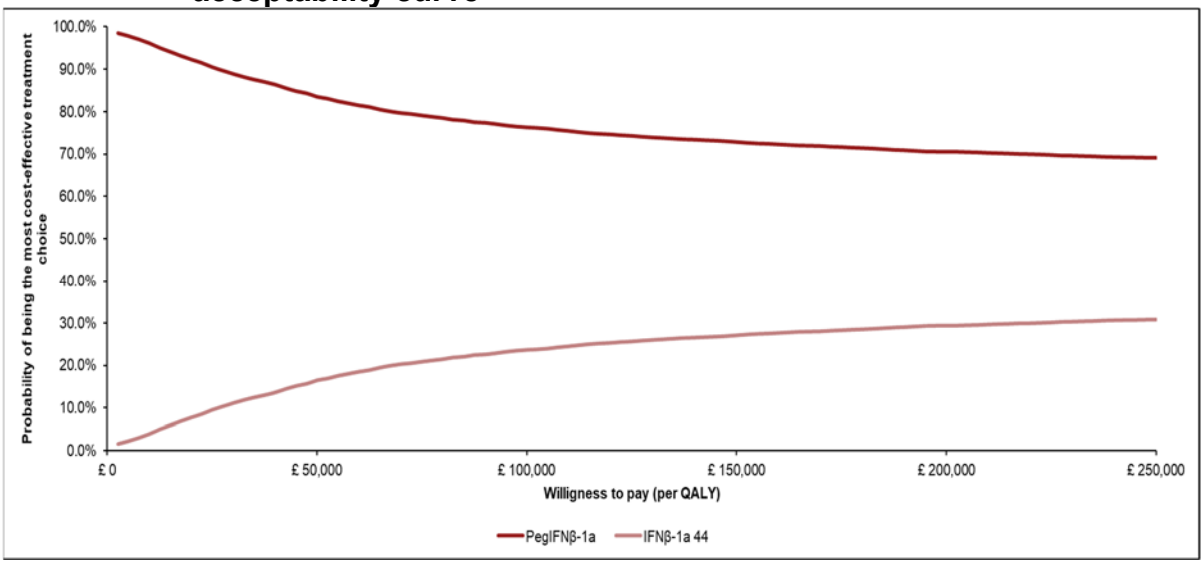
QALY = quality-adjusted life-year.

Figure 44. PegIFNβ-1a versus IFNβ-1a 44: PSA results over 50 years



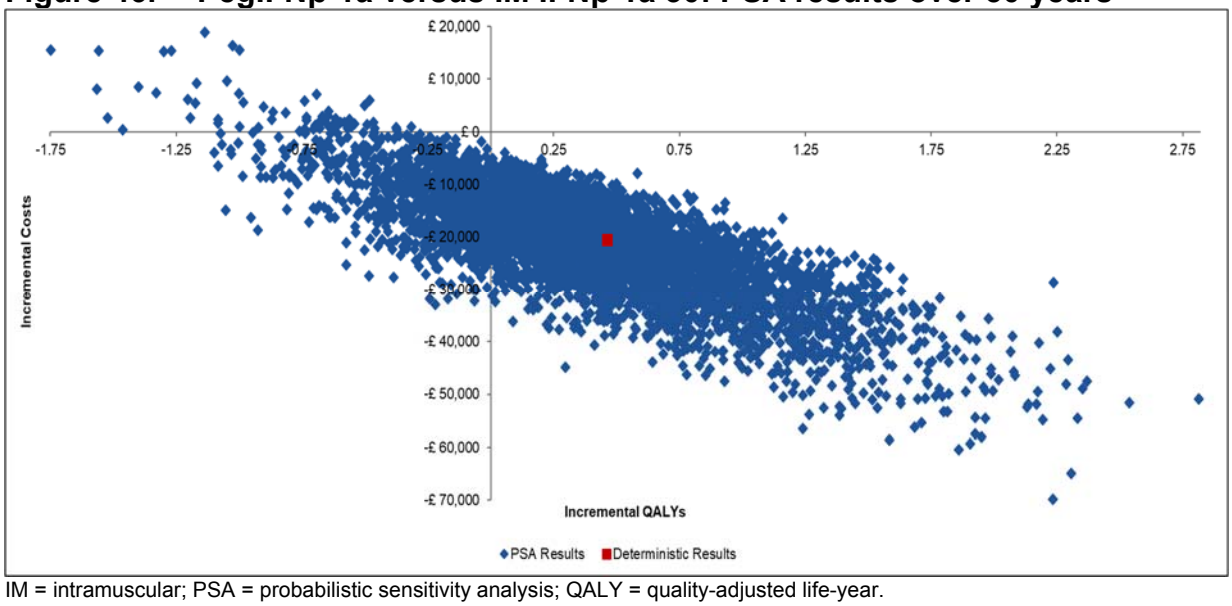
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SC = subcutaneous.

Figure 45. PegIFNβ-1a versus SC IFNβ-1a 44: cost-effectiveness acceptability curve



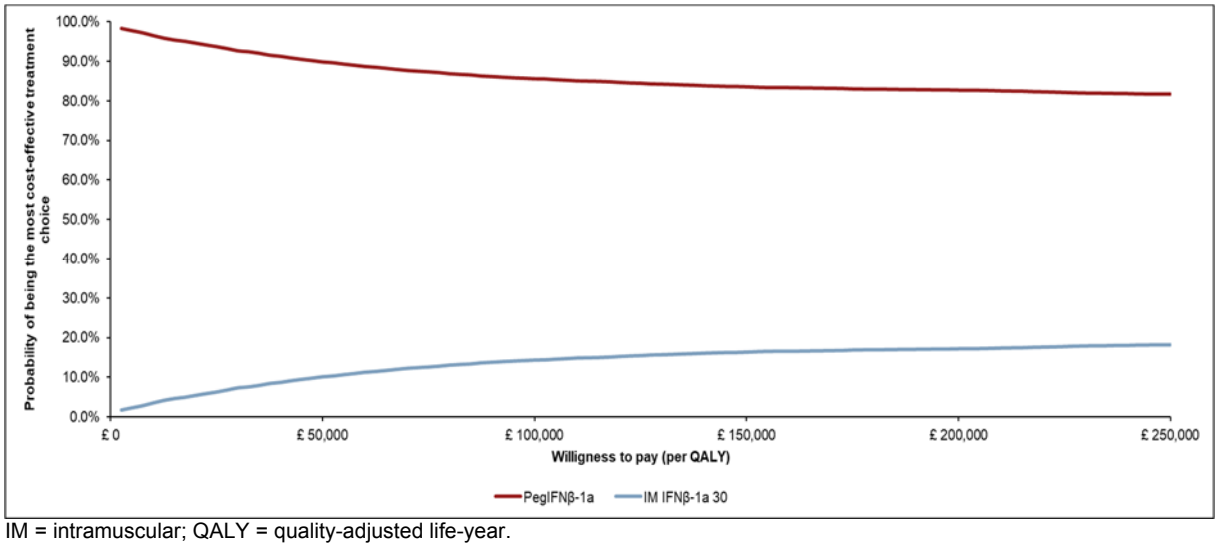
QALY = quality-adjusted life-year; SC = subcutaneous.

Figure 46. PegIFNβ-1a versus IM IFNβ-1a 30: PSA results over 50 years



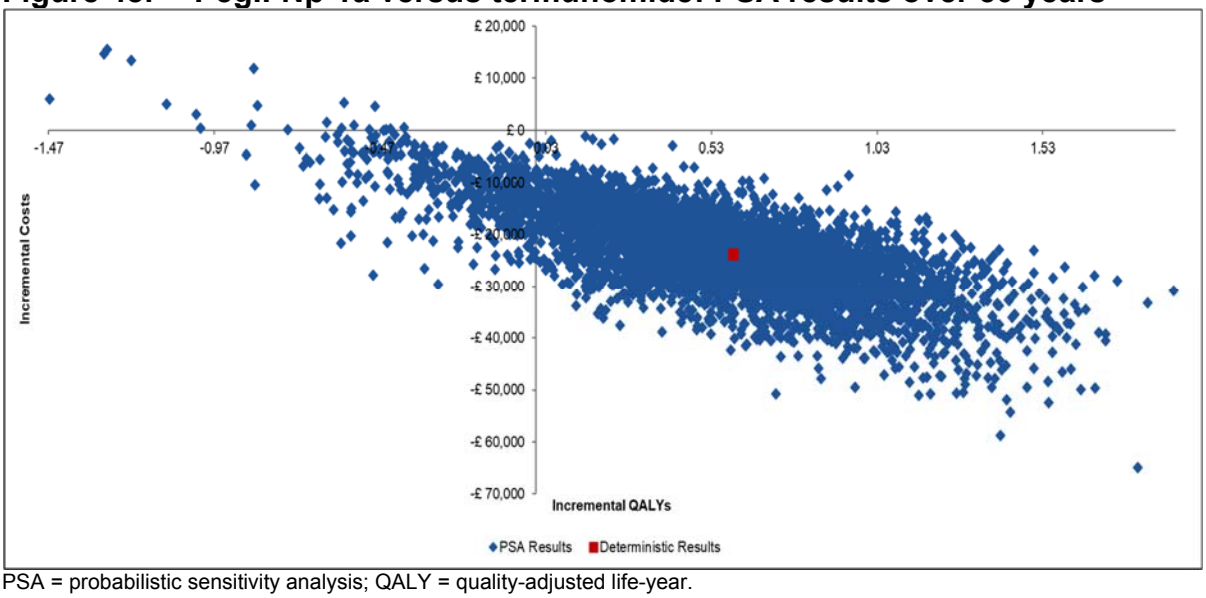
IM = intramuscular; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 47. PegIFNβ-1a versus IM IFNβ-1a 30: cost-effectiveness acceptability curve



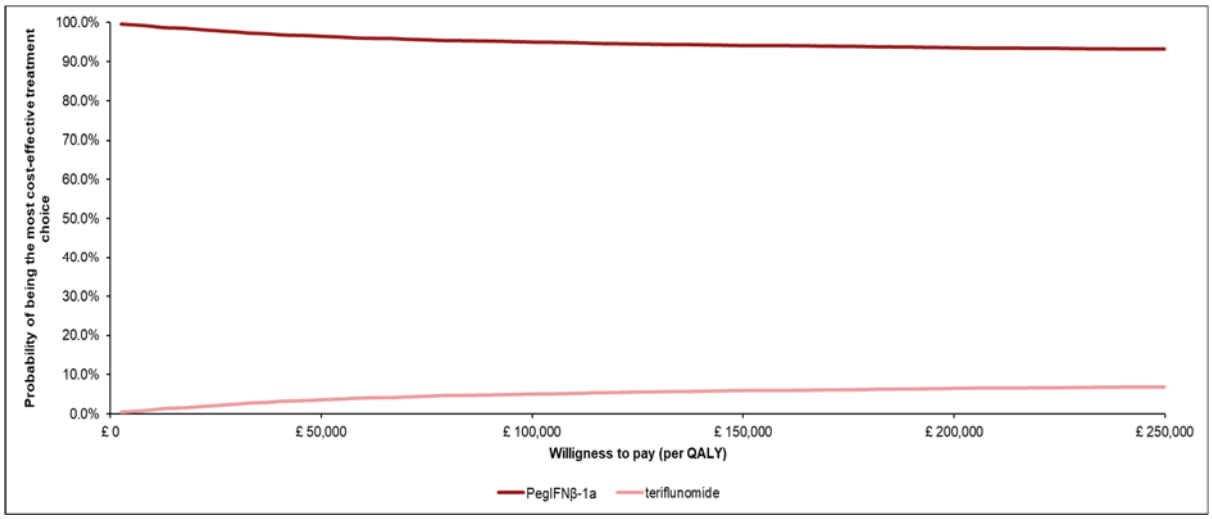
IM = intramuscular; QALY = quality-adjusted life-year.

Figure 48. PegIFNβ-1a versus teriflunomide: PSA results over 50 years



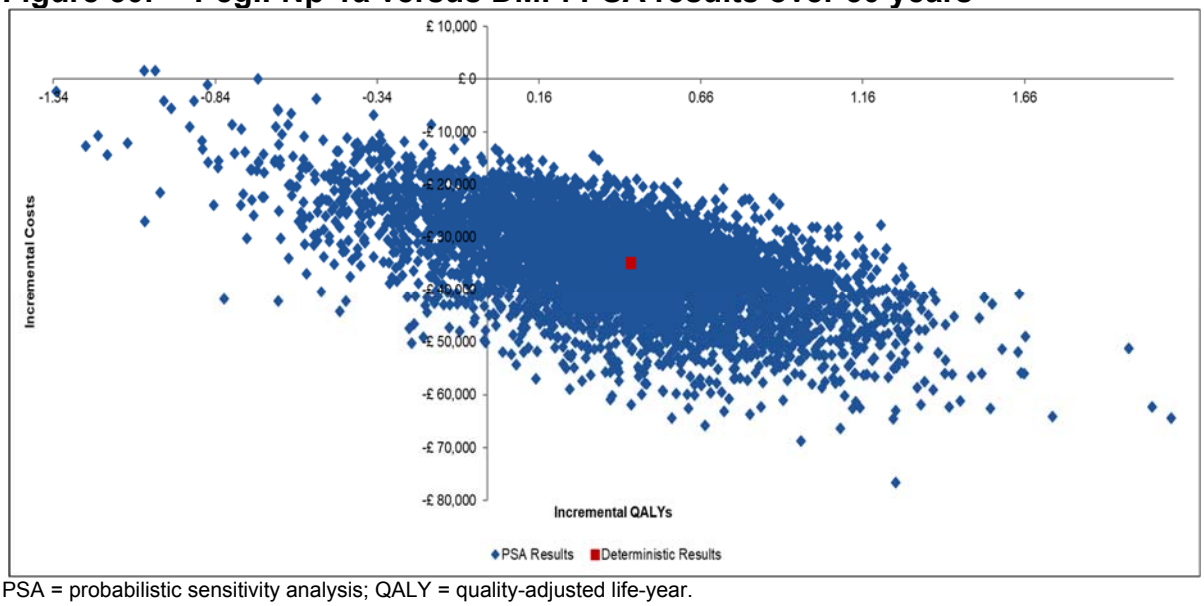
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 49. PegIFNβ-1a versus teriflunomide: cost-effectiveness acceptability curve



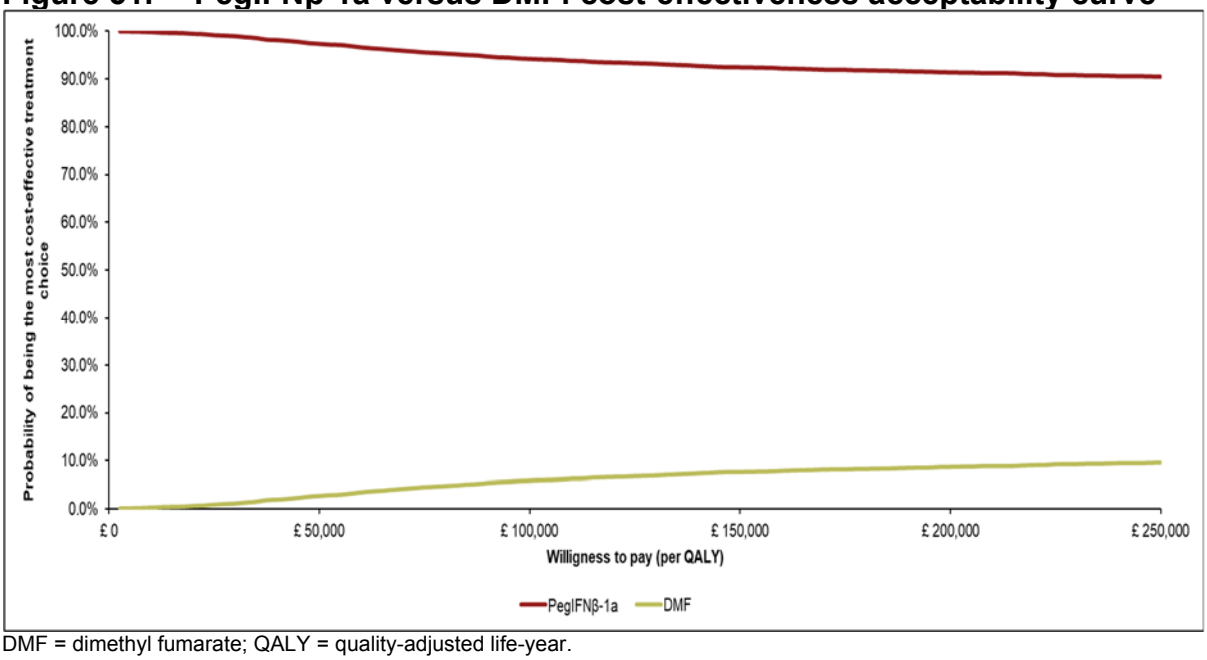
QALY = quality-adjusted life-year.

Figure 50. PegIFNβ-1a versus DMF: PSA results over 50 years



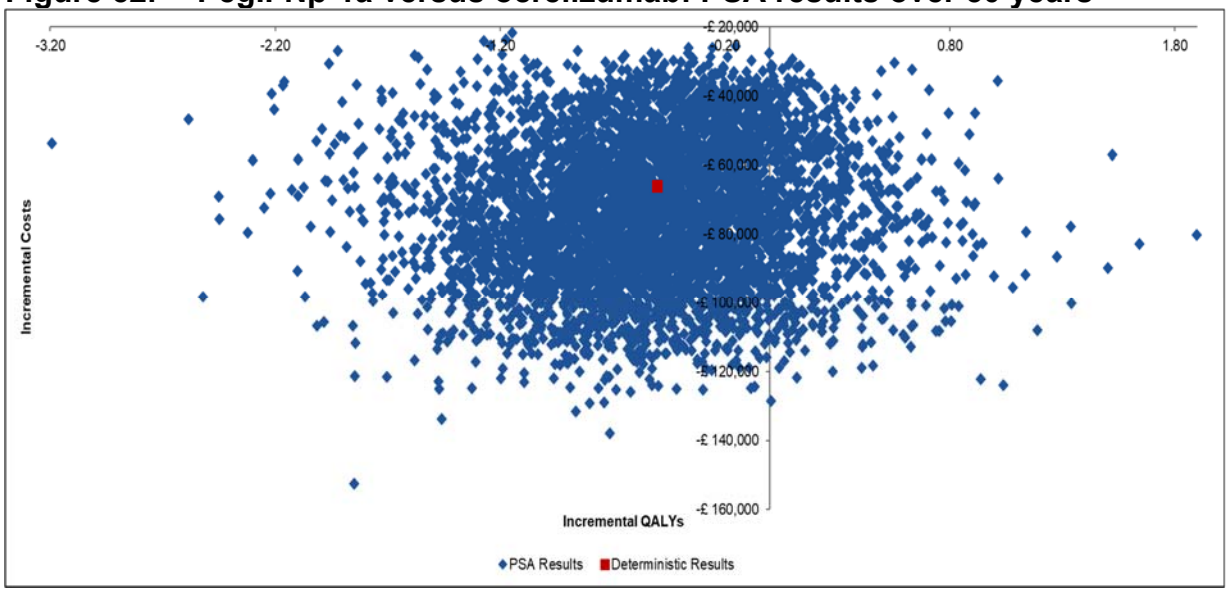
PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 51. PegIFNβ-1a versus DMF: cost-effectiveness acceptability curve



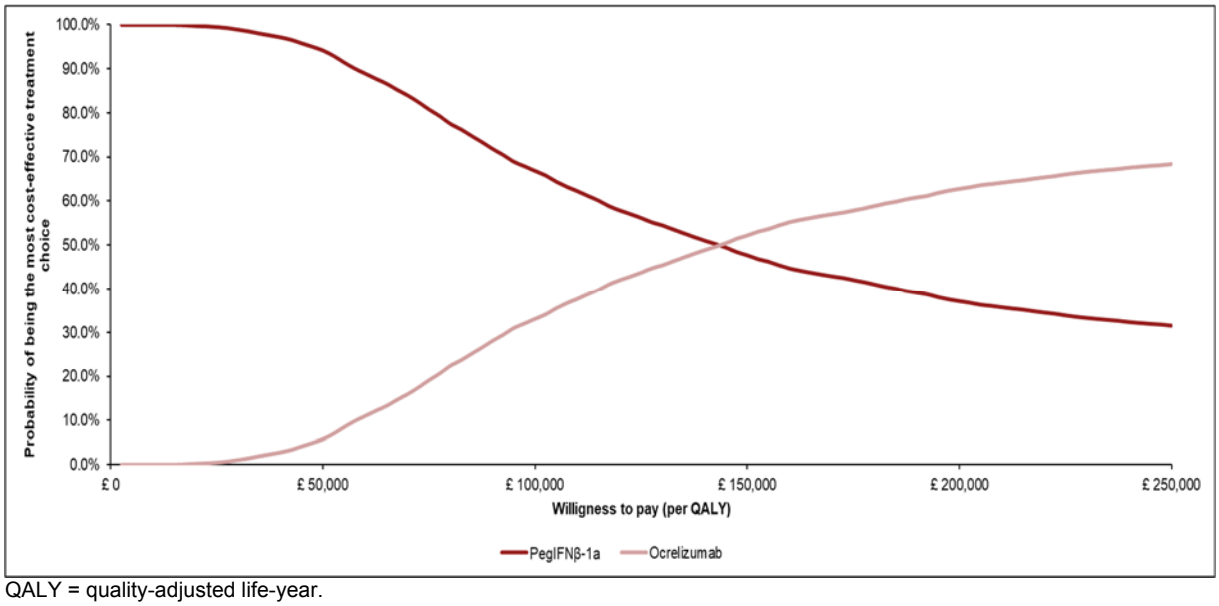
DMF = dimethyl fumarate; QALY = quality-adjusted life-year.

Figure 52. PegIFNβ-1a versus ocrelizumab: PSA results over 50 years



PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Figure 53. PegIFNβ-1a versus ocrelizumab: cost-effectiveness acceptability curve



QALY = quality-adjusted life-year.

B.3.8.2 Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was carried out to evaluate how sensitive the estimated incremental cost, incremental QALYs, and ICER were to changes in each model parameter. OWSAs were conducted by systematically and iteratively varying one model parameter while holding all others constant. Where a standard error or CI was not available for a selected parameter, a ± 20% variation from the base-case value was assumed for the lower and upper bounds.

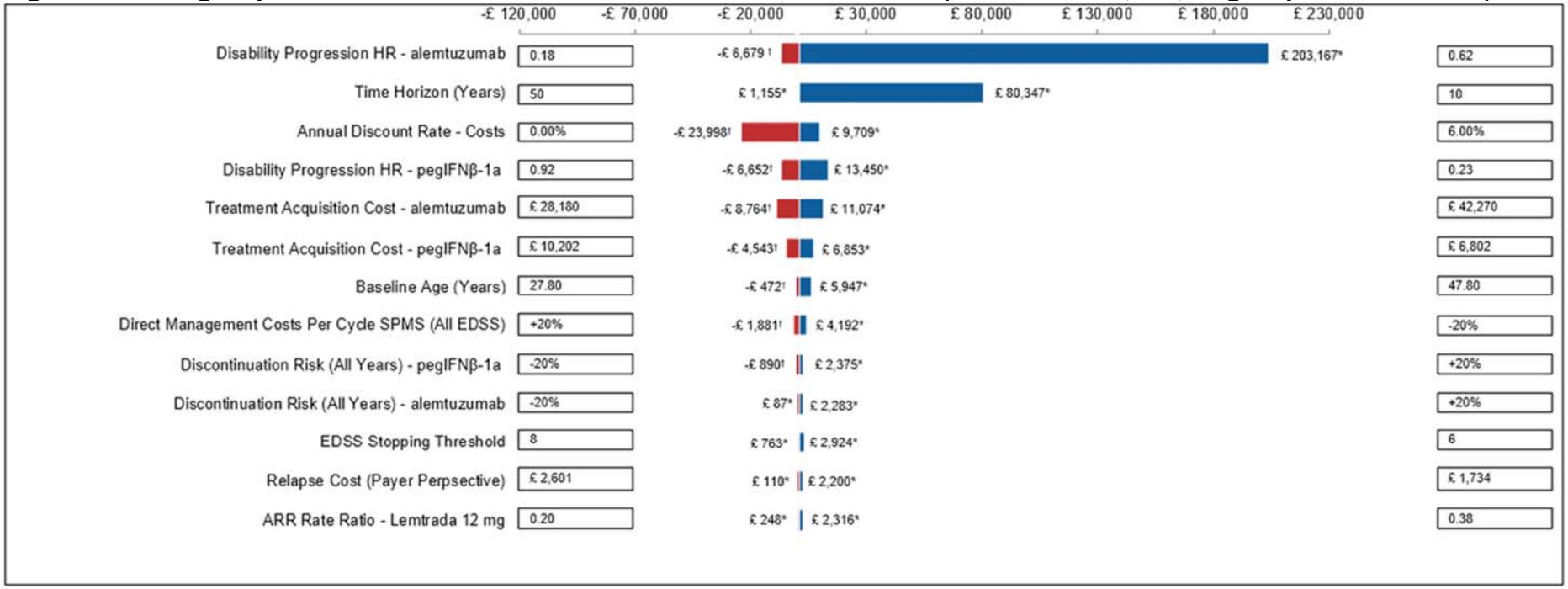
The results of the OWSA are presented as discounted per patient over 50 years. Tornado charts (Figure 54 to Figure 63) are used to illustrate the parameters that have the biggest impact on the results. In terms of the ICER, a willingness-to-pay threshold of £20,000 per QALY is used to determine cost-effectiveness.

The results from the OWSA show that the base-case results are robust, given that in most cases the OWSA results are in agreement with the base case.

- Compared with alemtuzumab (Figure 54), pegIFNβ-1a was a less costly and less effective in all but the following scenarios in which pegIFNβ-1a was dominated (more costly and less effective):
  - When the HR on disability progression for alemtuzumab was decreased to the lower bound of its 95% CI (i.e. alemtuzumab was assumed to better than in the base case)
  - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e. pegIFNβ-1a was assumed to worse than in the base case)
  - When the drug acquisition cost of alemtuzumab was using the lower bound, or the drug acquisition cost of pegIFNβ-1a was using the upper bound
  - When the baseline age was the lower bound
  - When the discontinuation rate of pegIFNβ-1a was lowered 20%
  - When the cost of disease management of EDSS in SPMS was increased 20%
- Compared with genGA 20 (Figure 55), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all but the following scenario where pegIFNβ-1a was dominated or cost-effective:
  - When the HR on disability progression for genGA 20 was decreased to the lower bound of its 95% CI (i.e. genGA 20 was assumed to better than in the base case)
  - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to worse than in the base case)
  - When the time horizon was reduced to 10 years (ICER = £1,904)
- Compared with genGA 40 (Figure 56), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all but the following scenario, in which pegIFNβ-1a was where pegIFNβ-1a was dominated:
  - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to worse than in the base case)
- Compared with GA 20 (Figure 57), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all scenarios where pegIFNβ-1a was dominated.
  - When the HR on disability progression for GA 20 was decreased to the lower bound of its 95% CI (i.e. GA 20 was assumed to better than in the base case)

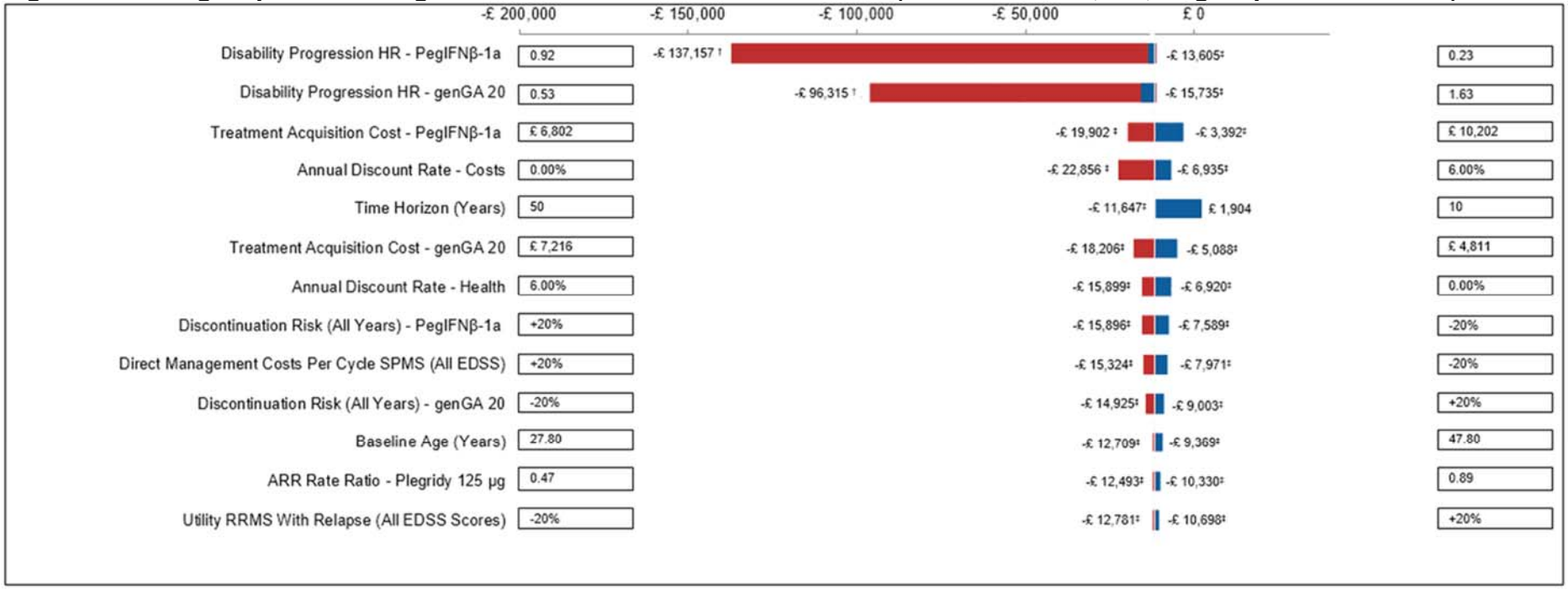
    - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to worse than in the base case)
- Compared with GA 40 (Figure 58), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all scenarios but the following scenario, in which pegIFNβ-1a was less costly and less effective:
    - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to worse than in the base case)
- Compared with SC IFNβ-1a 44 (Figure 59), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all but two scenarios, in which pegIFNβ-1a was less costly and less effective:
    - When the HR on disability progression for IFNβ-1a 44 was reduced to the lower bound of its 95% CI (i.e., SC IFNβ-1a 44 was assumed to perform better than in the base case)
    - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to perform worse than in the base case)
- Compared with IM IFNβ-1a 30 (Figure 60), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all but two scenarios in which pegIFNβ-1a was less costly and less effective:
    - When the HR on disability progression for IM IFNβ-1a 30 was reduced to the lower bound of its 95% CI (i.e., IM IFNβ-1a was assumed to perform better than in the base case)
    - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to perform worse than in the base case)
- Compared with teriflunomide (Figure 61), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all but one scenario in which pegIFNβ-1a was less costly and less effective:
    - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to perform worse than in the base case)
- Compared with DMF (Figure 62), pegIFNβ-1a was a dominant treatment (i.e., less costly and more effective) in all but one scenario in which pegIFNβ-1a was less costly and less effective:
    - When the HR on disability progression for pegIFNβ-1a was increased to the upper bound of its 95% CI (i.e., pegIFNβ-1a was assumed to perform worse than in the base case)
- Compared with ocrelizumab (Figure 63), pegIFNβ-1a was less costly and less effective in all but one scenario in which pegIFNβ-1a was dominant (i.e., was less costly and more effective):
    - When the HR on disability progression for ocrelizumab was increased to the upper bound of its 95% CI (i.e., ocrelizumab was assumed to perform worse than in the base case)

Figure 54. PegIFNβ-1a versus alemtuzumab: ICER results of the OWSA (base case: £1,155, PegIFNβ-1a dominated)



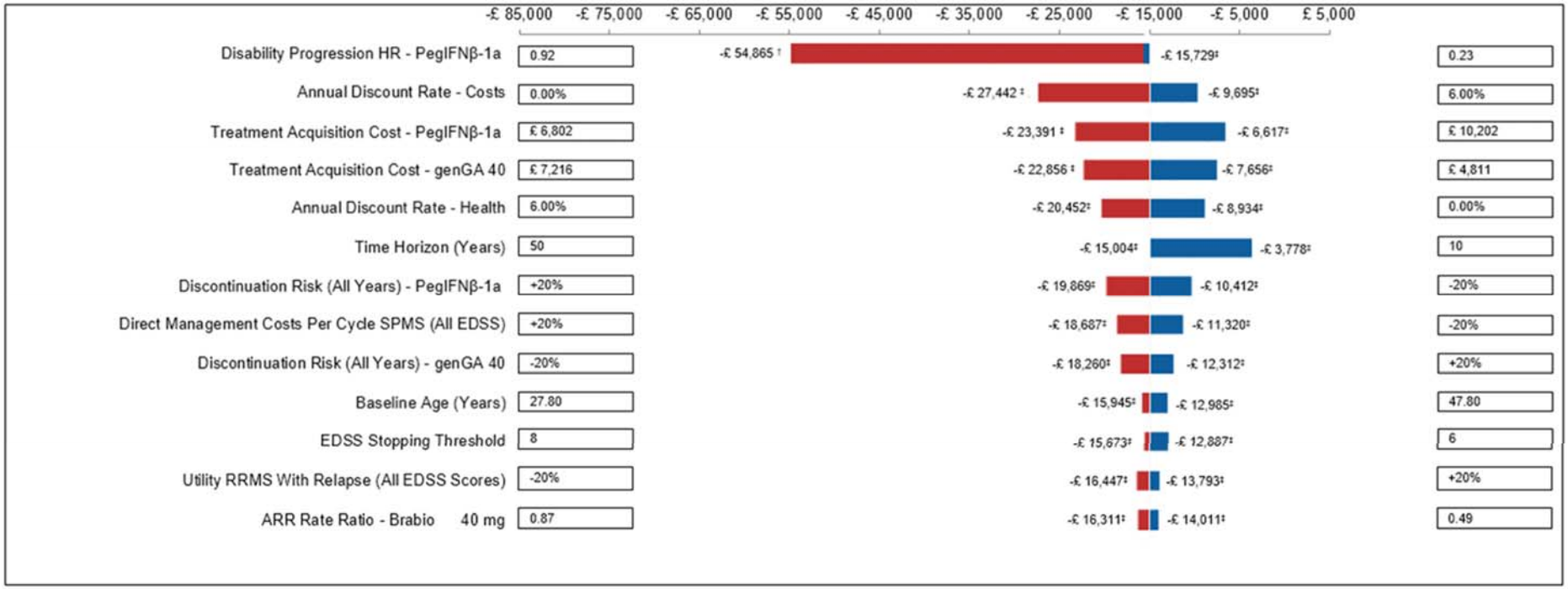
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
† PegIFNβ-1a dominated
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 55. PegIFNβ-1a versus genGA 20: ICER results of the OWSA (base case £-11,647, PegIFNβ-1a dominates)



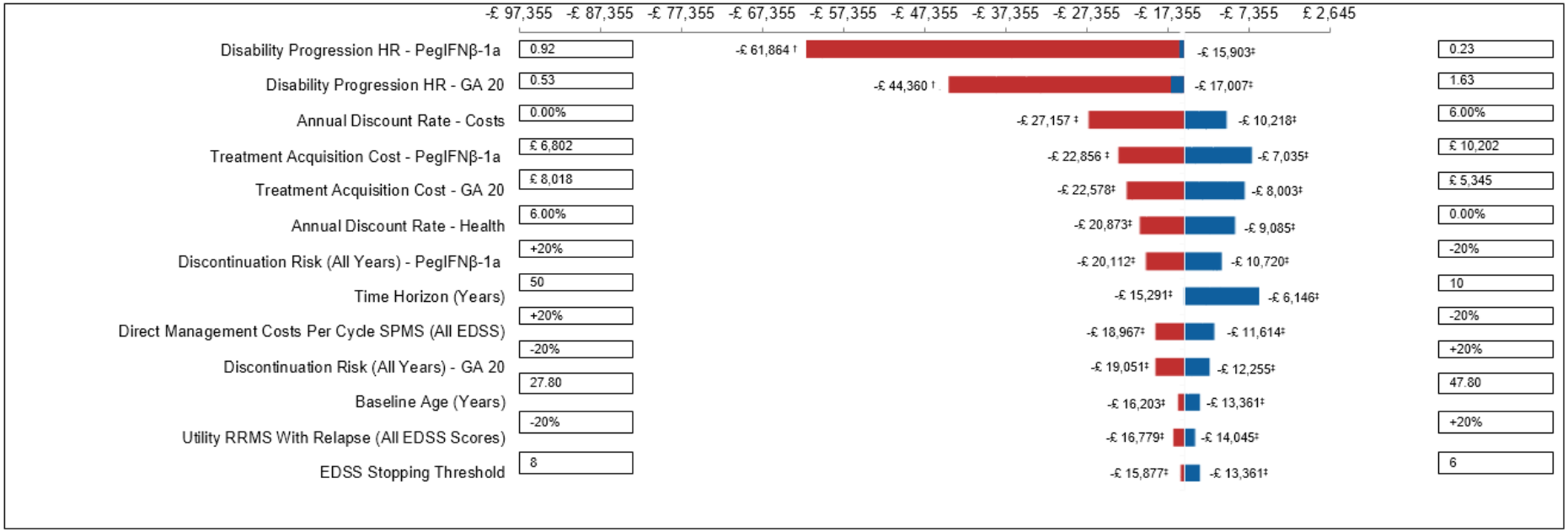
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; genGA = generic glatiramer acetate; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
† PegIFNβ-1a dominated
‡ PegIFNβ-1a dominates
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 56. PegIFNβ-1a versus genGA 40: ICER results of the OWSA (base case −£15,004, PegIFNβ-1a dominates)



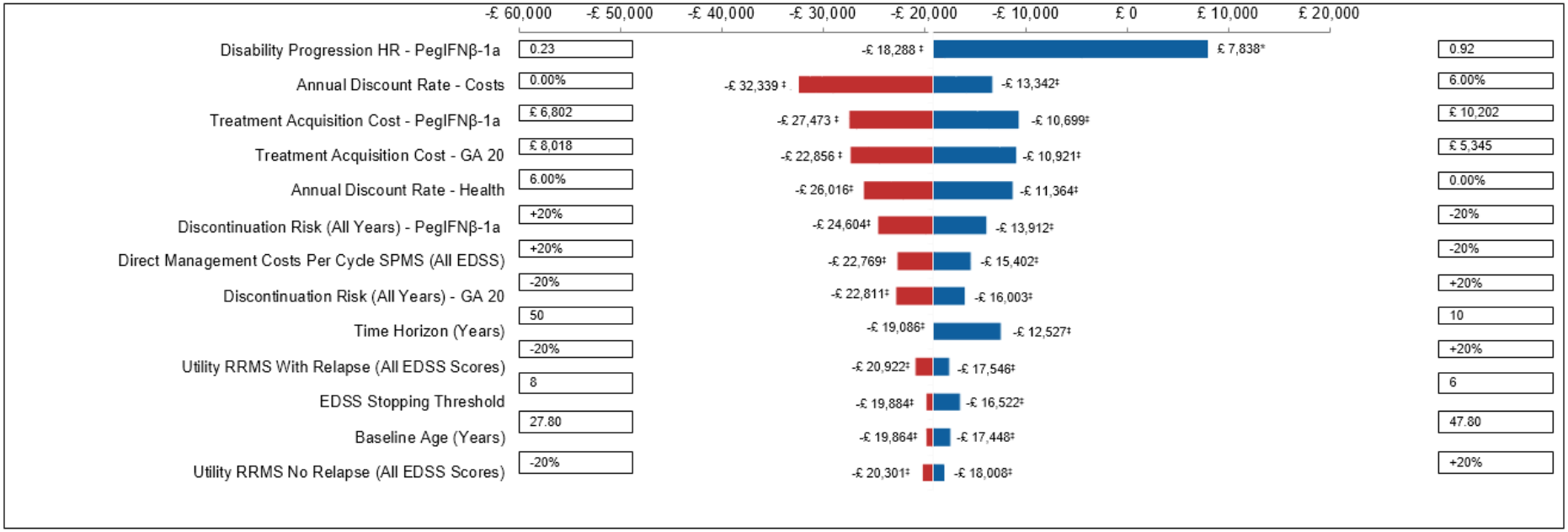
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; genGA = generic glatiramer acetate; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
† PegIFNβ-1a dominated
‡ PegIFNβ-1a dominates
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 57. PegIFNβ-1a versus GA 20: ICER results of the OWSA (base case −£15,291 PegIFNβ-1a dominates)



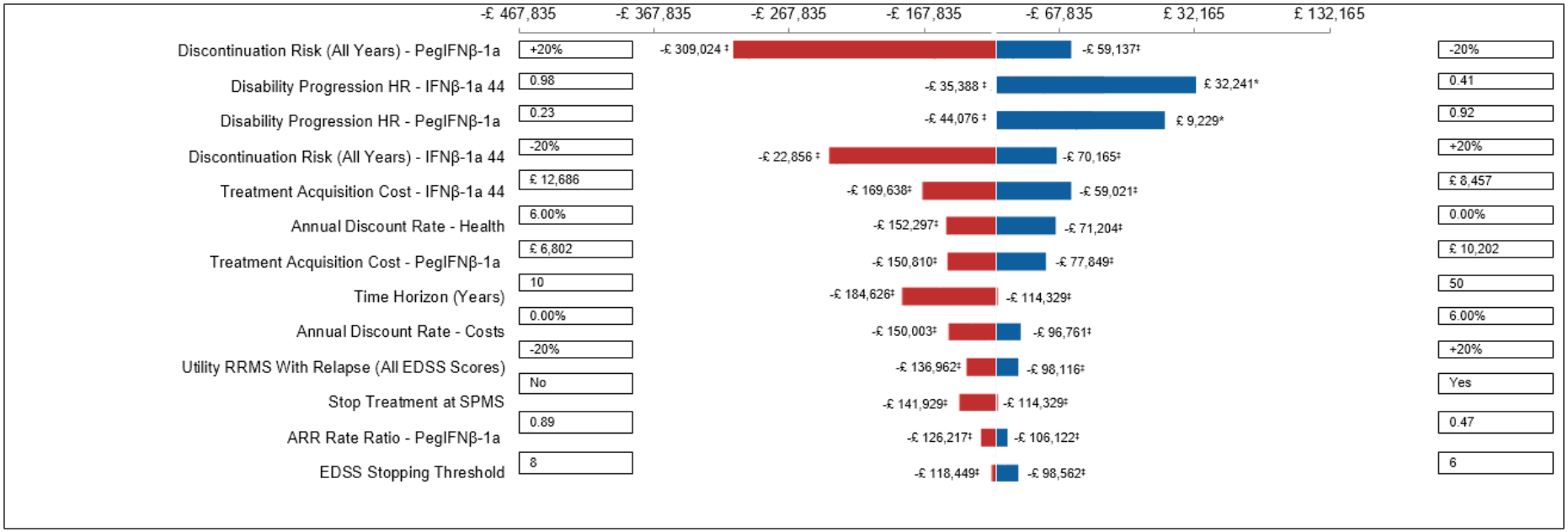
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
† PegIFNβ-1a dominated
‡ PegIFNβ-1a dominates
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 58. PegIFNβ-1a versus GA 40: ICER results of the OWSA (base case −£19,086, PegIFNβ-1a dominates)



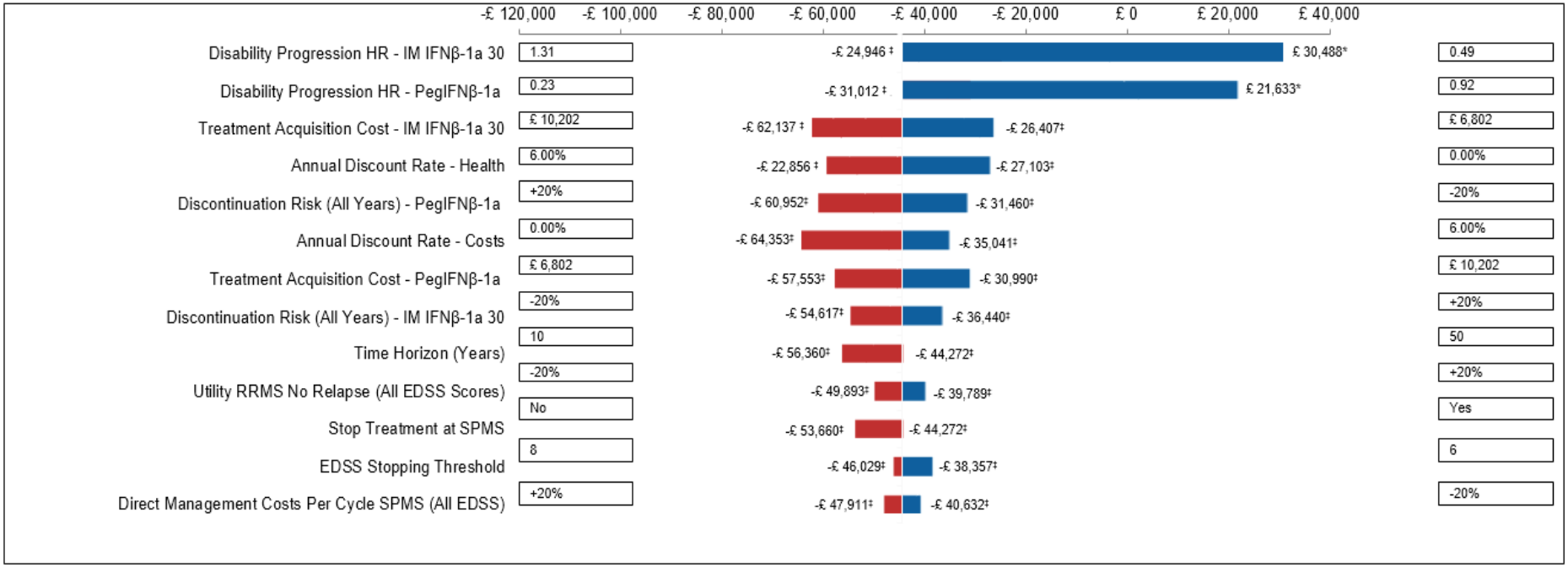
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
‡ PegIFNβ-1a dominates
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 59. PegIFNβ-1a versus IFNβ-1a 44: ICER results of the OWSA (base case −£114,329 PegIFNβ-1a dominates)



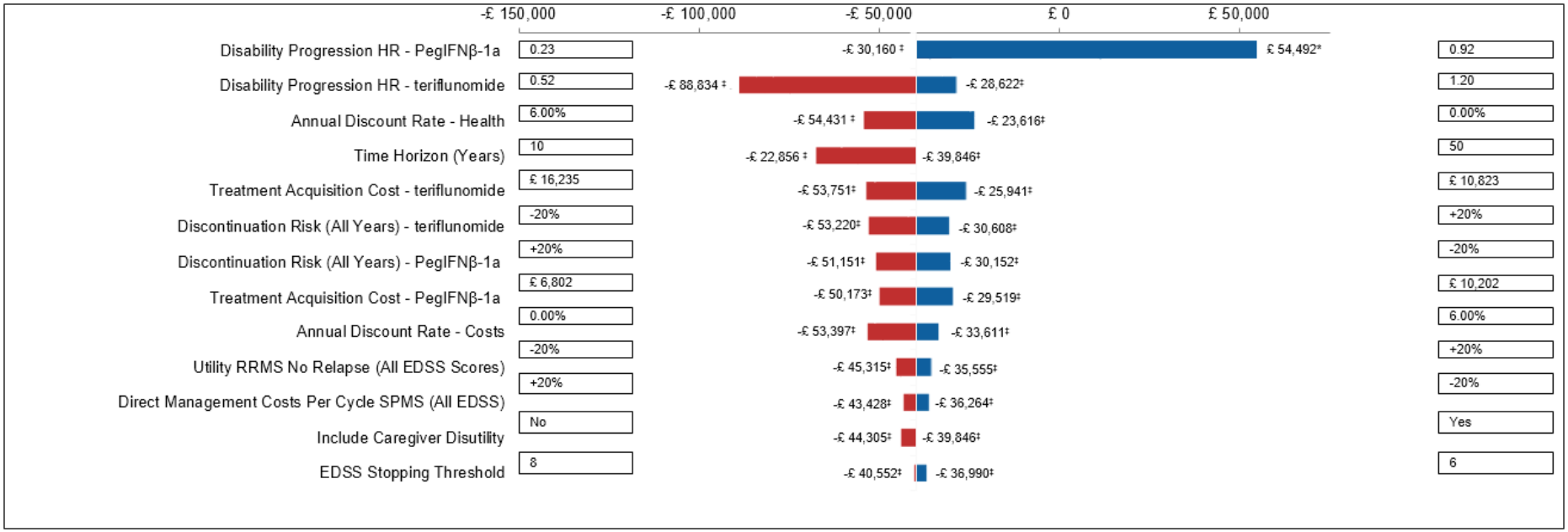
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
‡ PegIFNβ-1a dominates
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 60. PegIFNβ-1a versus IM IFNβ-1a 30: ICER results of the OWSA (base case −£44,272 PegIFNβ-1a dominates)



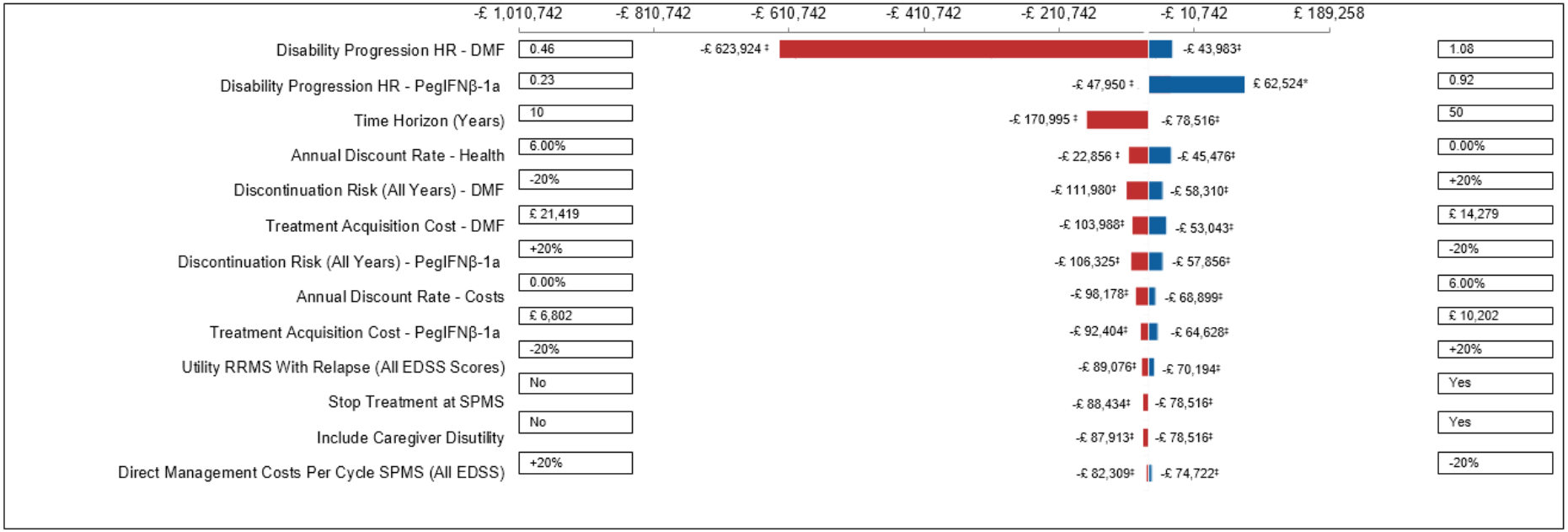
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; genGA = generic glatiramer acetate; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IM = intramuscular; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
‡ PegIFNβ-1a dominates
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 61. PegIFNβ-1a versus teriflunomide: ICER results of the OWSA (base case −£39,846, PegIFNβ-1a dominates)



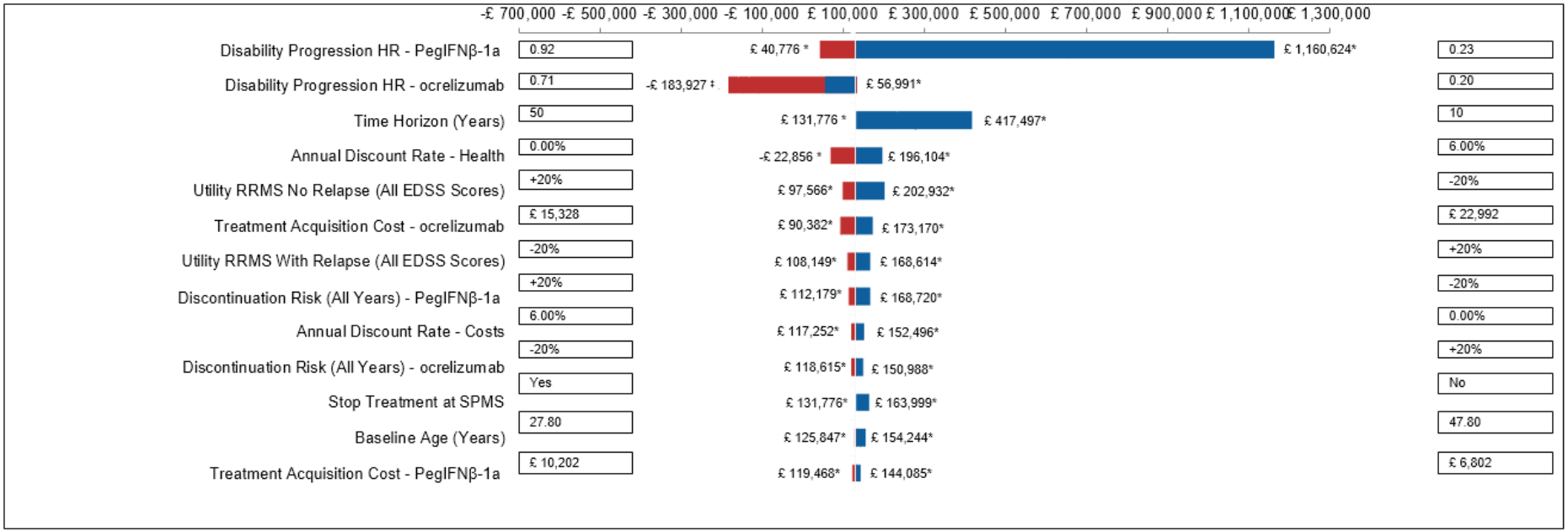
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis
‡ PegIFNβ-1a dominates
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 62. PegIFNβ-1a versus DMF: ICER results of the OWSA (base case: −£80,002, PegIFNβ-1a dominates)



ARR = annualised relapse rate; DMF = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
‡ PegIFNβ-1a dominates
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

Figure 63. PegIFNβ-1a versus ocrelizumab: ICER results of the OWSA (base case: £131,776, pegIFNβ-1a LCLE)



ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LCLE = less costly, less effective; OWSA = one-way sensitivity analysis; pegIFNβ-1a = pegylated interferon; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
‡ PegIFNβ-1a dominates
* PegIFNβ-1a less costly, less effective
Red bars indicate the ICER of the lower bound value.
Blue bars indicate the ICER of the upper bound value.

B.3.8.3 Scenario analysis

Scenario analyses (Table 48) were performed to evaluate how the model outcomes varied in relation to changes in key model parameter(s), and to examine whether the model results were robust to those variations.

Table 48. Description of the scenario analysis

Scenario	Description
BC – disc.	Base case discounted
S1	Time horizon: 20 years
S2	Discounting costs 0%; effects 1.5%
S3	Discounting costs 1.5%; effects 0%
S4	Patient characteristics from TA527 report; RSS
S5	Natural History relapse rate from TA527 report
S6	Natural History transition from RRMS to SPMS = 0
S7	Relative efficacy using CDP3M
S8	Discontinuations; parity assumptions 5% for all DMTs; ID 527 report
S9	Discontinuations; Weighted randomised controlled trial ADRs only
S10	Waning effect - none
S11	Adverse events - exclude from analysis
S12	Health state utility - from TA527 report
S13	Caregiver disutility - from Gani et al. (2008)[212]
S14	Health state costs – Tyas et al. (2007) [83] - 25% non-medical costs
S15	Health state costs - Tyas et al. (2007) [83] - 100% non-medical costs
S16	Health states costs BOI - 100% community & adaptations
S17	Mortality SMR 2.8 – Kingwell et al. (2012)[76]

ADR = adverse drug reaction; BOI = burden of illness; CDP = confirmed disability progression; RRMS = relapsing-remitting multiple sclerosis; RSS = Risk Sharing Scheme; SMR = standardised mortality ratio; SPMS = secondary-progressive multiple sclerosis; TA = technology appraisal.

Results of the scenario analyses using list prices demonstrated consistency with the base-case results where pegIFNβ-1a was dominant (i.e., less costly and more effective) when compared with GA 20, GA 40, genGA 20, genGA 40, IFNβ-1b 44, IFNβ-1b, IM IFNβ-1a 30, teriflunomide, and DMF. Against ocrelizumab, pegIFNβ-1a was less costly and less effective in all analyses; the ICERs for ocrelizumab relative to pegIFNβ-1a were consistently above the standard willingness-to-pay threshold of £20,000 to £30,000 per QALY gained. Compared with alemtuzumab, pegIFNβ-1a was either less costly and less effective or dominated (Table 49).

Table 49. Scenario analysis results

Scenario	pegIFNβ-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	ocrelizumab	alemtuzumab
Base case - discounted												
QALY	4.39	0.75	0.74	0.75	0.74	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£273,641	-£11,423	-£14,035	-£8,701	-£11,033	-£19,328	NA	-£20,557	-£23,796	-£34,865	-£66,027	-£1,250
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S1: Time horizon 20 years												
QALY	5.07	0.60	0.59	0.60	0.59	0.14	NA	0.38	0.47	0.35	-0.32	-0.67
Costs	£157,837	-£9,156	-£11,704	-£6,452	-£8,732	-£18,656	NA	-£18,907	-£22,015	-£33,398	-£68,109	-£10,952
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S2: Discount rates: 0% for costs and 1.5% for outcomes												
QALY	4.45	0.99	0.98	0.99	0.98	0.22	NA	0.61	0.79	0.60	-0.73	-1.58
Costs	£561,870	-£20,288	-£23,780	-£17,075	-£20,179	-£25,358	NA	-£29,882	-£31,888	-£43,596	-£76,408	£25,973
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S3: Discount rates: 1.5% for costs and 0% for outcomes												
QALY	4.20	1.26	1.23	1.26	1.23	0.27	NA	0.76	1.01	0.77	-1.00	-2.17
Costs	£403,699	-£15,830	-£18,895	-£12,847	-£15,578	-£22,439	NA	-£25,278	-£27,891	-£39,355	-£72,190	£11,287
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S4: Patient characteristics from TA527 report; RSS												
QALY	3.06	0.70	0.69	0.70	0.69	0.16	NA	0.44	0.56	0.41	-0.44	-0.97
Costs	£322,864	-£11,347	-£13,588	-£8,871	-£10,871	-£17,702	NA	-£18,999	-£22,924	-£32,978	-£58,626	-£3,127
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE

S5: Natural History relapse rate from ID527 report												
QALY	4.45	0.74	0.73	0.74	0.73	0.17	NA	0.46	0.59	0.44	-0.50	-1.08
Costs	£271,372	-£11,236	-£13,848	-£8,514	-£10,847	-£19,283	NA	-£20,431	-£23,633	-£34,753	-£66,197	-£1,535
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S6: Natural History transition from RRMS to SPMS = 0												
QALY	7.98	0.69	0.68	0.69	0.68	0.12	NA	0.40	0.57	0.41	-0.70	-1.48
Costs	£211,655	-£11,626	-£16,140	-£8,048	-£12,082	-£25,582	NA	-£27,410	-£25,247	-£39,670	-£100,057	£10,182
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S7: Relative efficacy using CDP-3M												
QALY	4.11	0.34	0.32	0.34	0.32	-0.14	0.40	0.02	0.17	0.13	-0.81	-1.85
Costs	£278,554	-£4,357	-£6,830	-£1,600	-£3,784	-£14,019	-£14,176	-£13,181	-£16,458	-£29,507	-£60,915	£12,604
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S8: Discontinuations; parity assumptions 5% for all DMTs; ID 527 report												
QALY	4.95	1.25	1.26	1.25	1.26	0.51	NA	0.96	0.92	0.66	-0.10	-0.22
Costs	£285,041	-£8,205	-£8,490	-£4,527	-£4,812	-£19,896	NA	-£14,977	-£43,875	-£64,217	-£65,168	£5,910
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S9: Discontinuations; Weighted RCT ADRs only												
QALY	4.93	1.20	1.21	1.20	1.21	0.42	NA	0.88	0.97	0.75	-0.50	-0.77
Costs	£284,511	-£13,884	-£12,848	-£9,608	-£8,730	-£24,125	NA	-£20,566	-£34,424	-£50,938	-£92,175	£12,966
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S10: Waning effect - none												
QALY	4.65	0.97	0.95	0.97	0.95	0.19	NA	0.57	0.79	0.60	-1.00	-2.18
Costs	£269,468	-£14,979	-£17,492	-£12,247	-£14,476	-£20,011	NA	-£22,473	-£26,943	-£37,621	-£65,144	£18,475

ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S11: Adverse events - excluded from analysis												
QALY	4.41	0.77	0.75	0.77	0.75	0.18	NA	0.48	0.62	0.46	-0.48	-1.07
Costs	£273,637	-£11,427	-£14,039	-£8,705	-£11,037	-£19,330	NA	-£20,560	-£23,800	-£34,860	-£66,031	-£1,048
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S12: Health state utility - from TA527 report												
QALY	4.20	0.73	0.72	0.73	0.72	0.17	NA	0.46	0.59	0.44	-0.50	-1.07
Costs	£273,641	-£11,423	-£14,035	-£8,701	-£11,033	-£19,328	NA	-£20,557	-£23,796	-£34,865	-£66,027	-£1,250
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S13: Caregiver disutility - from Gani. 2008												
QALY	4.66	0.75	0.74	0.75	0.74	0.17	NA	0.47	0.60	0.45	-0.51	-1.09
Costs	£273,641	-£11,423	-£14,035	-£8,701	-£11,033	-£19,328	NA	-£20,557	-£23,796	-£34,865	-£66,027	-£1,250
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S14: Disease management costs - Health state costs - Tyas 2007 - 25% non-medical costs												
QALY	4.39	0.75	0.74	0.75	0.74	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£284,293	-£9,134	-£11,784	-£6,412	-£8,782	-£18,830	NA	-£19,203	-£21,995	-£33,481	-£67,231	-£4,119
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S15: Disease management costs -Health state costs - Tyas 2007 -100% non-medical costs												
QALY	4.39	0.75	0.74	0.75	0.74	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£471,303	-£15,216	-£17,779	-£12,494	-£14,777	-£20,326	NA	-£22,910	-£26,739	-£37,218	-£62,512	£4,736
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
S16: Disease management costs - Health states costs BOI - 100% community & adaptations												

QALY	4.39	0.75	0.74	0.75	0.74	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£213,637	-£6,362	-£9,052	-£3,641	-£6,051	-£18,148	NA	-£17,538	-£19,869	-£31,786	-£69,088	-£7,726
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
S17: Mortality SMR – Kingwell 2012												
QALY	4.09	0.75	0.74	0.75	0.74	0.17	NA	0.47	0.60	0.44	-0.48	-1.05
Costs	£289,241	-£12,793	-£15,344	-£10,086	-£12,361	-£19,500	NA	-£21,220	-£24,859	-£35,642	-£64,223	£495
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated

ADR = adverse drug reaction; BOI = burden of illness; CDP = confirmed disability progression; DMF = dimethyl fumarate; DMT = disease-modifying therapy; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = , incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LCLE = less costly, less effective; MS = multiple sclerosis; NHS = National Health Service; PSS = personal social services; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; RSS = Risk Sharing Scheme; SC = subcutaneous; SMR = standardised mortality ratio; SPMS = secondary-progressive multiple sclerosis; TA = technology appraisal.

B.3.8.4 Summary of sensitivity analyses results

In Section B.3.8, it has been shown that the results are robust and not sensitive to changes in important parameters. The scenario analyses show that the presented base-case ICER is conservative in relation to most parameters.

B.3.9 Subgroup analysis

The specified subgroup of 'people who could not tolerate previous treatment' was not performed due to lack of clinical data.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The validation of the cost-effectiveness outcomes based on the economic model for pegIFNβ-1a and all comparators considered in the economic analysis conducted for this submission can be found in Appendix J. The breakdown of the clinical outcomes based on the economic model runs is also provided in Appendix J.

B.3.11 Interpretation and conclusions of economic evidence

- **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

The results are consistent with the previous evaluations of pegIFNβ-1a against other DMTs. For example, NICE TA527[170], which evaluated pegIFNβ-1a against IFNβ-1a, IFNβ-1b, and GA (excluded alemtuzumab) in the UK, suggested that "a longer-acting interferon (Plegridy®) was the most cost-effective option for RRMS…" using the Department of Health RSS base-case model and with individual HRs. This is the only UK-based economic evaluation that includes pegIFNβ-1a in the analysis. Centonze et al. (2018)[222] has conducted a cost-effectiveness analysis from a payer perspective on RRMS in Italy. The study has shown that pegIFNβ-1a was dominant against SC IFNβ-1a 44 and cost-effective versus all other DMTs included, using the same model structure as the one used to inform this dossier. PegIFNβ-1a was dominant against all comparators from a societal perspective. In an economic evaluation that included pegIFNβ-1a, Walter et al. (2019)[223] has shown that alemtuzumab is a cost-saving treatment option in the treatment of RRMS in Austria.

- **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?**

The economic evaluation is relevant to all adult patients with RRMS, as per the scope of this technology appraisal.

- **How relevant (generalisable) is the analysis to clinical practice in England?**

The patient population in ADVANCE, BCMS, and London, Ontario, data sets used to inform the economic analysis is reflective of adult patients with RRMS in the UK, as suggested in NICE TA527.[170] Therefore, the clinical outcomes are likely to be applicable to the patient population in England.

The economic model structure, QOL, and resource use/cost sources are in line with previous submissions to NICE on RRMS (see Section B.3.2.2).

The economic evaluation is relevant to all adult patients with RRMS that is not highly active or RES.

- **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

The main data sources and modelling approach are largely in line with the relevant NICE technology appraisals. The MTC conducted by Biogen to inform the HRs related to the CDP used the 6-month follow-up outcomes, which is the preferred approach by NICE. However, this meant that the treatment options IFNβ-1a 22, IFNβ-1b, GA 40, and genGA 40 had to be either excluded from the analyses or assumed at parity to GA 20 due to lack of data.

- **What further analyses could be carried out to enhance the robustness or completeness of the results?**

A scenario analyses in the absence of alemtuzumab, the dominant treatment options in the analysis conducted to inform this dossier, would help with understanding the findings specific to the remaining treatment options, particularly for IFNβ-1a and GA.

B.3.11.1 Concluding remarks of the economic evaluation

These analyses predicted that the health benefits observed in the ADVANCE trial for pegIFNβ-1a are expected to be sustained over a longer term after accounting for treatment discontinuation due to AEs and lack of efficacy. They are also expected to be gained at a lower cost than that of genGA 20, GA 20, SC IFNβ-1a 44, IM IFNβ-1a, teriflunomide, and DMF. Compared with these DMTs, the health benefits associated with pegIFNβ-1a in terms of delaying patient disability progression also translate to higher QALYs over time, hence making pegIFNβ-1a a dominant treatment (i.e., more effective and less expensive). For the comparison with ocrelizumab, pegIFNβ-1a returned less clinical benefit (QALYs) but was also less expensive; the additional cost-per-QALY that will be required to receive ocrelizumab instead of pegIFNβ-1a makes ocrelizumab a non-cost-effective treatment. Compared with alemtuzumab, pegIFNβ-1a had a higher total cost and lower QALYs, thus pegIFNβ-1a was a dominated treatment.

PegIFNβ-1a remains a valuable option in the treatment of patients with RRMS. The ADVANCE trial shows clinical benefit of pegIFNβ-1a in comparison with placebo, and the MTC shows clinical benefit of pegIFNβ-1a in comparison with other IFNs and other DMTs.

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Single technology appraisal

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 7th June 2019 from Biogen Idec. In general, they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by **5pm** on **Tuesday 16th July 2019**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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

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

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

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

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely
Carl Prescott
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on clinical-effectiveness data

LITERATURE SEARCHING

Search dates

A1. Company submission (CS), Document C (Appendices), Appendix D, section D.1.1. There is inconsistency in the search dates reported. For example, section D.1.1 states that '*All databases and resources were searched from inception to December 2018*'. However, Table 1, Table 2 and section D.1.1.2 provide dates of '13.8.18', '11.6.18' and 'inception to August 2018' respectively. Please clarify the correct search dates.

Response

All databases were searched from inception to December 2018 as per Appendix D section D1.1, the latest date in a series of search updates conducted (see response to A2 for more detail). Dates prior to December 2018 are typographical errors with the exception of the DARE database which ceased to exist in April 2015, therefore the search date of 11.6.18 is still valid.

Search results

A2. CS, Document C, Appendix D, sections D1.1 and D.3.1. Figure 1 (PRISMA flow diagram of the systematic review process).

a. **PRIORITY QUESTION.** There is a discrepancy in the search number (n=30,866) presented in Figure 1 compared to the combined number of hits for the individual searches (n=29,865 not including the references for the previous Biogen MTC [118] and handsearching [12]) listed in Tables 1 to 21. Please clarify the number of hits from the different searches.

Response

The original literature searches (MEDLINE, MEDLINE In-Process, MEDLINE Daily Update, Embase, CENTRAL, SCI) were conducted from database inception to October 2014. A supplementary search of PubMed was also carried out to identify advance publications not yet indexed by the main databases. All searches were updated in November 2015, February 2016, September 2016, May 2017, June 2018, August 2018 and December 2018. The combined results of these database searches for clinical effectiveness yielded 27,934 references.

Searches were also undertaken to identify relevant systematic reviews, technology appraisals, guidelines and guidance (CDSR, DARE, HTA, NICE, NIHR, CADTH, PROSPERO, KSR Evidence; searches conducted in October 2014, updated in November 2015, February 2016, September 2016, May 2017, June 2018, August 2018 and December 2018). These searches, intended to identify additional primary studies, retrieved a total number of 461 records. Additional searches performed in clinical trials registers (ClinicalTrials.gov, WHO ICTRP, PharmNetBund, EUCTR, ISRCTN; searches conducted in October 2014 and updated in November 2015, February 2016, September 2016, May 2017, June 2018, August 2018 and December 2018) to identify data from ongoing or unpublished clinical trials retrieved a further 2,296 records.

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The list of publications included in existing Biogen MTCs was also checked to identify any publications not retrieved by the main searches. This yielded 118 records that were predominantly conference abstracts of existing studies. A further 12 records were identified by handsearching reference lists of included studies and relevant systematic reviews.

For the May 2017, June 2018, August 2018 and December 2018 updates, searches were conducted to identify relevant Summary of Product Characteristics (SmPCs) and European Public Assessment Reports (EPARs). These searches retrieved 45 SmPCs and EPARs. The combined results of all 8 searches yielded 30,866 records before de-duplication. After removing 10,539 duplicates, a total of 20,327 references were available for screening of titles and abstracts (see Document C, Appendix D, sections D1.1 and D.3.1. Figure 1 [PRISMA flow diagram of the systematic review process]).

Titles and abstracts of 20,327 references were screened and 1,454 potentially relevant papers ordered as full texts. Screening of full text papers identified 561 relevant publications reporting 32 studies. A further six ongoing studies were reported in nine publications.

Table 1 and Table 2 show the rapid appraisal and clinical effectiveness record hits pre- and post de-duplication across the search dates.

Table 1: Rapid appraisal searches

Search Date	Records retrieved	After de-duplication*
Oct 2014	175	159
Nov 2015	238	102
Feb 2016	243	9
Sep 2016	282	34
May 2017	243	45
Jun 2018	335	60
Aug 2018	359	24
Dec 2018	395	28
Total Combined		**461**

* Duplicate records were removed from within the results of the update search AND between all previous search results

Table 2: Clinical effectiveness searches

Search Date	Records retrieved (d/bases)	Records after de-duplication (d/bases)*	Records retrieved (trials registers)	Records after de-duplication (trials registers)*	Combined records retrieved (d/bases & trials registers)	Combined records after de-duplication*
Oct 14	16260	10312	1629	1629†	17889	11941
Nov 15	19682	1887	1555	398	21237	2285
Feb 16	19972	325	1594	29	21566	354
Sep 16	21204	678	1811	53	23015	731
May 17	23322	1467	1772	64	25094	1531
Jun 18	27025	2061	1939	90	28964	2151
Aug 18	27358	280	1965	8	29323	288
Dec 18	27934	385	1997	25	29931	410
Total combined		**17395**		**2296**		**19691**

*Duplicate records were removed from within the results of the update search AND between all previous search results
† All trials records retrieved in the October 2014 searches were kept, including duplicate trials records

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b. Figure 1 shows that 118 and 12 records were retrieved using 'Biogen previous MTC' and 'handsearching' respectively. Please provide the list of references retrieved from these searches.

Response

Please find below the list of references or the 118 records from "Biogen previous MTC" (Table 3) and "handsearching" (Table 4).

Table 3. List of references for Biogen previous MTC

#	Reference
1	Zivadinov R, Dwyer M, Bergsland N, Hussein S, Durfee J, Ramasamy D, et al. Effect of alemtuzumab vs. interferon beta-1a on brain atrophy in patients with early, active relapsing-remitting multiple sclerosis. Paper presented at 63rd Annual Meeting of the American Academy of Neurology (AAN); 9-16 Apr 2011; Honolulu: United States. 2011.
2	Zhao GJ, Crablouse A, Li D, Riddehough A, Zhao Y, Cheng Y. Can changes of the third ventricular width on MRI demonstrate treatment effect in patients with multiple sclerosis? Paper presented at 19th World Congress of Neurology; 24-30 Oct 2009; Bangkok: Thailand. J Neurol Sci 2009;285(S1):S200.
3	Zhang A, Pace A, Hotermans C, Hyde R. A composite measure of multiple sclerosis disease progression in AFFIRM. Paper presented at 63rd Annual Meeting of the American Academy of Neurology (AAN); 9-16 Apr 2011; Honolulu: United States. 2011.
4	Zarbin M, Reder A, Collins W, Francis G, Zhang X, Zhao Y, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis (MS). Paper presented at 63rd Annual Meeting of the American Academy of Neurology (AAN); 9-16 Apr 2011; Hawaii: United States. 2011.
5	Wray S, CAMMS223 Study Group. Two annual cycles of alemtuzumab yield durable treatment response 24 months after last dose. Paper presented at 61st Annual Meeting of the American Academy of Neurology (AAN); 25 Apr-2 May 2009; Seattle: United States. 2009.
6	Weinstock-Guttman B, Bermel R, Bourdette D, Foulds P, You P, Rudick R. Improved quality of life in patients with relapsing-remitting multiple sclerosis on long-term intramuscular interferon beta-1a: a 15-year study. Paper presented at 61st Annual Meeting of the American Academy of Neurology (AAN); 25 Apr-2 May 2009; Seattle: United States. 2009.
7	Weinstock-Guttman B, Bermel R, Bourdette D, Foulds P, You P, Rudick R. Comparing patient-reported and physician-reported EDSS scores in patients from ASSURANCE. Paper presented at 61st Annual Meeting of the American Academy of Neurology (AAN); 25 Apr-2 May 2009; Seattle: United States. 2009.
8	Vollmer T, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen J, et al. Results of switching to laquinimod in the open-label extension phase of the BRAVO study. Paper presented at 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 18th Annual Conference of Rehabilitation in MS, RIMS; 2-5 Oct 2013; Copenhagen: Denmark. Mult Scler 2013;19(11 Suppl):489.
9	Traboulsee A, Uitdehaag BM, Kappos L, Sandberg-Wollheim M, Li D, Jongen P, et al. Measures of early clinical activity as prognostic factors for long-term clinical outcomes in relapsing-remitting multiple sclerosis. Paper presented at 62nd Annual Meeting of the American Academy of Neurology (AAN); 10-17 Apr 2010; Toronto: Canada. 2010.

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#	Reference
10	Traboulsee A, Uitdehaag BMJ, Kappos L, Sandberg-Wollheim M, Li D, Jongen P, et al. Measures of treatment adherence as prognostic factors for long-term outcomes in relapsing–remitting multiple sclerosis. Paper presented at 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 15th Annual Conference of Rehabilitation in MS, RIMS; 13-16 Oct 2010; Gothenburg: Sweden. Mult Scler 2010;16(10 Suppl):S165.
11	Traboulsee A, Uitdehaag B, Kappos L, Sandberg Wollheim M, Li D, Jongen P, et al. Baseline/pre-study characteristics and measures of early clinical and magnetic resonance imaging activity as prognostic factors for long-term outcomes in relapsing–remitting multiple sclerosis. Paper presented at 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 15th Annual Conference of Rehabilitation in MS, RIMS; 13-16 Oct 2010; Gothenburg: Sweden. Mult Scler 2010;16(10 Suppl):S283.
12	Sormani MP, Radue EW, De Stefano N, Sprenger T, Chin P, Francis G, et al. Does the effect of fingolimod on brain atrophy independently contribute to effects on disability? A patient-level analysis of the FREEDOMS study. Paper presented at 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 18th Annual Conference of Rehabilitation in MS, RIMS; 2-5 Oct 2013; Copenhagen: Denmark. Mult Scler 2013;19(11 Suppl):262-3.
13	Singer B, Comi G, Miller A, Olsson T, Wolinsky J, Kappos L, et al. Frequency of infections during treatment with teriflunomide: pooled data from three placebo-controlled teriflunomide studies (P01.171). Paper presented at 65th Annual Meeting of the American Academy of Neurology (AAN): 16-23 Mar 2013; San Diego: United States. Neurology 2013;80(1 MeetingAbstracts).
14	Sfikas N, Bergvall N, Chin P, Tomic D, Rosenstiel PV, Alsop J, et al. Effect of fingolimod in patients with no disability as measured by EDSS at baseline: post-hoc analyses of FREEDOMS I and II (P07.124). Paper presented at 65th Annual Meeting of the American Academy of Neurology (AAN): 16-23 Mar 2013; San Diego: United States. Neurology 2013;80(1 MeetingAbstracts).
15	Scott T, Laforet G, You X. Identifying patients with relapsing-remitting multiple sclerosis who have aggressive disease characterized by rapid disability progression (P05.093). Paper presented at 64th Annual Meeting of the American Academy of Neurology (AAN): 21-28 Apr 2012; New Orleans: United States. Neurology 2012;78(1 MeetingAbstracts).
16	Rocca MA, Camesasca F, Cook S, Comi G, Goodin DS, O'Connor PW, et al. Comparison of permanent black hole lesion number in relapsing-remitting multiple sclerosis with interferon beta-1b to glatiramer acetate. P46. Paper presented at Third Cooperative Meeting of the CMSC-ACTRIMS; 2-5 Jun 2010; San Antonio: United States. 2010: 49.
17	Reder A, Goodin D, Ebers G, Cutter G, Rametta M, Kremenchutzky M, et al. Survival outcomes and cause of death from the 21-year long-term follow-up study. (DX06). Paper presented at Fourth Cooperative Meeting of CMSC and ACTRIMS; 30 May-2 Jun 2012; San Diego: United States. Int J MS Care 2012;14(Suppl 2):39-40.
18	Radue E-W, Vera AD, Burtin P, Holdbrook F, Francis G, Kappos L. Fingolimod reduces brain volume loss in relapsing-remitting multiple sclerosis (RRMS) beyond its anti-inflammatory activity: results from FREEDOMS. Paper presented at 63rd Annual Meeting of the American Academy of Neurology (AAN); 9-16 Apr 2011; Honolulu: United States. 2011.

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#	Reference
19	Phillips JT, Fox RJ, Kita M, Hutchinson M, Miller D, Havrdova E, et al. Safety and tolerability of BG-12 in the phase 3 CONFIRM study. (DX31). Paper presented at Fourth Cooperative Meeting of CMSC and ACTRIMS; 30 May-2 Jun 2012; San Diego: United States. Int J MS Care 2012;14(Suppl 2):50.
20	Pelletier J, Karlsson G, Li B, Vera AD, Francis G, Cohen J, et al. Effect of fingolimod on multiple sclerosis functional composite (MSFC) defined disability progression in patients with relapsing remitting MS (RRMS): results from two phase III studies. Paper presented at 63rd Annual Meeting of the American Academy of Neurology (AAN); 9-16 Apr 2011; Honolulu: United States. 2011.
21	O'Connor P, Briggs A, Carita P, Bégo-Le-Bagousse G. Impact on health-related quality of life of teriflunomide treatment by estimating utilities in patients with relapsing multiple sclerosis: results from TEMSO post hoc analysis. Paper presented at Twenty-second meeting of the European Neurological Society; 9-12 Jun; Prague: Czech Republic. 2012.
22	Nakamura K, Rudick R, Lee J-C, Foulds P, Fisher E. Effect of intramuscular interferon beta-1a on gray matter atrophy in relapsing-remitting multiple sclerosis. Paper presented at 62nd Annual Meeting of the American Academy of Neurology (AAN); 10-17 Apr 2010; Toronto: Canada. 2010.
23	Munschauer F, Giovannoni G, Lublin F, O'Connor P, Phillips JT, Polman C, et al. Sustained improvement in physical disability with natalizumab in patients with relapsing multiple sclerosis. Paper presented at 61st Annual Meeting of the American Academy of Neurology (AAN); 25 Apr-2 May 2009; Seattle: United States. 2009.
24	Munschauer F, Giovannoni G, Miller D, Rudick R, O'Connor P, Polman C, et al. Improvement in EDSS corresponds with improvement in quality of life in patients with multiple sclerosis. Paper presented at 62nd Annual Meeting of the American Academy of Neurology (AAN); 10-17 Apr 2010; Toronto: Canada. 2010.
25	Miller A, Lublin F, O'Connor P, Taniou C, Dive-Pouletty C. Impact of relapses with sequelae on disability, health-related quality of life, and fatigue in a population with relapsing forms of multiple sclerosis using data from TEMSO, a pivotal phase III teriflunomide trial (P07.082). Paper presented at 64th Annual Meeting of the American Academy of Neurology (AAN): 21-28 Apr 2012; New Orleans: United States. Neurology 2012;78(1 MeetingAbstracts).
26	Lublin F, Cutter G, Giovannoni G, Polman C, Paes D, Patel R, et al. Natalizumab reduces the disabling amplitude of multiple sclerosis relapses and improves post-relapse residual disability. Paper presented at 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 18th Annual Conference of Rehabilitation in MS, RIMS; 2-5 Oct 2013; Copenhagen: Denmark. Mult Scler 2013;19(11 Suppl):213-4.
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108	Freedman M, Confavreux C, Olsson T, Comi G, Aaron Miller MD, Wolinsky J, et al. Teriflunomide efficacy and safety analyses: results from TEMSO and TOWER. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: P5.
109	Nelson F, Salter A, Narayana P, Gustafson T, Conwit R, Wang J, et al. MRI outcomes and MS diagnosis criteria in the CombiRx trial. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: 3.2.
110	Gustafson T, Powell CS, Salter A, Wang J, Lublin FD, Wolinsky J, et al. Data management and montitoring in the CombiRx randomized trial. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX32.
111	Jeffery D, Cohen JA, Meng X, Hashmonay R. Effect of fingolimod on brain atrophy: MRI data from phase 3 studies. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX37.
112	Bashir K, Cofield SS, Cutter G, Wolinsky J, Gustafson T, Conwit R, et al. Clinical outcomes and MS diagnosis criteria in the CombiRx trial. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: P42.
113	Hohlfeld R, Meng X, Hashmonay R, Tenenbaum N. Long-term safety and tolerability of fingolimod in relapsing-remitting MS. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX55.

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#	Reference
114	Yu CC, Lancia S, Tutlam N, Xu J, Naismith RT. High monthly T2 lesion burden associated with improved EDSS upon starting MS treatment. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX61
115	Henson LJ, Arnold DL, Canada M, Cohen JA, Coles AJ, Confavreux C, et al. Durable effects of alemtuzumab on relapse rate over time in CARE-MS II. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX38
116	Fernandez O. Alemtuzumab in the treatment of multiple sclerosis. J Inflamm Res 2014;7:19-27.
117	Randhawa S, Meng X, Hashmonay R. Cardiac effects of fingolimod: first-dose observation. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX50
118	Agius M, Jeffery D, Meng X, Hashmonay R, DiBernardo A. Fingolimod efficacy and safety vs. placebo: phase 3 FREEDOMS II study. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX09.

Table 4. List of references - hand searches

#	Reference
1	Heron Evidence Development. An update to SR and MTC of DMTs in relapsing remitting multiple sclerosis. Version 1.0. Report. May 2014: Heron Evidence Development, 2014
2	Biogen Idec Inc. Clinical study report. Full final. Study Number: 205MS202. A double-blind, multicenter, extension study to evaluate the safety and efficacy of DAC HYP in subjects with multiple sclerosis who have completed treatment in study 205MS201 (SELECT). Cambridge, MA: Biogen Idec Inc, 2013
3	Biogen Idec Inc. Clinical study report. Full final. Study Number: 205MS301. Multicenter, double-blind, randomized, parallel-group, monotherapy, active-control study to determine the efficacy and safety of daclizumab high yield process (DAC HYP) versus avonex® (interferon β-1a) in patients with relapsing-remitting multiple sclerosis. Cambridge, MA: Biogen Idec Inc, 2015
4	Biogen Idec Inc. Clinical study report. Full final. Study Number: 205MS201. Multicenter, double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of daclizumab HYP (DAC HYP) as a monotherapy treatment in subjects with relapsing-remitting multiple sclerosis. Cambridge, MA: Biogen Idec Inc, 2013
5	Biogen Idec Inc. Clinical study report. Full final. Study Number: 109MS302. A randomized, multicenter, placebo-controlled and active reference (glatiramer acetate) comparison study to evaluate the efficacy and safety of BG00012 in subjects with relapsing-remitting multiple sclerosis. Cambridge, MA: Biogen Idec Inc, 2012
6	Biogen Idec Inc. Clinical study report. Full final. Study Number: 109MS301. A randomized, multicenter, double-blind, placebo-controlled, dose-comparison study to determine the efficacy and safety of BG00012 in subjects with relapsing-remitting multiple sclerosis. Cambridge, MA: Biogen Idec Inc, 2012
7	Biogen Avonex, Multiple Sclerosis Collaborative Research Group (MSCRG). Integrated clinical/statistical report. Study Number: NS 26321. Intramuscular interferon beta-la versus placebo as treatment for multiple sclerosis. Part IV: BIOGEN Inc, 1995

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#	Reference
8	Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444-52.
9	Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13(3):227-31.
10	European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis [Internet]. London: European Medicines Agency, 2006 accessed 11.2.15. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003485.pdf
11	Biogen Idec. 105MS301 Final - TLGs. Year 2 trial results. 2014.
12	Biogen Idec. 105MS301 Interim - TLGs. Year 1 trial results. 2013.

A3. CS, Document C, Appendix D, sections D.3.1 and D.3.2.1; Appendix L, section L.3.12.1. 'GLOW' is listed in Table 25 (Studies excluded from key analyses) but no reference has been provided.

a. Please provide a reference for this study.

Response:

References for GLOW are available in Document C, Appendix D, Section 3.2, table 26 (p58) and are as follows:

Teva Pharmaceutical Industries. A clinical study in patients with multiple sclerosis to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) 20 mg/0.5 ml (experimental drug). EUCTR2011-005550-57-LV. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2012 [accessed 15.10.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005550-57 http://ClinicalTrials.gov/show/NCT01578785 NLM Identifier: NCT01578785

Teva Pharmaceutical Industries. An efficacy, safety and tolerability study of glatiramer acetate (GA) 20 mg/0.5 ml new formulation administered daily by subcutaneous (SC) injection in subjects with relapsing-remitting multiple sclerosis (RRMS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012-2012 (Terminated) [cited 2014 Oct 14]. Available from: http://ClinicalTrials.gov/show/NCT01578785 NLM Identifier: NCT01578785

b. GLOW also appears in Table 26 (List of included studies) along with 2 references, and in the network diagram in Figure 15. Please clarify whether GLOW is an included or excluded study.

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Response:

Key analyses are in reference to ARR and CDP3M and CDP6M only which do not include GLOW. GLOW was only included in the network for adverse events.

ADVANCE and ATTAIN

Patient characteristics

A4. PRIORITY QUESTION. CS, Document B, section B.2.3.1.2. Based on Table 7, please provide a table of patient characteristics for the arms at the start and at the end of ADVANCE and ATTAIN.

Response:

As clarified on the teleconference (9th July), Biogen have provided baseline charcteristics at the start of each study (patients must have received 1 dose of pegIFNβ-1a) and at the end of the study for the subset of completers across ADVANCE & ATTAIN (defined at patients who reach the 96 week timepoint in both studies, respectively). The placebo only treatment group in ADVANCE is for those patients who received Placebo in Year 1 and withdrew before Year 2. These summary tables are provided in accompaniment to this document.

Generalisability of population

A5. PRIORITY QUESTION. CS, Document B, sections B.2.3.1.2 and B.3.11. Section B.3.11 states that '*The patient population in ADVANCE … is reflective of adult patients with relapsing-remitting multiple sclerosis (RRMS) in the UK*'. However, only 14 patients were enrolled from the UK. Please clarify why the population in ADVANCE is considered to be generalisable to the UK.

Response:

ADVANCE included only 14 UK patients, and most patients were from Eastern Europe. Subgroup analysis by region has been performed for ADVANCE (see response 7) and suggests that the efficacy of pegIFN is broadly similar across all populations, regardless of region.

Document B, section 2.9.3, Table 17, presents baseline characteristics from other comparator studies relevant to this appraisal. These studies have been used in prior appraisals for the respective technologies and all deemed generalisable to the UK. Biogen do not believe the baseline characteristics of ADVANCE significantly differ from these reported studies.

Annualised relapse rate (ARR)

A6. CS, Document B, section B.2.4, section B.2.6.1.1 and section B.2.6.1.2. CS, Document C, Appendix L, section L.3.13. For ADVANCE, Table 10 (section B.2.4) states that the annualised relapse rate at 1 year (the primary end point) '*was analysed using negative binomial regression, adjusted for baseline Expanded Disability Status Scale (EDSS) score (< 4 vs. ≥ 4), baseline age (< 40 vs. ≥ 40 years), and baseline relapse rate (number of relapses in 3 years prior to study entry divided by 3)*'. For ADVANCE, Newsome et al. (2018) states that the annualised relapse rate was adjusted for the same characteristics, that is, '*baseline EDSS score (<4.0 versus ⩾4.0), baseline relapse rate, and*

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age (<40 versus ⩾40 years)'. However, there is discrepancy in the reporting of the annualised relapse rate at 1 year for the peginterferon beta-1a Q2W arm in ADVANCE in Document B (please see table below). Please clarify the discrepancy in reported annualised relapse rates.

Document location of information	ARR for peginterferon beta-1a Q2W at 1 year	Reported data source in document
Document B, section B2.6.1.1, Table 11	0.256	Calabresi et al. (2014)[11]
Document C, Appendix L, section L.3.13	0.256	Source not provided
Document B, section B.2.6.1.2, Figure 3	0.241	Newsome et al. (2018)[124]

Response:

For clarification, the Newsome et al 2018 publication relates to ATTAIN, 0.241 is therefore the ARR for the ITT population for the patients who entered this extension study; 0.256 is the ARR for the ITT population in ADVANCE as reported in the Calabresi et al (2014) publication.

A7. PRIORITY QUESTION. CS, Document B, section B.2.7.1. Based on subgroup analyses of annualised relapse rates at 1 year, the company submission states that '*the efficacy of peginterferon beta-1a was similar in all patients regardless of their sex, age, body weight, geographical region, or disease status at the initiation of treatment (Figure 8)*'. However, Figure 8 does not provide a subgroup analysis based on geographical region. Please provide this information.

Response:

Please find the requested subgroup analyses from the 1-year analysis of ADVANCE for ARR (INEC confirmed relapses) comparing pegIFNβ-1a Q2W (Figure 1) and Q4W (Figure 2) against placebo.

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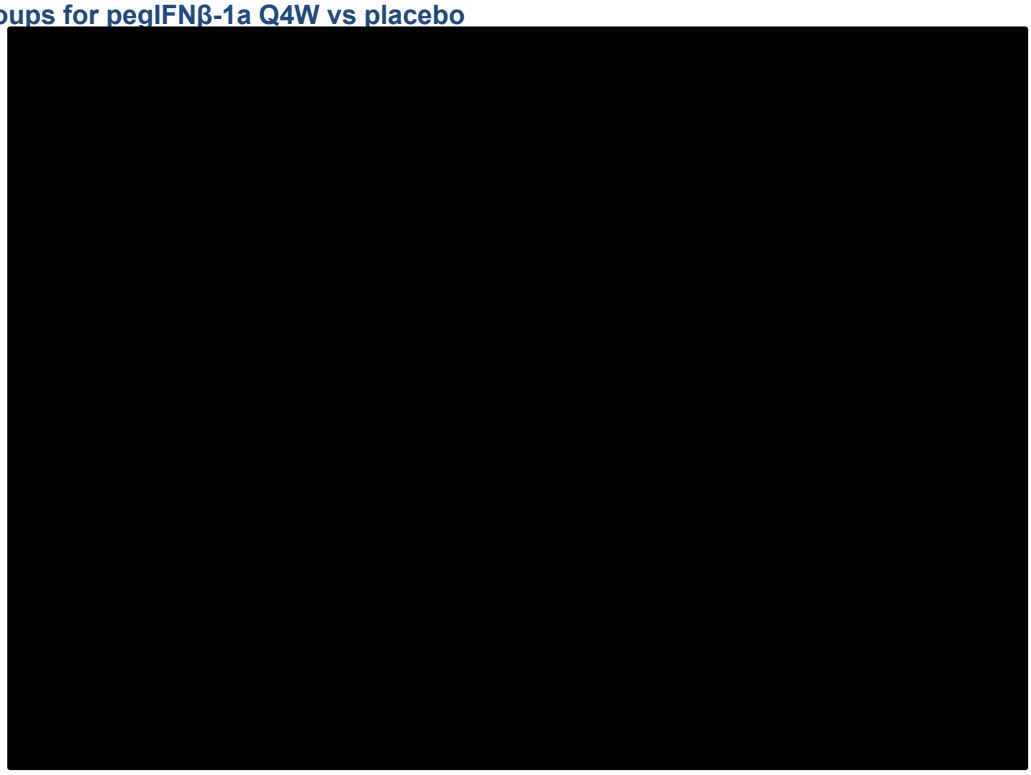
Figure 1. ARR (INEC confirmed relapses) at 1 year – rate ratio and 95% CI by demographic subgroups for peglFNβ-1a Q2W vs placebo

Figure 2. ARR (INEC confirmed relapses) at 1 year – rate ratio and 95% CI by demographic subgroups for peglFNβ-1a Q4W vs placebo



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NETWORK META-ANALYSIS

Included studies

A8. PRIORITY QUESTION. CS, Document C, section D.2.1.1. CS, Document B, sections B.2.9.3 and B.2.10.3. Section D.2.1.1 states that '*A narrative summary of all of the included studies is presented in Section B.2.10.3 in Document B or in the meta-analysis results section below. This includes a summary of the key study characteristics (e.g. study design, population size, year, inclusion criteria, baseline population characteristics) and methodological quality (according to the Cochrane Collaboration risk of bias tool) of the studies*'. However, section B.2.10.3 only refers to adverse reactions specifically in ADVANCE and ATTAIN. In addition, no details are included in the meta-analysis results section in Document C. Table 17 (section B.2.9.3) provides only the baseline patient characteristics of included studies. Please provide all the information stated above for all included studies for any reported outcome.

Response

Requested information are available in the following tables (with the exception of baseline characteristics already provided in Document B, section 2.9.3, table 17):

- Table 5: Study details
- Table 6: Population sizes and interventions assessed
- Table 7: Distribution of MS Subtypes
- Table 8: Previous treatments prior to enrolment
- Table 9: Methodological quality

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Table 5. Study details of studies included in the systematic review

Study ID	Trial Registry number	Main Publication	Diagnosis Criteria	Age	EDSS	Previous Relapses	Previous treatment
ADVANCE	NCT00906399	Calabresi 2014	McDonald 2005	18-65 years	0-5.0	≥2 in previous 3 years with ≥1 within past 12 months	Mixed[1,2]
APEX	NCT01838668	Mori 2017	NR	NR	0-5.0	NR	Treatment Naïve
BEYOND	NCT00099502	O'Connor 2009	McDonald	18-55 years	0-5.0	≥1 in year before study	Treatment Naïve
Boiko 2017	NCT02753088	Boiko 2017	McDonald 2005	NR	0-5.5	At least one exacerbation or at least one identified focus accumulating gadolinium on T1 MRI scans	NR
Bornstein 1987	NR	Bornstein 1987	Poser	20-35 years	0-6.0	≥2 exacerbations in 2 years before admission	NR
BRAVO	NCT00605215	Vollmer 2014	McDonald 2005	18-55 years	0-5.5	≥1 in previous year, 2 in previous 2 years, or 1 in previous 1–2 years and 1 or more GdE lesion in the previous year	Treatment Naïve
Calabrese 2012	NR	Calabrese 2011	McDonald 2005	18-55 years	0-5.0	NR	NR
CAMMS223	NCT00050778	CAMMS223 Trial Investigators 2008	McDonald	NR	0-3.0	≥2 clinical episodes during previous 2 years	Treatment Naïve
CARE MS-I	NCT00530348	Cohen 2012	McDonald 2005	18-50 years	0-3.0	≥2 in previous 2 years and ≥1 in previous year	Treatment Naïve
CARE MS-II	NCT00548405	Coles 2012	McDonald 2005	18-55 years	0-5.0	≥2 attacks in previous 2 years with ≥1 in previous year	Mixed
CombiRx	NCT00211887	Lublin 2013	Other	18-60 years	0-5.5	≥2 exacerbations in prior 3 years, where 1 exacerbation could be an MRI change	NR

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Study ID	Trial Registry number	Main Publication	Diagnosis Criteria	Age	EDSS	Previous Relapses	Previous treatment
CONFIRM	NCT00451451	Fox 2012	McDonald 2005	18-55 years	0-5.0	≥1 in previous 12 months or ≥1 Gd-enhanced lesion 0 to 6 weeks before randomisation	Mixed[1,2]
Copolymer I study	NCT00004814	Johnson 1995	Poser	18-45 years	0-5.0	Onset of relapse > 1 year before randomisation	NR
Crentsil 2012	NR	Crentsil 2012	NR	NR	NR	NR	NR
DEFINE	NCT00420212	Gold 2012	McDonald 2005	18-55 years	0-5.0	≥1 within 12 months before randomisation or a brain MRI scan, obtained within 6 weeks before randomisation, that showed ≥1 Gd-enhanced lesion	Mixed[1,2]
Etemadifar 2006	NR	Etemadifar 2006	Poser	15-50 years	0-5.0	≥2 within 2-year period to treatment	NR
EVIDENCE	NR	Panitch 2002	Poser	NR	0-5.5	≥2 exacerbations of MS in prior 2 years	NR
GALA	NCT01067521	Khan 2013	McDonald 2005	18-55 years	0-5.5	1 in 12 months prior to screening, 2 in 24 months prior to screening, or 1 between 12 and 24 months prior to screening	Mixed
GLOW	NCT01578785	Teva Pharmaceutical Industries 2014	McDonald 2010	18-55 years	0-5.5	Either ≥1 in 12 mths prior to screening, or ≥2 in 24 months prior to screening, or 1 between 12 and 24 months prior to screening with ≥1 documented T1-Gd-enhanced lesion in a MRI performed within 12 months prior to screening	NR
IFNB MS study	NR	The IFNB Multiple Sclerosis Study Group 1993	Poser	18-50 years	0-5.5	≥2 acute exacerbations during previous 2 years	NR

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Study ID	Trial Registry number	Main Publication	Diagnosis Criteria	Age	EDSS	Previous Relapses	Previous treatment
INCOMIN	NR	Durelli 2002	Poser	18-50 years	1-3·5	2 during preceding 2 years	NR
Mokhber 2014	NR	Mokhber 2014	McDonald	NR	NR	NR	Treatment Naïve
Mokhber 2015	IRCT201404195280N16	Mokhber 2015	McDonald 2010	NR	NR	NR	Treatment Naïve
MSCRG	NR	Jacobs 1996	Poser	18-55 years	1.0-3.5	≥2 within previous 3 years	NR
O'Connor 2006	NCT00228163	O'Connor 2006	Poser	18-65 years	0-6.0	2 in previous 3 years, and 1 during preceding year	NR
OPERA I	NCT01247327	Hauser 2017	McDonald 2010	18-55 years	0-5.5	≥ 2 within previous 2 years or 1 within the year before screening	Mixed
OPERA II	NCT01412333	Hauser 2017	McDonald 2010	18-55 years	0-5.5	≥ 2 within previous 2 years or 1 within the year before screening	Mixed
PRISMS	NR	PRISMS study group 1999	Schumacher	NR	0-5.0	≥2 in preceding 2 years	NR
REGARD	NCT00078338	Mikol 2008	McDonald	18-60 years	0-5·5	≥1 in preceding 12 months	NR
TEMSO	NCT00134563	O'Connor 2011	McDonald	18-55 years	0-5.5	≥2 in previous 2 yrs or 1 during preceding year	Mixed[1]
TENERE	NCT00883337	Vermersch 2014	McDonald 2005	≥18 years	0-5.5	NR	Mixed
TOWER	NCT00751881	Confavreux 2014	McDonald 2005	18-55 years	0-5·5	≥1 in previous year or ≥2 in previous 2 years	Mixed

EDSS = Expanded Disability Status Scale, MRI = magnetic resonance imaging, NR = not reported
1 Reports treatment-naïve as a sub-group analysis for CDP3M; 2 Reports treatment-naïve as a sub-group analysis for CDP6M

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Table 6. Summary of interventions assessed in studies included in the systematic review

Study ID	Total Randomised	Treatment arm	Administration	No. pts randomised	No. pts received treatment	No. pts discon study
ADVANCE	1512	PEG IFN beta-1a, 125 mcg, q4w	SC	500	500	62
		PEG IFN beta-1a 125 mcg q2w	SC	512	512	74
		Placebo	SC	500	500	44
		Placebo	IV Infusion	315	312	31
APEX	115	Dimethyl Fumarate 240 mg bid	Oral	56	NR	NR
		Placebo	Oral	58	NR	NR
BEYOND	2244	GA 20 mg qd	SC	448	445	71
		IFN beta-1b 250 mcg qad	SC	897	888	104
		IFN beta-1b 500 mcg qad	SC	899	887	161
Boiko 2017	158	GA 20 mg qd (Copaxone, Teva)[1]	SC	NR	61	NR
		GA 20 mg qd (Timexon, Biocad)[1]	SC	NR	61	NR
		Placebo	SC	NR	28	NR
Bornstein 1987	50	GA 20 mg qd	SC	25	25	3
		Placebo	SC	25	NR	4
BRAVO	1331	IFN beta-1a 30 mcg qw	IM	447	442	69
		Placebo	Oral	450	449	91
		Laquinimod 0.6 mg once-daily	Oral	434	433	81
Calabrese 2012	165	GA 20 mg qd	SC	55	55	NR
		IFN beta-1a 30 mcg qw	IM	55	55	NR
		IFN beta-1a 44 mcg, tiw	SC	55	55	NR
CAMMS223	334	IFN beta-1a 44 mcg, tiw	SC	111	107	45
		Alemtuzumab 12 mg qd	IV Infusion	113	108	21
		Alemtuzumab 24 mg qd	IV Infusion	110	108	18
CARE MS-I	581	IFN beta-1a 44 mcg tiw	SC	195	187	22
		Alemtuzumab 12 mg qd	IV Infusion	386	376	19
CARE MS-II	840	IFN beta-1a 44 mcg tiw	SC	231	202	56
		Alemtuzumab 12 mg qd	IV Infusion	436	426	20
		Alemtuzumab 24 mg qd	IV Infusion	173	170	9
CombiRx	509	GA 20 mg qd	SC	259	259	36

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Study ID	Total Randomised	Treatment arm	Administration	No. pts randomised	No. pts received treatment	No. pts discon study
		IFN beta-1a 30 mcg qw	IM	250	250	56
CONFIRM	1430	Dimethyl Fumarate 240 mg bid	Oral	362	359	75
		Dimethyl Fumarate 240 mg tid	Oral	345	345	72
		GA 20 mg qd	SC	360	350	58
		Placebo	Oral	363	363	85
Copolymer I Study	251	GA 20 mg qd	SC	125	NR	19
		Placebo	SC	126	NR	17
Crentsil 2012	NR	Interferon-beta 1a IM	IM	NR	NR	NR
		Interferon-beta 1a SC	SC	NR	NR	NR
		Interferon-beta 1b	NR	NR	NR	NR
		Glatiramer acetate	NR	NR	NR	NR
DEFINE	1237	Dimethyl Fumarate 240 mg bid	Oral	411	410	95
		Dimethyl Fumarate 240 mg tid	Oral	416	416	96
		Placebo	Oral	410	408	91
Etemadifar 2006	90	IFN beta-1a 30 mcg qw	IM	30	30	NR
		IFN beta-1a 44 mcg tiw	SC	30	30	NR
		IFN beta-1b 250 mcg qad	SC	30	30	NR
EVIDENCE	677	IFN beta-1a 30 mcg qw	IM	338	337	14
		IFN beta-1a 44 mcg tiw	SC	339	339	14
GALA	1404	GA 40mg tiw	SC	943	943	84
		Placebo	SC	461	461	31
GLOW	178	GA 20 mg qd	SC	119	NR	119
		Placebo	SC	59	NR	59
IFNB MS study	372	IFN beta-1b 250 mcg qad	SC	124	NR	48
		IFN beta-1b 50 mcg qad	SC	125	NR	57
		Placebo	SC	123	NR	49
INCOMIN	188	IFN beta-1a 30 mcg qw	IM	92	NR	19
		IFN beta-1b 250 mcg qad	SC	96	NR	11
Mokhber 2014	69	IFN beta-1a 30 mcg qw	IM	23	NR	3
		IFN beta-1a 44 mcg, tiw	SC	23	NR	0

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Study ID	Total Randomised	Treatment arm	Administration	No. pts randomised	No. pts received treatment	No. pts discon study
		IFN beta-1b 250 mcg qad	SC	23	NR	1
Mokhber 2015	69	IFN beta-1a 30 mcg qw	IM	23	NR	3
		IFN beta-1a 44 mcg, tiw	SC	23	NR	2
		IFN beta-1b 250 mcg qad	SC	23	NR	4
MSCRG	301	IFN beta-1a 30 mcg qw	IM	158	NR	73
		Placebo	IM	143	NR	56
O'Connor 2006	179	Teriflunomide 14 mg qd	Oral	57	NR	4
		Teriflunomide 7 mg qd	Oral	61	NR	2
		Placebo	Oral	61	NR	11
OPERA I	821	Ocrelizumab 600 mg q24w	IV	410	366	44
		IFN beta-1a 44 mcg tiw	SC	411	340	71
OPERA II	835	Ocrelizumab 600 mg q24w	IV	417	360	57
		IFN beta-1a 44 mcg tiw	SC	418	320	98
PRISMS	560	IFN beta-1a 44 mcg tiw	SC	184	184	5
		IFN beta-1a 22 mcg tiw	SC	189	189	12
		Placebo	SC	187	187	10
REGARD	764	GA 20 mg qd	SC	378	375	5
		IFN beta-1a 44 mcg, tiw	SC	386	383	20
TEMSO	1088	Teriflunomide 7 mg qd	Oral	366	365	69
		Teriflunomide 14 mg qd	Oral	359	358	75
		Placebo	Oral	363	363	73
TENERE	324	IFN beta-1a 44 mcg, tiw	SC	104	101	33
		Teriflunomide 7 mg qd	Oral	109	109	20
		Teriflunomide 14 mg qd	Oral	111	111	22
TOWER	1169	Teriflunomide 7 mg qd	Oral	408	407	134
		Teriflunomide 14 mg qd	Oral	372	370	126
		Placebo	Oral	389	388	125

[1]The Boiko 2017 study also included a biosimilar GA drug arm (BCD-063, Biocad, Russia) (n=61), which was not included in any analyses

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Table 7. Distribution of multiple sclerosis subtypes in studies included in the systematic review

Study ID	Treatment	Total N	MS subtype	Population comments[1]
ADVANCE	PEG IFN beta-1a 125 mcg q2w	512	CIS: n = 0, 0% RRMS: n = 512, 100% SPMS: n = 0, 0% Other = NR	RRMS was an inclusion criterion
	PEG IFN beta-1a, 125 mcg, q4w	500	CIS: n = 0, 0% RRMS: n = 500, 100% SPMS: n = 0, 0% Other = NR	
	Placebo	500	RRMS: n = 500, 100% SPMS: n = 0, 0% Other = NR	
APEX	Dimethyl Fumarate 240 mg bid	56	RRMS: n = 56, 100% SPMS: n = 0, 0% Other = NR	RRMS was an inclusion criterion
	Placebo	58	RRMS: n = 58, 100% SPMS: n = 0, 0% Other = NR	
BEYOND	IFN beta-1b 250 mcg qad	897	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	Patients with progressive forms of MS were excluded
	IFN beta-1b 500 mcg qad	899	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	
	GA 20 mg qd	448	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
Boiko 2017	GA 20 mg qd (Copaxone, Teva)[2]	61	RRMS: n = 61, 100% SPMS: n = 0, 0% Other = NR	RRMS was an inclusion criterion
	GA 20 mg qd (Timexon, Biocad)	61	RRMS: n = 61, 100% SPMS: n = 0, 0% Other = NR	
	Placebo	28	RRMS: n = 28, 100% SPMS: n = 0, 0% Other = NR	
Bornstein 1987	Placebo	25	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	Patients were required to fulfil the Poser criteria for definite multiple sclerosis
	GA 20 mg qd	25	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	
BRAVO	IFN beta-1a 30 mcg qw	447	CIS: n = 0, 0% RRMS: n = 447, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	Laquinimod 0.6 mg qd	434	CIS: n = 0, 0% RRMS: n = 434, 100% SPMS: n = 0, 0% Other = NR	
	Placebo	450	CIS: n = 0, 0% RRMS: n = 450, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1a 30 mcg qw	47	CIS: n = 0, 0%	Diagnosis with RRMS was an inclusion criterion

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
Calabrese 2012			RRMS: n = 47, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1a 44 mcg tiw	46	CIS: n = 0, 0% RRMS: n = 46, 100% SPMS: n = 0, 0% Other = NR	
	GA 20 mg qd	48	CIS: n = 0, 0% RRMS: n = 48, 100% SPMS: n = 0, 0% Other = NR	
CAMMS223	Alemtuzumab 12 mg qd	112	CIS: n = 0, 0% RRMS: n = 112, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	Alemtuzumab 24 mg qd	110	CIS: n = 0, 0% RRMS: n = 110, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1a 44 mcg tiw	111	CIS: n = 0, 0% RRMS: n = 111, 100% SPMS: n = 0, 0% Other = NR	
CARE MS-I	Alemtuzumab 12 mg qd	376	CIS: n = 0, 0% RRMS: n = 376, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1a 44 mcg tiw	187	CIS: n = 0, 0% RRMS: n = 187, 100% SPMS: n = 0, 0% Other = NR	
CARE MS-II	Alemtuzumab 12 mg qd	426	CIS: n = 0, 0%	Diagnosis with RRMS was an inclusion criterion

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
			RRMS: n = 426, 100% SPMS: n = 0, 0% Other = NR	
	Alemtuzumab 24 mg qd	170	CIS: n = 0, 0% RRMS: n = 170, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1a 44 mcg tiw	202	CIS: n = 0, 0% RRMS: n = 202, 100% SPMS: n = 0, 0% Other = NR	
CombiRx	IFN beta-1a 30 mcg qw	250	CIS: n = 0, 0% RRMS: n = 250, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	GA 20 mg qd	259	CIS: n = 0, 0% RRMS: n = 259, 100% SPMS: n = 0, 0% Other = NR	
CONFIRM	Dimethyl Fumarate, 240 mg bid	359	CIS: n = 0, 0% RRMS: n = 359, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	Dimethyl Fumarate, 240 mg tid	345	CIS: n = 0, 0% RRMS: n = 345, 100% SPMS: n = 0, 0% Other = NR	
	GA 20 mg qd	350	CIS: n = 0, 0% RRMS: n = 350, 100% SPMS: n = 0, 0% Other = NR	
	Placebo	363	CIS: n = 0, 0%	

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
			RRMS: n = 363, 100% SPMS: n = 0, 0% Other = NR	
Copolymer I Study	Placebo	126	CIS: n = 0, 0% RRMS: n = 126, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	GA 20 mg qd	125	CIS: n = 0, 0% RRMS: n = 125, 100% SPMS: n = 0, 0% Other = NR	
Crentsil 2012	Interferon-beta 1a IM	NR	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	NR
	Interferon-beta 1a SC	NR	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	
	Interferon-beta 1b	NR	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	
	Glatiramer acetate	NR	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	
DEFINE	Dimethyl Fumarate, 240 mg bid	410	CIS: n = 0, 0% RRMS: n = 410, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	Dimethyl Fumarate, 240 mg tid	416	CIS: n = 0, 0%	

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
			RRMS: n = 416, 100% SPMS: n = 0, 0% Other = NR	
	Placebo	408	CIS: n = 0, 0% RRMS: n = 408, 100% SPMS: n = 0, 0% Other = NR	
Etemadifar 2006	IFN beta-1a 30 mcg qw	30	CIS: n = 0, 0% RRMS: n = 30, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with clinically or laboratory supported relapsing MS was an inclusion criterion
	IFN beta-1a 44 mcg tiw	30	CIS: n = 0, 0% RRMS: n = 30, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1b 250 mcg qad	30	CIS: n = 0, 0% RRMS: n = 30, 100% SPMS: n = 0, 0% Other = NR	
EVIDENCE	IFN beta-1a 30 mcg qw	338	CIS: n = 0, 0% RRMS: n = 338, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1a 44 mcg tiw	339	CIS: n = 0, 0% RRMS: n = 339, 100% SPMS: n = 0, 0% Other = NR	
GALA	GA 40mg tiw	943	CIS: n = 0, 0% RRMS: n = 943, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	Placebo	461	CIS: n = 0, 0%	

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
			RRMS: n = 461, 100% SPMS: n = 0, 0% Other = NR	
GLOW	Placebo	59	CIS: n = 0, 0% RRMS: n = 59, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	GA 20 mg qd	119	CIS: n = 0, 0% RRMS: n = 119, 100% SPMS: n = 0, 0% Other = NR	
IFNB MS study	IFN beta-1b 50 mcg qad	125	CIS: n = 0, 0% RRMS: n = 125, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1b 500 mcg qad	124	CIS: n = 0, 0% RRMS: n = 124, 100% SPMS: n = 0, 0% Other = NR	
	Placebo	123	CIS: n = 0, 0% RRMS: n = 123, 100% SPMS: n = 0, 0% Other = NR	
INCOMIN	IFN beta-1a 30 mcg qw	92	CIS: n = 0, 0% RRMS: n = 92, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1b 250 mcg qad	96	CIS: n = 0, 0% RRMS: n = 96, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1a 30 mcg qw	23	CIS: n = 0, 0%	Diagnosis with RRMS was an inclusion criterion

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
Mokhber 2014			RRMS: n = 23, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1a 44 mcg tiw	23	CIS: n = 0, 0% RRMS: n = 23, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1b 250 mcg qad	23	CIS: n = 0, 0% RRMS: n = 23, 100% SPMS: n = 0, 0% Other = NR	
Mokhber 2015	IFN beta-1a 30 mcg qw	20	CIS: n = 0, 0% RRMS: n = 20, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1a 44 mcg tiw	23	CIS: n = 0, 0% RRMS: n = 23, 100% SPMS: n = 0, 0% Other = NR	
	IFN beta-1b 250 mcg qad	22	CIS: n = 0, 0% RRMS: n = 22, 100% SPMS: n = 0, 0% Other = NR	
MSCRG	IFN beta-1a 30 mcg qw	158	CIS: n = 0, 0% RRMS: n = 158, 100% SPMS: n = 0, 0% Other = NR	The study enrolled patients with relapsing MS. Defined as patients with complete remissions (returned to baseline preexacerbation disability status) and patients with incomplete remissions (did not return to their baseline preexacerbation disability status because of new residua)
	Placebo	143	CIS: n = 0, 0% RRMS: n = 143, 100% SPMS: n = 0, 0% Other = NR	
	Teriflunomide 7 mg qd	61	CIS: n = 0, 0%	NR

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
O'Connor 2006			RRMS: n = 54, 88.5% SPMS: n = 7, 11.5% Other = NR	
	Teriflunomide 14 mg qd	57	CIS: n = 0, 0% RRMS: n = 50, 87.7% SPMS: n = 7, 12.3% Other = NR	
	Placebo	61	CIS: n = 0, 0% RRMS: n = 53, 86.9% SPMS: n = 8, 13.1% Other = NR	
OPERA I	Ocrelizumab 600 mg q24w	410	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1a 44 mcg tiw	411	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	
OPERA II	Ocrelizumab 600 mg q24w	417	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	Diagnosis with RRMS was an inclusion criterion
	IFN beta-1a 44 mcg tiw	418	CIS: n = NR RRMS: n = NR SPMS: n = NR Other = NR	
PRISMS	IFN beta-1a 22 mcg tiw	189	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	Enrolled patients had clinically definite or laboratory-supported definite MS. Adults with relapsing/remitting MS were eligible for study if they had had at least two relapses in the preceding 2 years and had Kurtzke EDSS scores of 0–5.
	IFN beta-1a 44 mcg tiw	184	CIS: n = 0, 0%	

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
			RRMS: n = NR SPMS: n = NR Other = NR	
	Placebo	187	CIS: n = 0, 0% RRMS: n = NR SPMS: n = NR Other = NR	
REGARD	IFN beta-1a 44 mcg tiw	386	CIS: n = 0, 0% RRMS: n = 386, 100% SPMS: n = 0, 0% Other = NR	Diagnosis with RRMS was an inclusion criterion
	GA 20 mg qd	378	CIS: n = 0, 0% RRMS: n = 378, 100% SPMS: n = 0, 0% Other = NR	
TEMSO	Placebo	363	CIS: n = 0, 0% RRMS: n = 329, 90.6% SPMS: n = 22, 6.1% Other = Progressive relapsing (n=12, 3.3%)	NR
	Teriflunomide 7 mg qd	366	CIS: n = 0, 0% RRMS: n = 333, 91% SPMS: n = 17, 4.6% Other = Progressive relapsing (n=16, 4.4%)	
	Teriflunomide 14 mg qd	359	CIS: n = 0, 0% RRMS: n = 333, 92.8% SPMS: n = 12, 3.3% Other = Progressive relapsing (n=14, 3.9%)	
TENERE	Teriflunomide 14 mg qd	111	CIS: n = 0, 0%	NR

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Study ID	Treatment	Total N	MS subtype	Population comments[1]
			RRMS: n = 108, 97.3% SPMS: n = 1, 0.9% Other = Progressive relapsing (n=2, 1.8%)	
	Teriflunomide 7 mg qd	109	CIS: n = 0, 0% RRMS: n = 108, 97.3% SPMS: n = 0, 0% Other = 0, 0%	
	IFN beta-1a 44 mcg tiw	104	CIS: n = 0, 0% RRMS: n = 108, 97.3% SPMS: n = 1, 0.9% Other = 0, 0%	
TOWER	Teriflunomide 14 mg qd	372	CIS: n = 0, 0% RRMS: n = 366, 99% SPMS: n = 2, 1% Other = Progressive relapsing (n=2, 1%)	NR
	Teriflunomide 7 mg qd	408	CIS: n = 0, 0% RRMS: n = 393, 96% SPMS: n = 3, 1% Other = Progressive relapsing (n=12, 3%)	
	Placebo	389	CIS: n = 0, 0% RRMS: n = 379, 97% SPMS: n = 4, 1% Other = Progressive relapsing (n=6, 2%)	

1. If a study reported that diagnosis with a particular subtype was an inclusion criterion and no further information was given it was assumed that all enrolled patients had that subtype of MS; 2. Only this group was considered for the analyses.
bid = twice daily; CIS = Clinically Isolated Syndrome; qad = every other day; GA = Glatiramer acetate; IFN = interferon; IM = intramuscular; mcg = microgram; MS = multiple sclerosis; NR = not reported; PEG = polyethylene glycolated; RRMS = Relapsing-remitting MS; SD = standard deviation; SPMS = Secondary progressive MS; q2w = once every 2 weeks; q4w = once every 4 weeks; qd = once daily; tid = 3 times a day; tiw = 3 times a week

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Table 8. Previous treatment prior to enrolment

Study ID	Treatment	Total N	Previous Treatment, n (%)	Previous treatment details
ADVANCE	PEG IFN beta-1a 125 mcg q2w	512	Yes = 39 (8) No = 473 (92.4)	Previous treatment with disease modifying treatment
	PEG IFN beta-1a 125 mcg q4w	500	Yes = 39 (8) No = 461 (92.2)	
	Placebo	500	Yes = 35 (7) No = 465 (93)	
APEX	Dimethyl Fumarate 240 mg bid	56	NR	NR
	Placebo	58	NR	
BEYOND	IFN beta-1b 250 mcg qad	897	NR	Patients who were treatment experienced or had participated in previous trials of drugs for multiple sclerosis were excluded
	IFN beta-1b 500 mcg qad	899	NR	
	GA 20 mg qd	448	NR	
Boiko 2017	GA 20 mg qd	61	NR	81.97% (n=50) patients had hormone therapy
	Placebo	28	NR	82.14% (n=23) had hormone therapy
Bornstein 1987	Placebo	25	NR	NR
	GA 20 mg qd	25	NR	
BRAVO	IFN beta-1a 30 mcg qw	447	Yes = 42 (9.4) No = 405 (90.6)	Prior disease modifying treatment for MS at any time before study entry including mitoxantrone, immunoglobulin, IgG, glatiramer acetate, IFNb drugs, meglumine acridonacetate, and azathioprine
	Laquinimod 0.6 mg once-daily	434	Yes = 30 (6.9) No = 404 (93.1)	
	Placebo	450	Yes = 27 (6) No = 423 (94)	
Calabrese 2012	IFN beta-1a 30 mcg qw	47	NR	NR
	IFN beta-1a 44 mcg tiw	46	NR	
	GA 20 mg qd	48	NR	
CAMMS223	Alemtuzumab 12 mg qd	112	Yes = 0 (0) No = 112 (100)	Previous treatment with DMT was an exclusion criterion
	Alemtuzumab 24 mg qd	110	Yes = 0 (0) No = 110 (100)	
	IFN beta-1a 44 mcg tiw	111	Yes = 0 (0) No = 111 (100)	

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Study ID	Treatment	Total N	Previous Treatment, n (%)	Previous treatment details
CARE MS-I	Alemtuzumab 12 mg qd	376	Yes = 0 (0) No = 376 (100)	Key exclusion criteria were previous multiple sclerosis disease therapy (apart from corticosteroids), previous immunosuppressive, investigational, or monoclonal antibody therapy.
	IFN beta-1a 44 mcg tiw	187	Yes = 0 (0) No = 187 (100)	
CARE MS-II	Alemtuzumab 12 mg qd	426	Yes = 426 (100) No = 0 (0)	At least one relapse while on interferon beta or glatiramer after at least 6 months of treatment was an inclusion criterion.
	Alemtuzumab 24 mg qd	170	Yes = 170 (100) No = 0 (0)	
	IFN beta-1a 44 mcg tiw	202	Yes = 202 (100) No = 0 (0)	
CombiRx	IFN beta-1a 30 mcg qw	250	NR	NR
	GA 20 mg qd	259	NR	
CONFIRM	Dimethyl Fumarate, 240 mg bid	359	Yes = 101 (28) No = 244 (72)	Any prior approved DMT including exposure to interferon beta-1a, interferon beta-1b, natalizumab or glatiramer acetate. Patients may also have received other non-approved therapies for MS
	Dimethyl Fumarate 240 mg tid	345	Yes = 100 (29) No = 259 (71)	
	GA 20 mg qd	350	Yes = 103 (29) No = 247 (71)	
	Placebo	363	Yes = 111 (31) No = 252 (69)	
Copolymer I Study	GA 20 mg qd	125	NR	NR
	Placebo	126	NR	
Crentsil 2012	Interferon-beta 1a IM	NR	NR	NR
	Interferon-beta 1a SC	NR	NR	
	Interferon-beta 1b	NR	NR	
	Glatiramer acetate	NR	NR	
DEFINE	Dimethyl Fumarate 240 mg bid	410	Yes = 162 (40) No = 248 (60)	Previous use of approved medications for MS. Approved medications include interferon beta-1a, interferon beta-1b, glatiramer acetate and natalizumab. Patients may have received more than
	Dimethyl Fumarate 240 mg tid	416	Yes = 168 (40) No = 248 (60)	

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Study ID	Treatment	Total N	Previous Treatment, n (%)	Previous treatment details
	Placebo	408	Yes = 172 (42) No = 236 (58)	one prior therapy for MS. Patients may have received other non-approved therapies for MS
Etemadifar 2006	IFN beta-1a 30 mcg qw	30	NR	NR
	IFN beta-1a 44 mcg tiw	30	NR	
	IFN beta-1b 250 mcg qad	30	NR	
EVIDENCE	IFN beta-1a 30 mcg qw	338	NR	NR
	IFN beta-1a 44 mcg tiw	339	NR	
GALA	GA 40mg tiw	943	Yes = 128 (13.6) No = 815 (86.4)	Prior DMT treatment. Type of DMT not defined
	Placebo	461	Yes = 63 (13.7) No = 398 (86.3)	
GLOW	Placebo	59	NR	NR
	GA 20 mg qd	119	NR	
IFNB MS study	IFN beta-1b 50 mcg qad	125	NR	NR
	IFN beta-1b 500 mcg qad	124	NR	
	Placebo	123	NR	
INCOMIN	IFN beta-1a 30 mcg qw	92	NR	NR
	IFN beta-1b 250 mcg qad	96	NR	
Mokhber 2014	IFN beta-1a 30 mcg qw	23	NR	NR
	IFN beta-1a 44 mcg tiw	23	NR	
	IFN beta-1b 250 mcg qad	23	NR	
Mokhber 2015	IFN beta-1a 30 mcg qw	20	Yes = 0 (0) No = 20 (100)	Previous disease modifying treatment was an exclusion criterion
	IFN beta-1a 44 mcg tiw	23	Yes = 0 (0) No = 23 (100)	
	IFN beta-1b 250 mcg qad	22	Yes = 0 (0) No = 22 (100)	
MSCRG	IFN beta-1a 30 mcg qw	158	Yes = 128 (81) No = 30 (19)	Administered within 60 days prior to the first day of injection of study medication. Medications used by at least 10% of group included Ascorbic acid, Nicotinamide, Riboflavin, Thiamine hydrochloride,
	Placebo	143	Yes = 130 (91) No = 13 (9)	

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Study ID	Treatment	Total N	Previous Treatment, n (%)	Previous treatment details
				Retinol, Ergocalciferol, Folic acid, Panthenol, Paracetamol, Ibuprofen, Amantadine, Acetylsalicylic acid, Baclofen, Pyridoxine hydrochloride, Tocopherol, Vitamins, Calcium pantothenate
O'Connor 2006	Teriflunomide 7 mg qd	61	NR	NR
	Teriflunomide 14 mg qd	57	NR	
	Placebo	61	NR	
OPERA I	Ocrelizumab 600 mg q24w	408	Yes = 107 (26) No = 301 (74)	NR
	IFN beta-1a 44 mcg tiw	409	Yes = 117 (29) No = 292 (71)	
OPERA II	Ocrelizumab 600 mg q24w	417	Yes = 113 (27) No = 304 (73)	NR
	IFN beta-1a 44 mcg tiw	417	Yes = 103 (25) No = 314 (75)	
PRISMS	IFN beta-1a 22 mcg tiw	189	Yes = 128 (81) No = 30 (19)	NR
	IFN beta-1a 44 mcg tiw	184	Yes = 130 (91) No = 13 (9)	
	Placebo	187	Yes = 128 (81) No = 30 (19)	
REGARD	IFN beta-1a 44 mcg tiw	386	Yes = 130 (91) No = 13 (9)	Steroid treatment in the previous 6 months
	GA 20 mg qd	378	Yes = 128 (81) No = 30 (19)	
TEMSO	Placebo	363	Yes = 90 (24.8) No = 273 (75.2)	Use of DMT in previous 2 years including interferon beta-1a, interferon beta-1b, glatiramer acetate. Patients may have received more than one previous therapy
	Teriflunomide 7 mg qd	366	Yes = 102 (27.9) No = 264 (72.1)	
	Teriflunomide 14 mg qd	359	Yes = 102 (28.4) No = 257 (71.6)	

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Study ID	Treatment	Total N	Previous Treatment, n (%)	Previous treatment details
TENERE	Teriflunomide 14 mg qd	111	Yes = 13 (11.7) No = 98 (88.3)	Use of DMT in previous 2 years: IFN beta-1a, IFN beta-1b, Glatiramer acetate. Patients may have received more than one DMT
	Teriflunomide 7 mg qd	109	Yes = 23 (21.1) No = 86 (78.9)	
	IFN beta-1a 44 mcg tiw	104	Yes = 25 (24.0) No = 79 (76)	
TOWER	Teriflunomide 14 mg qd	372	Yes = 126 (34.0) No = 246 (66.0)	Use of MS medication in the previous 2 years: IFN beta-1a, IFN beta-1b, Glatiramer Acetate. Patients may have received more than 1 prior medication
	Teriflunomide 7 mg qd	408	Yes = 123 (30.0) No = 285 (70)	
	Placebo	389	Yes = 135 (35.0) No = 254 (65.0)	

bid = twice daily; DMT = disease-modifying treatment; qad = every other day; GA = Glatiramer acetate; IFN = interferon; IM = intramuscular; mcg = microgram; NR = not reported; PEG = polyethylene glycolated; q2w = once every 2 weeks; q4w = once every 4 weeks; qd = once daily; tid = 3 times a day; tiw = 3 times a week

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Table 9. Risk of bias of included studies

Study ID	Randomisation	Allocation Concealment	Participant Blinding	Caregiver Blinding	Assessor Blinding	Incomplete Outcome Data	Selective Reporting
ADVANCE	Unclear	Low	Low	Low	Low	Low	Low
APEX	Unclear	Unclear	Low	Low	Unclear	Low	Low
BEYOND	Low	Low	Low	Low	Low	Low	Low
Boiko 2017	Unclear	Unclear	Low	Low	Low	High	Low
Bornstein 1987	Unclear	Unclear	Unclear	High	Unclear	High	Low
BRAVO	Low	Unclear	High	High	Low	Low	Low
Calabrese 2012	Low	Unclear	Unclear	Unclear	Low	High	Unclear
CAMMS223	Low	Unclear	High	High	High	Low	Low
CARE MS-I	Unclear	Low	High	High	Low	Low	Low
CARE MS-II	Unclear	Low	High	High	Low	Low	High
CombiRx	Low	Low	Low	Low	Low	Unclear	Unclear
CONFIRM	Low	Low	Low	Low	Low	Low	Low
Copolymer I	Unclear	Low	Low	Low	Low	Low	Low
Crentsil 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
DEFINE	Unclear	Low	Low	Low	Low	Low	Low
Etemadifar 2006	Unclear	Unclear	High	High	Low	Low	Low
EVIDENCE	Low	Low	High	Low	Low	Low	Low
GALA	Low	Low	Low	Low	Low	Low	Low
GLOW	Unclear	Unclear	Low	Low	Unclear	High	Unclear
IFNB MS study	Unclear	Unclear	Low	Low	Low	Unclear	Low
INCOMIN	Low	Low	High	High	High	Low	Low
Mokhber 2014	Low	Unclear	Unclear	Unclear	Low	Low	Unclear

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Study ID	Randomisation	Allocation Concealment	Participant Blinding	Caregiver Blinding	Assessor Blinding	Incomplete Outcome Data	Selective Reporting
Mokhber 2015	Low	Unclear	High	Unclear	Low	Low	Low
MSCRG	Low	Low	Low	Low	Low	Low	High
O'Connor 2006	Unclear	Unclear	Low	Low	Low	Low	Low
OPERA I	Low	Unclear	Low	Low	Low	Low	Low
OPERA II	Low	Unclear	Low	Low	Low	Low	Low
PRISMS	Low	Unclear	Low	Low	Low	Low	Low
REGARD	Low	Unclear	High	High	Low	Low	Low
TEMSO	Unclear	Unclear	Unclear	Low	Low	Low	High
TENERE	Low	Low	High	High	High	Low	Low
TOWER	Low	Low	Low	Low	Low	Low	Low

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A9. PRIORITY QUESTION. CS, Document B, section B.2.9.3.3. The company submission states that the INCOMIN study was not included in the network meta-analysis for the outcome 'disability progression after 6 months (CDP6M)' because it did not report data for this outcome.

a. INCOMIN 2002 reports the rate ratio for this outcome for interferon beta-1b 250 mcg end of day (information can be found in Melendez-Torres et al. [2017]). Please clarify the rationale for not calculating the hazard ratio from the reported rate ratio.

Response:

Rate ratio and hazard ratios can be defined as:

- The rate ratio is the ratio of the incidence rate in the treatment and control groups over the whole study period which is the total number of events divided by the total person-years of the study (the combined follow-up times of everyone) for each group. This involves the total number of events so counts more than one event per patient.

- The hazard ratio is the ratio of the hazard per group which is on a per patient basis and is the time to the first event for each patient and if they do not experience the event they are censored at the last known time. This effect size only includes one event per patient.

A hazard ratio is taken from a survival analysis in the original study whereas a rate ratio is not. According to section 9.2.6 of the Cochrane Handbook,[1] time-to-event data can sometimes be analysed as dichotomous data if the status of all patients at a fixed time point is known. However, there is no suggestion of assuming rate and hazard ratios are equivalent and can be included in the same analysis. Therefore, we did not include INCOMIN in the CDP6M network.

b. Please provide an updated network meta-analysis including INCOMIN 2002.

Response:

In response to this request, we have prepared a sensitivity analysis of CDP6M, including the rate ratio from Durelli et al. 2002[2], into the existing network which used hazard ratio for the already included studies. Figure 3 (which is based on CS, Document B, Section 2.9.3.3, Figure 18) shows the revised network and Figure 4 shows the results of the sensitivity analyses which is based on CS, Document B, Section 2.9.3.3, Figure 19).

In previous TAs including TA533, the INCOMIN trial has been noted as an outlier as the CDP3M and CDP6M MTC outputs for IFNB-1b are inconsistent (INCOMIN is the only study informing CDP-24 for IFNB-1b) with the general trend of CDP3M and CDP6M for all other technologies.

[1] Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011 [accessed 7.8.14]. Available from: http://www.cochrane-handbook.org/

[2] Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359(9316):1453-60.

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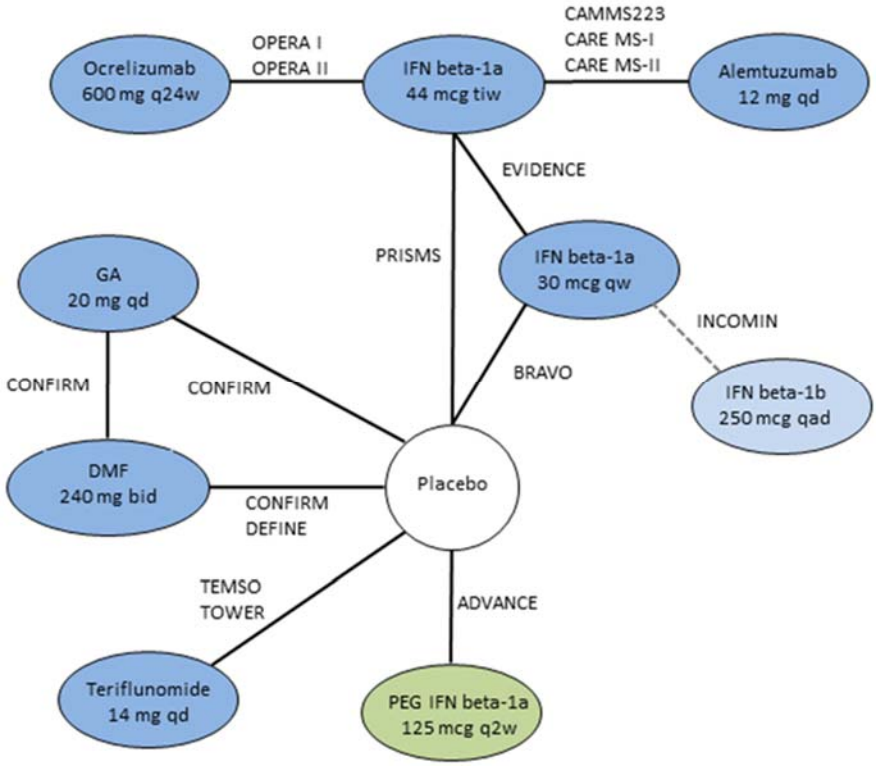
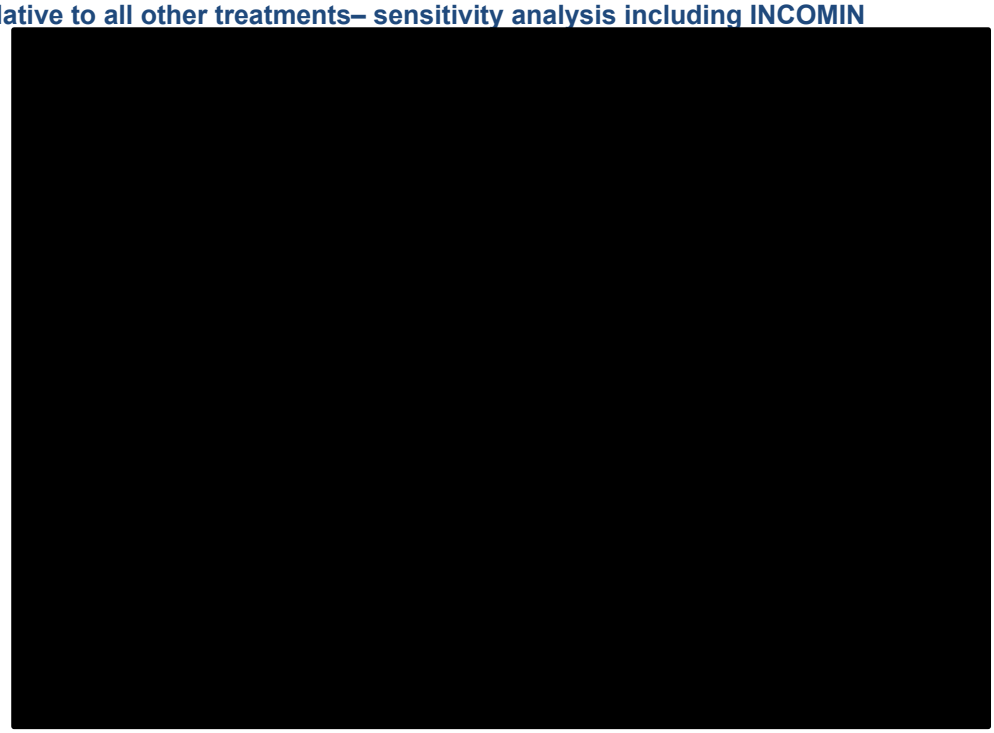
Figure 3. Overall network for disability progression confirmed after 6 months (CDP6M) – sensitivity analysis including INCOMIN



bid = twice daily; DMF = dimethyl fumarate; PEG IFN = pegylated interferon; q24w = once every 24 weeks; qad = every other day; qd = once daily; tiw = 3 times a week

Figure 4. Disability progression confirmed after 6 months (CDP6M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments– sensitivity analysis including INCOMIN



bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly

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A10. CS, Document B, section B.2.9.3, section B.2.9.3.1, section B.2.9.3.2 and section B.2.9.3.3. CS, Document C, Appendix D, section D.3.1; Appendix L, section L.3.1.2, section L.3.2.2 and section L.3.3.2. In section B.2.9.3, Table 16 (Final inclusion in the mixed-treatment comparison for the overall relapsing-remitting multiple sclerosis population) shows that 2 included studies, APEX and Etemadifar 2006 did not report 3 outcomes (ARR, CDP3M and CDP6M). These studies also do not appear in the network diagrams for these outcomes in Figures 14 (ARR), 16 (CDP3M) and 18 (CDP6M). In addition, they do not appear in the mixed treatment comparisons or direct meta-analyses for these outcomes in Appendix L. However, they are not included in Table 25 (Studies excluded from key analysis) [Appendix D, section D.3.1].

a. Please clarify if the information in Table 16 is correct.

Response:

Table 16 is correct with the exception of APEX and Etemadifar 2006 which were not included in any MTC. Both studies should have been instead included in Table 25 (studies excluded from key analyses).

b. Please clarify if APEX and Etemadifar 2006 were included in at least one analysis presented elsewhere.

Response:

Neither study was included in any MTC. The Etemadifar 2006 study was not included in any network as this study enrolled mostly RES RRMS patients and the APEX did not report key outcomes of ARR and CDP; other outcomes (e.g. AEs) were not reported at comparable timepoints.

c. **PRIORITY QUESTION.** For Figures 14, 16 and 18, please provide SUCRA (surface under the cumulative ranking curve) diagrams or equivalent tables of ranking to describe the unified ranking of treatments for these mixed treatment comparisons.

Response:

The requested ranking tables were calculated using gemtc 0.8-2 in R[3] and are provided below. For CDP6M, we have provided two versions, namely a version without INCOMIN (in line with original submission) and with INCOMIN (in line with the response to question A9b).

- Table 10: Ranking table –ARR
- Table 11: Ranking table – CDP3M
- Table 12: Ranking table – CDP6M
- Table 13: Ranking table –CDP6M – sensitivity analysis including INCOMIN

[3] van Valkenhoef G, Kuiper J. gemtc: network meta-analysis using Bayesian methods. R package version 0.8-2 [Internet]. 2016 [accessed 13.10.17]. Available from: https://cran.r-project.org/web/packages/gemtc/index.html

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Table 10. Ranking table – Annualised relapse rate (ARR)

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9	Rank10	Rank11
Alemtuzumab 12 mg qd	[redacted]										
Ocrelizumab 600 mg q24w	[redacted]										
DMF 240 mg bid	[redacted]										
PEG IFN beta-1a 125 mcg q2w	[redacted]										
GA 40 mg tiw	[redacted]										
IFN beta-1b 250 mcg qad	[redacted]										
GA 20 mg qd	[redacted]										
IFN beta-1a 44 mcg tiw	[redacted]										
IFN beta-1a 30 mcg qw	[redacted]										
Teriflunomide 14 mg qd	[redacted]										
Placebo	[redacted]										

ARR = annualised relapse rate; bid = twice daily; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; tiw = three times weekly

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Table 11. Ranking table – Confirmed disease progression after three months (CDP3M)

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9	Rank10	Rank11
Alemtuzumab 12 mg qd	[redacted]										
Ocrelizumab 600 mg q24w	[redacted]										
PEG IFN beta-1a 125 mcg q2w	[redacted]										
IFN beta-1b 250 mcg qad	[redacted]										
Teriflunomide 14 mg qd	[redacted]										
DMF 240 mg bid	[redacted]										
IFN beta-1a 22 mcg tiw	[redacted]										
GA 20 mg qd	[redacted]										
IFN beta-1a 30 mcg qw	[redacted]										
IFN beta-1a 44 mcg tiw	[redacted]										
Placebo	[redacted]										

CDP3M = confirmed disease progression after three months; bid = twice daily; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; tiw = three times weekly

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Table 12. Ranking table – Confirmed disease progression after six months (CDP6M)

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9
Alemtuzumab 12 mg qd	[redacted]								
Ocrelizumab 600 mg q24w	[redacted]								
PEG IFN beta-1a 125 mcg q2w	[redacted]								
DMF 240 mg bid	[redacted]								
GA 20 mg qd	[redacted]								
Teriflunomide 14 mg qd	[redacted]								
IFN beta-1a 30 mcg qw	[redacted]								
IFN beta-1a 44 mcg tiw	[redacted]								
Placebo	[redacted]								

CDP6M = confirmed disease progression after six months; bid = twice daily; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; tiw = three times weekly

Table 13. Ranking table – Confirmed disease progression after six months (CDP6M) – sensitivity analysis including INCOMIN

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9	Rank10
IFN beta-1b 250 mcg qad	[redacted]									
Alemtuzumab 12 mg qd	[redacted]									
Ocrelizumab 600 mg q24w	[redacted]									
PEG IFN beta-1a 125 mcg q2w	[redacted]									
DMF 240 mg bid	[redacted]									
GA 20 mg qd	[redacted]									
Teriflunomide 14 mg qd	[redacted]									
IFN beta-1a 30 mcg qw	[redacted]									
IFN beta-1a 44 mcg tiw	[redacted]									
Placebo	[redacted]									

CDP6M = confirmed disease progression after six months; bid = twice daily; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; tiw = three times weekly

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A11. CS, Document C, Appendix D, section D.3.2.1; Appendix L, section L.3.15.1. Document 'Biogen Plegridy – Full Report – Main - 20190222'. The Biogen Plegridy Full Report Main document[131] (section 6.1, p122) states that '*Due to lack of relevant studies, no MTCs or indirect comparisons of treatment discontinuation due to adverse events were possible*'. In addition, section L.3.15.1 (Document C) states that '*Two studies reported data on the proportion of patients who discontinued treatment due to adverse events (AEs) after 1 year (ADVANCE, GALA). There was heterogeneity in the reporting of discontinuation between studies; One study reported study discontinuation due to AEs (ADVANCE) while one study did not specify which definition was used (GALA). Given the heterogeneity between studies and the lack of appropriate data to assess the impact of heterogeneity, we did not consider it valid to perform a quantitative meta-analysis for discontinuation due to AEs*'. However, Khan et al. (2017)'s paper on the GALA study (Document C, Reference 129) reports discontinuations due to adverse events at the end of the 1-year placebo-controlled period (see Figure 2 in the paper: 29/943 for glatiramer acetate 40 vs. 6/461 for placebo). Khan et al. (2017) is not included in Table 26 (List of included studies) [Document C, section D.3.2.1].

a. Please clarify the rationale for excluding Khan et al. (2017) in the meta-analysis.

Response:

Khan et al 2017 is a more recent publication of Khan et al 2013 (Document C, Table 26, p60) which is already included in the meta-analysis for adverse events leading to discontinuation for GALA. Khan 2013 reports the cited discontinuations due to adverse events at the end of the 1-year placebo-controlled period (29/943 for glatiramer acetate 40 vs. 6/461 for placebo). These input data can be found in "The Biogen Plegridy Full Report Main document"[131] (section 5.7, p118, table 43)

b. Please provide an updated network meta-analysis including Khan et al. (2017).

Response:

As these data were already included network meta-analysis provided in Document C, appendix L, section 3.15.1, no update has been conducted.

Outcomes

A12. CS, Document B, section B.2.9.3. Section B.2.9.3 states that '*It was decided after a protocol modification in May 2015 to consider time points other than 12 or 24 months for ARR, as this is an annualised measure expressed as relapses per patient-year*'. However, these additionally included studies having timepoints other than 12 or 24 months for annualised relapse rates '*… were not considered for any other outcomes*'. Please provide further justification for including and combining time points other than 12 or 24 months for only the annualised relapse rate.

Response:

The text "*were not considered for any other outcomes*" is an error. It is stated later in the same paragraph that "*two additional studies (EVIDENCE, TOWER) providing 11 months or 18 months of data, respectively, were further considered for inclusion in the base-case analysis for CDP3M and CDP6M*". Further detail is provided below.

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There was some variation in the follow-up time between studies. Several studies reported one year outcomes after 48 weeks (11 months) of follow-up. Therefore, any study where one year outcomes were reported at ≥ 11 months and ≤ 13 months was considered for potential inclusion in the analysis of 12 month outcomes. The actual follow-up period for two year outcomes ranged from 96 weeks (22.2 months) to 108 weeks (24.9 months). Therefore, any study where two year outcomes were reported at ≥22 months and ≤25 months was considered for potential inclusion in the analysis of 24 month outcomes.

In order to achieve a comparison with PEG IFN beta-1a and inform the economic model, the treatment under appraisal, 11, 18, and 24 month follow-ups were pooled for the key outcomes of ARR, CDP3M and CDP6M outcomes, where possible. All other outcomes (including relapses requiring hospitalisation, relapses requiring IV corticosteroids, mortality, NEDA, symptoms of MS (cognition, fatigue and visual impairment), quality of life, any AE, any SAE, treatment discontinuation due to any cause or treatment discontinuation due to AE) were informed by 12 month follow-up data alone.

There were seven studies included in the systematic review that did not report relevant outcome data at either 12 months or 24 months (CombiRx, Crentsil 2012, Mokhber 2014, Mokhber 2015, O'Connor 2006, TENERE, TOWER). Following a protocol modification in May 2015, it was decided to consider time points other than 12 or 24 months for ARR as this is an annualised measure expressed as relapses per patient-year. There were three studies that reported ARR data at time points other than 12 or 24 months (CAMMS223, 36 months; CombiRx, 36 months; TENERE, ~14-15 months; TOWER, ~18-19 months). These studies were consequently considered for inclusion in the analysis. One study (CAMMS223) also reported ARR at 36 months follow-up, which allowed this study to be considered for inclusion in the combined analysis of ARR (in addition to other outcomes). Two additional studies (EVIDENCE, TOWER) providing 11 months or 18 months of data, respectively, were further considered for inclusion in the base case analysis for CDP3M and CDP6M.

Inconsistency

A13. CS, Document C, Appendix D, section D.2.5; Appendix L, sections L.3.12 and L.3.13. Section D.2.5 states that '*Inconsistency in the mixed treatment comparison (MTC) networks was investigated using a combination of graphical and statistical methods. For those networks with the potential for inconsistency, the node splitting method to check for evidence of inconsistency was used*'. For those networks with the potential for inconsistency, please clarify where the evidence of statistically significant inconsistency has been reported. In particular, for networks where no closed loops are formed, such as networks for adverse events (section L.3.12) and serious adverse events (section L.3.13).

Response:

Annualised relapse rate (ARR)

Inconsistency occurs in loops of evidence where the effect estimates are derived from both direct and indirect evidence. In the network for this outcome, there were 11 treatment comparisons with the potential for inconsistency (Figure 5).

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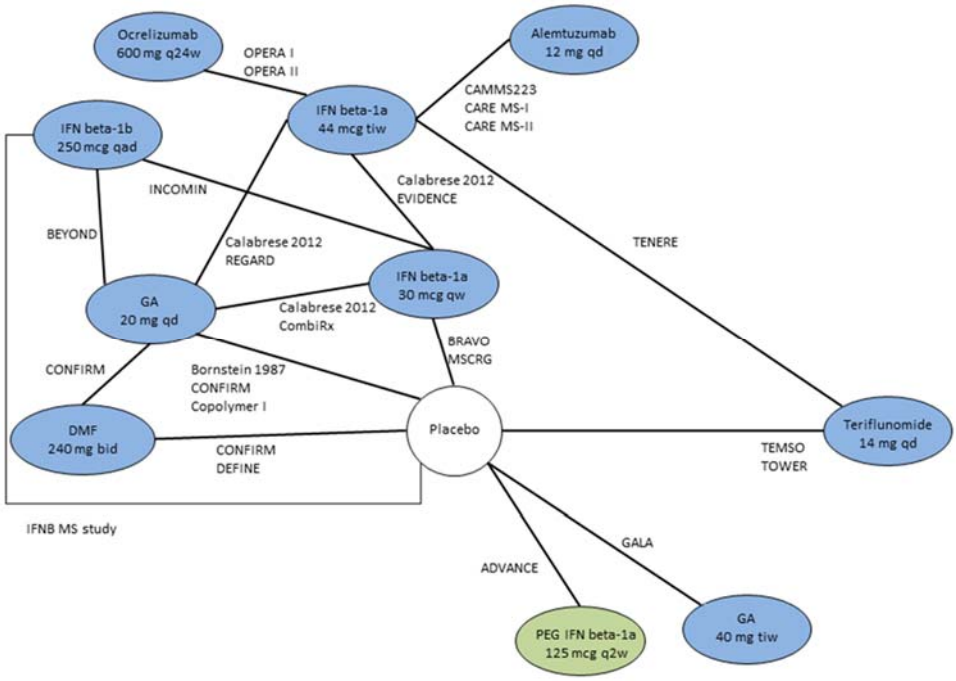
Figure 5. Overall network for ARR



DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly.

We tested the presence of inconsistency in the ARR network using the node splitting method. There was no evidence of statistically significant inconsistency in any of the 11 treatment comparisons (Figure 6).

An inconsistency factor (IF) of exactly 1 would indicate that the indirect and direct estimates of the treatment comparison were exactly equal. As each treatment effect in a given loop includes a degree of uncertainty, some deviation from IF=1 is expected as illustrated by the variation in the IF values around one in Figure 6.

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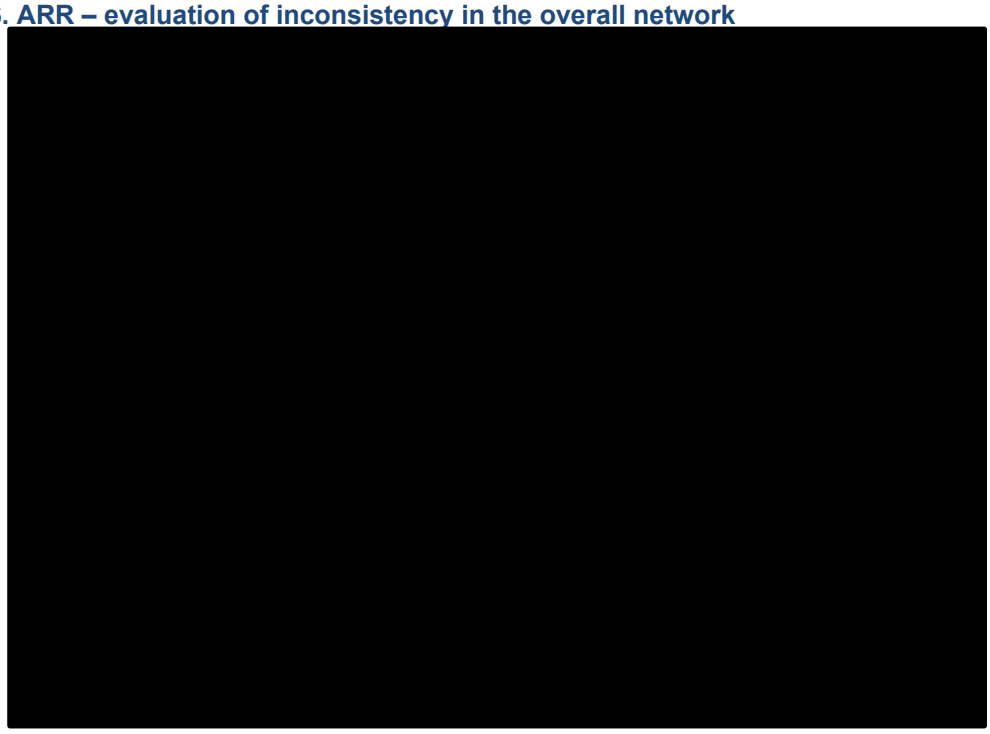
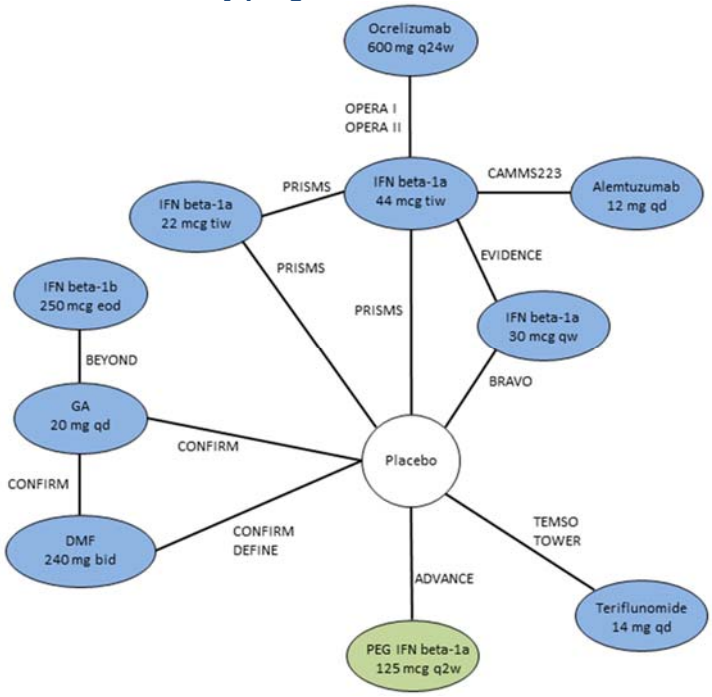
Figure 6. ARR – evaluation of inconsistency in the overall network



Confirmed disability progression at 3 months (CDP3M)

In the network for this outcome, there were six treatment comparisons with the potential for inconsistency (Figure 7).

Figure 7. Overall network for disability progression confirmed after three months (CDP3M)



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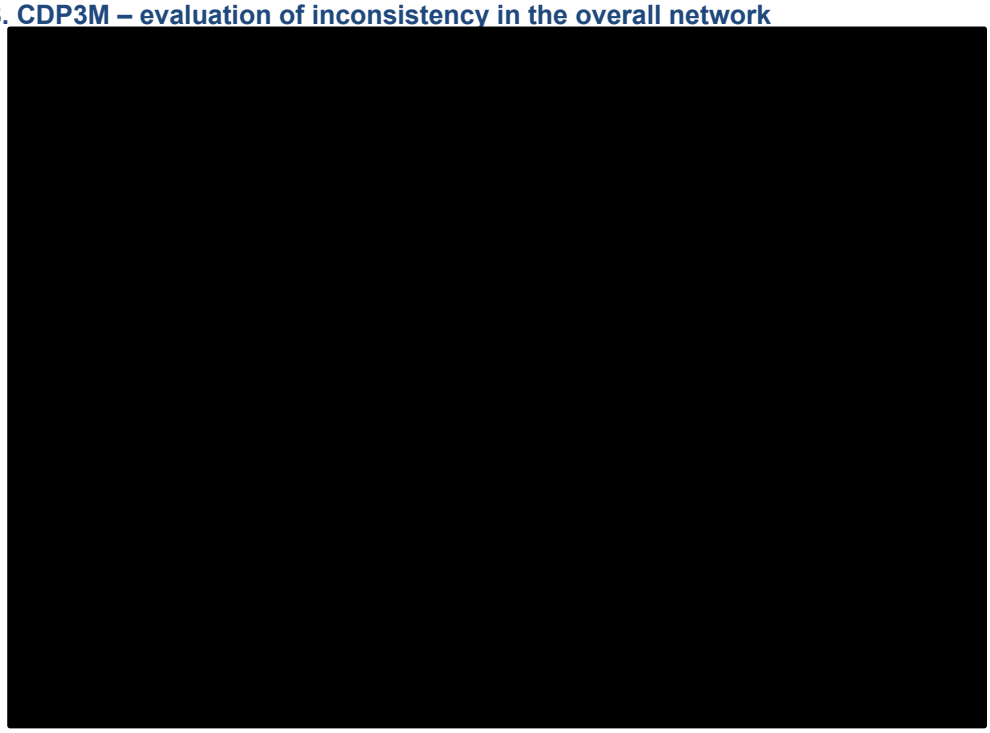
We tested the presence of inconsistency in the CDP3M network using the node splitting method. There was no evidence of statistically significant inconsistency in any of the six treatment comparisons (Figure 8).

Figure 8. CDP3M – evaluation of inconsistency in the overall network



Confirmed disability progression at 6 months (CDP6M)

In the network for this outcome, there were six treatment comparisons with the potential for inconsistency (Figure 9).

We tested the presence of inconsistency in the CDP6M network using the node splitting method. There was no evidence of statistically significant inconsistency in any of the six treatment comparisons (Figure 10).

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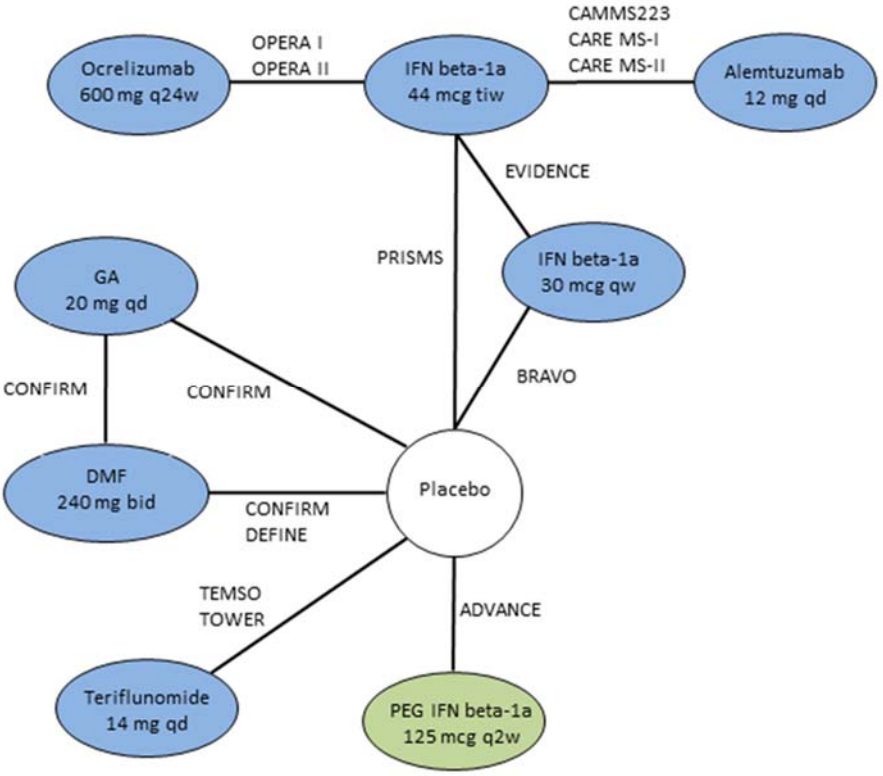
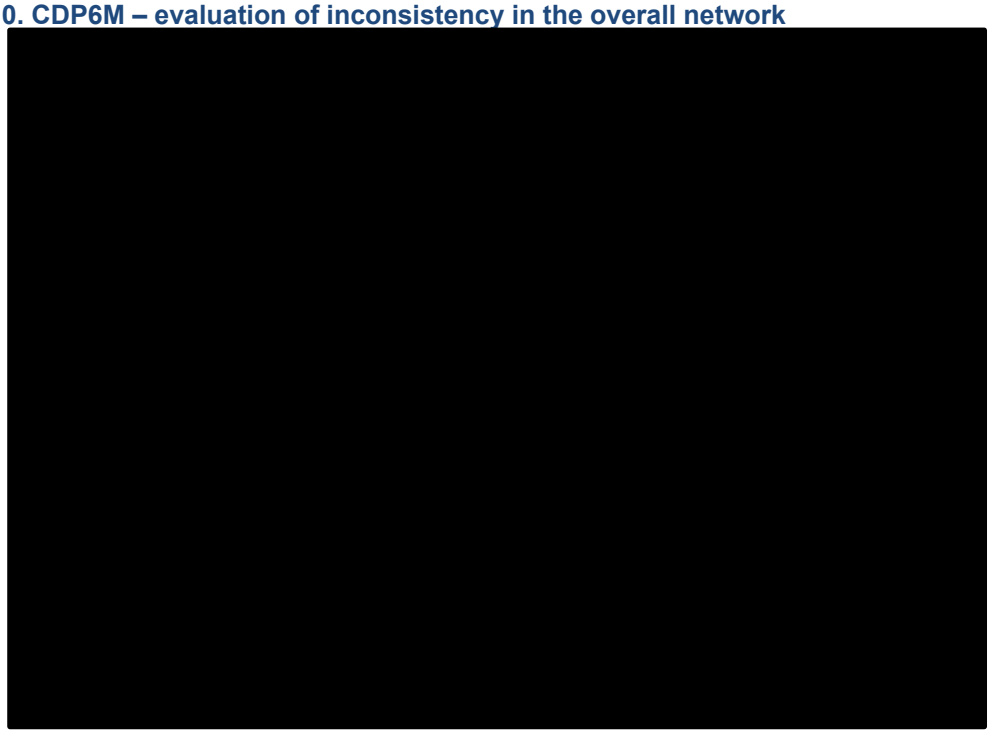
Figure 9. Overall network for disability progression confirmed after 6 months (CDP6M)



bid = twice daily; DMF = dimethyl fumarate; PEG IFN = pegylated interferon; qad = every other day; q24w = once every 24 weeks; qd = once daily; tiw = 3 times a week.

Figure 10. CDP6M – evaluation of inconsistency in the overall network



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Any adverse events, serious adverse event and treatment discontinuation due to any cause.

We planned to assess inconsistency in the network using a combination of graphical assessment of the network structure and node splitting where potential inconsistency may be present. Inconsistency can only occur in closed loops where direct and indirect evidence for a given treatment comparison is derived from different studies. In the network for any adverse event and treatment discontinuation due to any cause, no closed loops were formed. In the network for any serious adverse event there was only one closed loop which was formed by a single three arm study (CONFIRM). Since a single study cannot be inconsistent with itself, there is no potential for inconsistency in these networks.

Sensitivity analysis

A14. Document 'Biogen Plegridy – Full Report – Main - 20190222' and document 'Biogen Plegridy – Full Report – Appendices - 20190222'. Risk of bias was reported in the Biogen Plegridy Full Report Main document (p75), with 4 out of 32 trials rated as low risk of bias in all domains. Sensitivity analysis excluding studies at higher risk of bias cannot be found in the Biogen Plegridy Full Report Main document or The Biogen Plegridy Full Report Appendices document. Please provide a sensitivity analysis excluding studies at higher risk of bias.

Response:

For this request, we removed 16 studies from the networks in line with question A10 (APEX and Etemadifar 2006) or for having at least one domain rated as "High" risk of bias (ROB) as presented in response A8, Table 9 (Boiko 2017, Bornstein 1987, BRAVO, Calabrese 2012, CAMMS223, CARE MS-I, CARE MS-II, EVIDENCE, INCOMIN, Mokhber, MSCRG, REGARD, TEMSO, and TOWER).

Results of the sensitivity analyses are presented below:

- Annualised relapse rate
    - Figure 11. Overall network for annualised relapse rate (ARR) – Sensitivity analysis excluding studies rated as high ROB: Overall network for annualised relapse rate – Sensitivity analysis excluding studies rated as high ROB (based on CS, Document B, section 2.9.3.1, figure 14)
    - Figure 12. Annualised relapse rate of pegIFNβ-1a relative to all other treatments – Sensitivity analysis excluding studies rated as high ROB: Annualised relapse rate of pegIFNβ-1a relative to all other treatments – Sensitivity analysis excluding studies rated as high ROB (based on CS, Document B, section 2.9.3.1, Figure 15)
- Confirmed disease progression after three months (CDP3M)
    - Figure 13: Overall network for disability progression confirmed after three months (CDP3M) – Sensitivity analysis excluding studies rated as high ROB (based on CS, Document B, section 2.9.3.2, figure 16)
    - Figure 14: Disability progression confirmed after 3 months (CDP3M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments – Sensitivity analysis

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excluding studies rated as high ROB (based on CS, Document B, section 2.9.3.2, Figure 17)

- Confirmed disease progression after six months (CDP6M)
    - Figure 15: Overall network for disability progression confirmed after six months (CDP6M) – Sensitivity analysis excluding studies rated as high ROB (based on CS, Document B, section 2.9.3.3, Figure 18)
    - Figure 16: Disability progression confirmed after 6 months (CDP6M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments – Sensitivity analysis excluding studies rated as high ROB (based on CS, Document B, section 2.9.3.3, Figure 19).

No networks were possible for:

- Mortality (CS, Document C, Appendix L, Section 3.7, Figure 12) due to removal of Boiko 2017
- Any adverse events (CS, Document C, Appendix L, Section 3.12, Figure 15) due to removal of Boiko 2017 and GLOW
- Any serious AE (CS, Document C, Appendix L, Figure 18) due to removal of Boiko 2017
- Treatment discontinuation due to any cause (CS, Document C, Appendix L, Section 3.14, Figure 21) due to removal of Boiko 2017.

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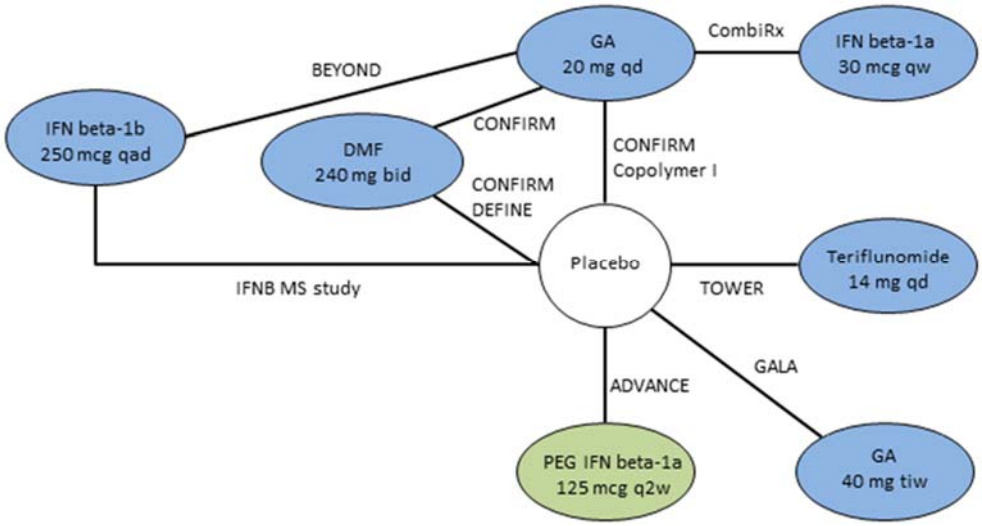
Figure 11. Overall network for annualised relapse rate (ARR) – Sensitivity analysis excluding studies rated as high ROB



ARR = annualised relapse rate; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q2w = once every other week; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; ROB = risk of bias; tiw = three times weekly

Figure 12. Annualised relapse rate of pegIFNβ-1a relative to all other treatments – Sensitivity analysis excluding studies rated as high ROB

bid = twice daily; dmf = dimethyl fumarate; pegifnβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qd = once daily; qw = once weekly; rob = risk of bias; tiw = three times weekly

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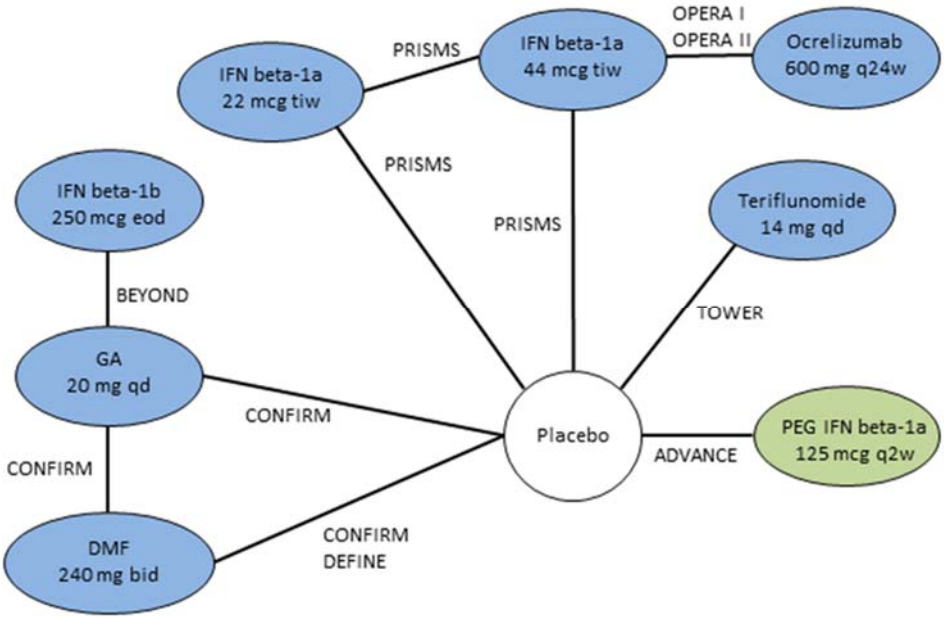
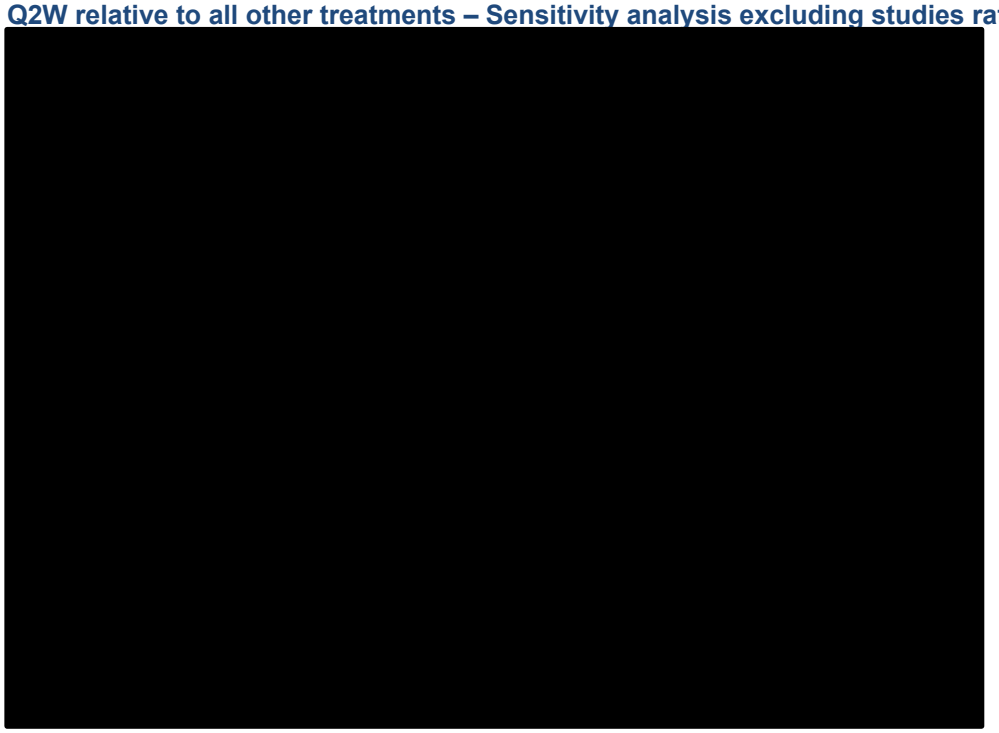
Figure 13. Overall network for disability progression confirmed after three months (CDP3M) – Sensitivity analysis excluding studies rated as high ROB



CDP3M = confirmed disease progression after three months; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q2w = once every other week; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; ROB = risk of bias; tiw = three times weekly

Figure 14.Disability progression confirmed after 3 months (CDP3M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments – Sensitivity analysis excluding studies rated as high ROB



bid = twice daily; CDP3M = confirmed disease progression after 3 months; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; qad = every other day; q24w = once every 24 weeks; qd = once daily; ROB = risk of bias; tiw = 3 times a week

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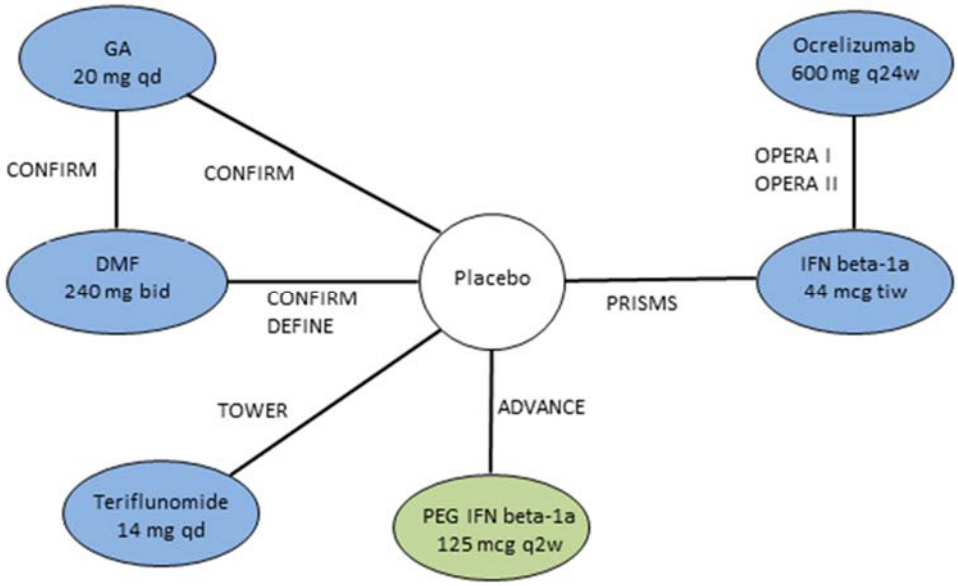
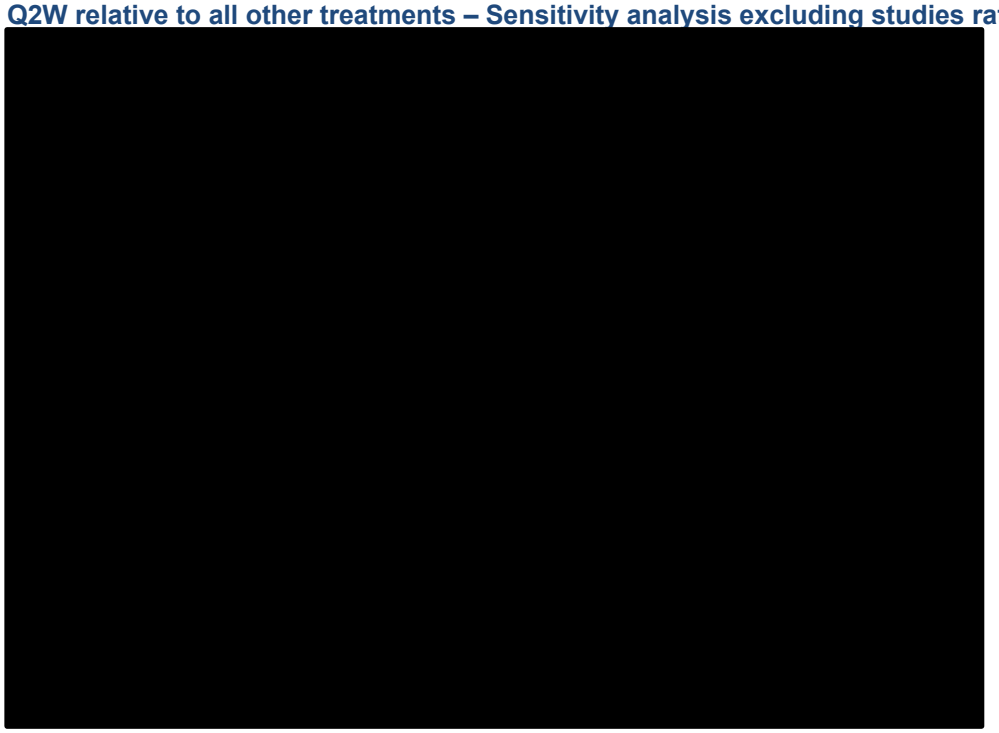
Figure 15. Overall network for disability progression confirmed after six months (CDP6M) – Sensitivity analysis excluding studies rated as high ROB



CDP6M = confirmed disease progression after six months; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q2w = once every other week; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; ROB = risk of bias; tiw = three times weekly

Figure 16. Disability progression confirmed after 6 months (CDP6M) for pegIFNβ-1a 125 mcg Q2W relative to all other treatments – Sensitivity analysis excluding studies rated as high ROB



CDP6M = confirmed disease progression after six months; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q2w = once every other week; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; ROB = risk of bias; tiw = three times weekly

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PLEGRIDY OBSERVATIONAL PROGRAMME (POP) STUDY

A15. CS, Document B, section B.2.11. The Plegridy Observational Programme (POP) is an ongoing, 5-year study exploring the long-term safety profile and effectiveness of peginterferon beta-1a Q2W for patients with newly diagnosed and non-newly diagnosed relapsing MS in the real-world setting.

a. Section B.2.11 states that '…*33% of newly diagnosed patients and 35% of non-newly diagnosed patients … had discontinued peginterferon beta-1a'* in the POP study. These figures are higher than the discontinuation rates because of adverse events for peginterferon beta-1a in ADVANCE at 1 and 2 years (5% and 6% respectively) and ATTAIN (5%) [sections B.2.13.2.1 and B.2.13.2.2]. Please provide a rationale for the higher discontinuation rates observed in the POP study.

Response:

The discontinuation rates from the 2nd interim analysis of POP cite "discontinuation for any reason", whereas the the cited proportions in the clarification question from ADVANCE and ATTAIN are discontinuations due to AEs only. These proportions are therefore not comparable.

Comparing discontinuation rates from ADVANCE/ATTAIN for due to any reason in the continuously treated pegIFNβ-1a Q2W patient population, which for ADVANCE at 48 and 96 weeks was 14% and 20%, respectively. Of the 376 patients who entered year 1 of ATTAIN on continuous pegIFNβ-1a Q2W 25% discontinued due to any reason by the end of the study.

Differences primarily reflect those between a blinded, randomized, controlled Phase 3 study (ADVANCE), an optional open-label extension study (ATTAIN), and an open-label, observational Phase 4 study that reflects the real-world patient population and clinical practices. Additionally, there is a significant increase of available treatment options for patient since the time of ADVANCE/ATTAIN clinical trials. Moreover, the POP study numbers reflect only the 2nd interim analysis (where 89% and 38& of patients [n=963] had completed ≥ 12 and ≥ 24 months of treatment, respectively) and does not include the full enrolled patient population; the completed study is expected to read out in 2022.

b. Figure 31 shows the proportion of patients switching from peginterferon beta-1a to another disease-modifying therapy because of stopping treatment due to adverse events or lack of efficacy. Please provide further details on the reasons for patients switching treatment because of adverse events or lack of efficacy. For example, discontinuation by type of adverse event/serious adverse event or because of problems with adherence or patient choice etc.

Response:

These broad categories were selected by study investigators from a pre-specified list of reasons for discontinuing pegIFNβ-1a in the CRF; therefore, no additional data are available regarding additional details on the reasons for discontinuing pegIFNβ-1a and switching to another DMT.

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MISSING INFORMATION

A16. PRIORITY QUESTION. Please provide the following missing documents or clarify which reference they are in the Reference pack(s):

a. The appendices for the clinical study report (CSR) of ADVANCE 2013. Please provide the sections of the appendix which outlines the reasons why participants 'withdrew consent' and details of 'other' reasons for withdrawal, including numbers who withdrew due to relapse or lack of effect (**CSR ADVANCE 2013, section 10.1.2, p126**). This information is provided as a combined figure for both years 1 and 2 (ADVANCE and ATTAIN) in the CSR, with reference to Appendices. However, the appendices were not included in the reference pack. In particular, reference to Table 3 in Appendix 16.2.1 and Tables 9 and 12 in Appendix 16.2.7.

Response:

Following the clarification call on 9th July 2019, the requested tables from the appendices have been provided in accompaniment to this document.

b. 'ADVANCE trial data on file' (**CS, Document B, Reference 182. CS, Document C, Reference 117**).

Response:

The data for which this reference is cited are available within Calabresi et al 2014 (table 3, p 6), Document B, reference number 11.

c. 'Novartis data on file. HR vs placebo for 3-month confirmed disability progression (with the definition of progression adjusted to match that from the AFFIRM trial), pooled FREEDOMSþ FREEDOMS II RES sub-group. Camberley, Surrey, UK: 2016' (**CS, Document C, Reference 39**).

Response:

This data on file reference is cited within Montgomery et al 2017 (ref number 293). Biogen do not have access to the data on file reference.

d. 'Biogen Idec data on file. Cost-effectiveness analysis of Tecfidera® in patients with relapsing remitting multiple sclerosis. Version 18.0 technical report. Oct 2013' (**CS, Document C, Reference 87**).

Response:

This report is cited within the Mauskopf et al 2016 publication relating to "Treatment efficacy from an MTC and an SLR". All required information is either available in Mauskopf et al 2016

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(Document C, reference number 97) or Hutchinson et al 2014 (Document C, Reference number 88).

Section B: Clarification on cost-effectiveness data

LITERATURE SEARCHING

Databases

B1. CS, Document C, Appendix G, section G.1.1.1. EconLit is included in the electronic databases searched for the economic systematic review. Please clarify whether this search was conducted in 'EconLit' or 'Econlit with Full Text' database.

Response:

This search was conducted in 'EconLit'. As Econlit includes both full-text and conference proceedings and 'Econlit with Full Text' includes full-text publications only, 'EconLit' was preferred for a more comprehensive search.

Included and excluded studies

B2. CS, Document C, Appendix G, section G.2. Figure 3 (PRISMA flow diagram for economic systematic review) shows the number of included and excluded references. Please provide:

a. a list of included studies and all related references for eligibility (level 2) screening.

Response:

Please see below the list of included studies and the updated PRISMA for CS, Document C, Appendix G, section 2, Figure 3 as described below.

Upon review of the included list of studies, two studies (Djambazov et al., 2017 and Martin et al., 2018) that were further excluded but not indicated as such in the original submission have been identified. The list of studies and the PRISMA diagram (Figure 17) are updated to reflect the correct number of studies included (197, opposed to 199).

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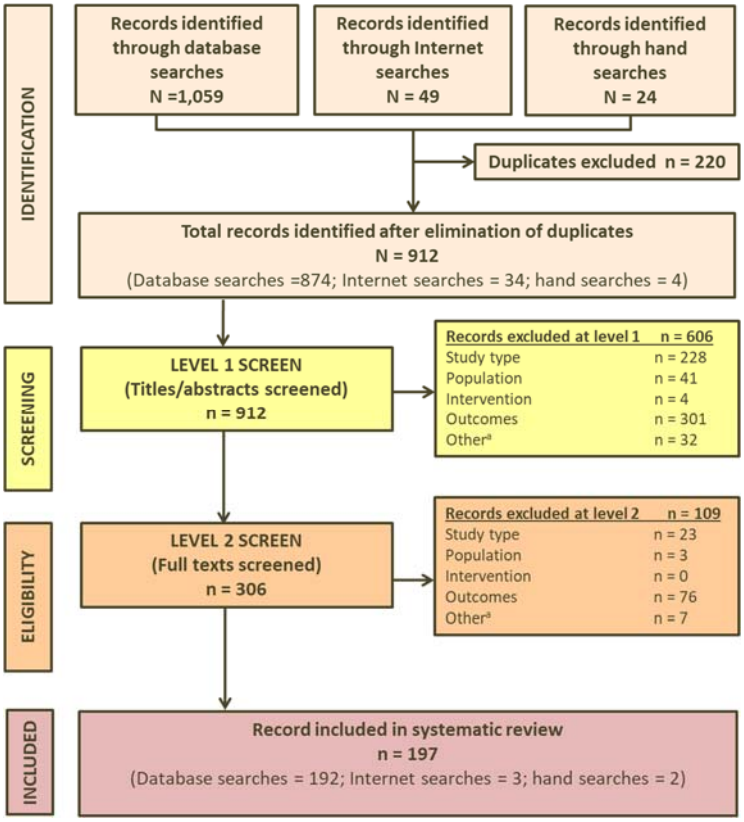
Figure 17. Updated PRISMA flow chart



[a] includes non-English language and duplicate publications

Table 14. List of included studies

#	Reference
1	Chen J, Taylor BV, Blizzard L, Simpson S, Palmer AJ, van der Mei IAF. Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data. Journal of neurology, neurosurgery, and psychiatry. 2018;89(11):1200-1207.
2	Noon KM, Montgomery SM, Adlard NE, Kroes MA. When does economic model type become a decisive factor in health technology appraisals? Learning from the expanding treatment options for relapsing–remitting multiple sclerosis. Journal of Medical Economics. 2018;21(10):983-992.
3	Piena MA, Heisen M, Wormhoudt LW, Wingerden JV, Frequin STFM, Uitdehaag BMJ. Cost-minimization analysis of alemtuzumab compared to fingolimod and natalizumab for the treatment of active relapsing-remitting multiple sclerosis in the Netherlands. Journal of Medical Economics. 2018;21(10):968-976.
4	Afolabi D, Albor C, Zalewski L, Altmann DR, Baker D, Schmierer K. Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis. Multiple Sclerosis Journal. 2018;24(11):1461-1468.
5	Hahn N, Palmer KE, Klocke S, Delate T. Therapeutic Interferon Interchange in Relapsing Multiple Sclerosis Lowers Health Care and Pharmacy Expenditures with Comparable Safety. The Permanente journal. 2018;22.
6	Tinelli M, Kanavos P, Efthymiadou O, Visintin E, Grimaccia F, Mossman J. Using IMPrESS to guide policy change in multiple sclerosis. Multiple Sclerosis Journal. 2018;24(9):1251-1255.
7	Hettle R, Harty G, Wong SL. Cost-effectiveness of cladribine tablets, alemtuzumab, and natalizumab in the treatment of relapsing-remitting multiple sclerosis with high disease activity in England. Journal of Medical Economics. 2018;21(7):676-686.
8	Gyllensten H, Kavaliunas A, Alexanderson K, Hillert J, Tinghög P, Friberg E. Costs and quality of life by disability among people with multiple sclerosis: a register-based study in Sweden. Multiple Sclerosis Journal - Experimental, Translational and Clinical. 2018;4(3).

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#	Reference
9	Hernandez L, Toro-Diaz H, Cele C, Harrington A, Kinter E, Lundqvist T. Dimethyl Fumarate demonstrates Costeffectiveness vs Teriflunomide in Treatment-naïve Patients with Relapsingremitting Multiple Sclerosis in Sweden. European Journal of Neurology. 2018;25:138.
10	Rao D, Heidari E, Kamal KM, Dashputre AA. Cost-effectiveness of daclizumab versus interferon beta-1a in the treatment of patients with relapsing-remitting multiple sclerosis in the United States. Value in Health. 2018;21:S206.
11	Djambazov S, Slavchev G, Dineva T, Panayotov P, Vekov T. Cost-effectiveness analysis of cladribine tablets for treatment of patients with relapsing-remitting multiple sclerosis in Bulgaria. Value in Health. 2018;21:S206.
12	Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. JAMA Neurology. 2018;75(3):320-327.
13	Marangi A, Farina G, Vicenzi V, Forlivesi S, Benedetti MD. Pharmacoepidemiology of multiple sclerosis treatment in veneto region: An observational study. Neuroepidemiology. 2018;50(1-2):90.
14	Lambe T, Duarte R, Mahon J, Nevitt S, Greenhalgh J, Boland A, et al. Cladribine Tablets for the First-Line Treatment of Relapsing-Remitting Multiple Sclerosis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics. 2018.
15	Palace J, Duddy M, Lawton M, Bregenzer T, Zhu F, Boggild M, et al. Assessing the long-term effectiveness of interferon-beta and glatiramer acetate in multiple sclerosis: Final 10-year results from the UK multiple sclerosis risk-sharing scheme. Journal of Neurology, Neurosurgery and Psychiatry. 2018.
16	Zimmermann M, Brouwer E, Tice JA, Seidner M, Loos AM, Liu S, et al. Disease-Modifying Therapies for Relapsing–Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. CNS Drugs. 2018.
17	Kheirandish M, Varahrami V, Kebriaeezade A, Cheraghali AM. Impact of economic sanctions on access to noncommunicable diseases medicines in the islamic republic of Iran. Eastern Mediterranean Health Journal. 2018;24(1):42-51.
18	Hashemi-Meshkini A, Zekri HS, Karimi-Yazdi H, Zaboli P, Sahraian MA, Nikfar S. Pegylated versus non-pegylated interferon beta Ia in patients with relapsing-remitting multiple sclerosis: A cost-effectiveness analysis. Iranian Journal of Neurology. 2018;17(3):123-128.
19	Alsaqa'aby MF, Vaidya V, Khreis N, Al Khairallah T, Al-Jedai AH. Cost-effectiveness of oral agents in relapsing-remitting multiple sclerosis compared to interferon-based therapy in Saudi Arabia. Annals of Saudi Medicine. 2017;37(6):433-443.
20	Frasco MA, Shih T, Incerti D, Diaz Espinosa O, Vania DK, Thomas N. Incremental net monetary benefit of ocrelizumab relative to subcutaneous interferon β-1a. Journal of Medical Economics. 2017;20(10):1074-1082.
21	Yang H, Duchesneau E, Foster R, Guerin A, Ma E, Thomas NP. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. Journal of Medical Economics. 2017;20(10):1056-1065.
22	Chirikov V, Ma I, Joshi N, Patel D, Smith A, Giambrone C, et al. Clinical and economic evaluation of alemtuzumab compared to ocrelizumab in the treatment of relapsing forms of multiple sclerosis in the United States: A payer perspective. Multiple Sclerosis Journal. 2017;23(3):885.
23	Zarkali A, Lux D, Tredwell B, Guck N, Beaumont J, Redmond I, et al. The changing landscape of disease modifying treatments: Cost implications for healthcare systems. Multiple Sclerosis Journal. 2017;23(3):159.
24	Ruiz L, Toro-Diaz H, Cele C, Hernandez L, Harrington A. Cost-effectiveness analysis of peginterferon beta-1a vs. first-line injectable disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis in Spain. Value in Health. 2017;20(9):A723.
25	Tempest M, Bougeard C, Harrington A, Xaplanteris L. The cost-effectiveness of daclizumab beta vs fingolimod for the treatment of relapsing-remitting multiple sclerosis patients with inadequate response to prior treatment in Scotland. Value in Health. 2017;20(9):A723-A724.
26	Lee J, Ko S. The cost effectiveness of fingolimod for the treatment multiple sclerosis in Korea. Value in Health. 2017;20(9):A724.
27	Ruiz L, Machado M, Toro-Diaz H, Cele C, Hernandez L, Harrington A. Cost effectiveness analysis of dimethyl fumarate versus teriflunomide for the treatment of multiple sclerosis. Value in Health. 2017;20(9):A724.
28	Wong SL, Hohnhorst PV, Hettle R, Konings P. Health state utilities in patients with relapsing remitting multiple sclerosis treated with cladribine tablets. Value in Health. 2017;20(9):A725.

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#	Reference
29	Leandersson A, Kagström S, Forsberg L, Hillert J, Nilsson P, Dahle C, et al. A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of alemtuzumab (IMSE 3). Multiple Sclerosis Journal. 2017;23(3):888-889.
30	Grabenhorst L, Haase R, Cornelissen C, Sparring V, Ziemssen T. The impact of fingolimod on the economic burden of multiple sclerosis: Results from two non-interventional studies conducted in Germany. Multiple Sclerosis Journal. 2017;23(3):480-481.
31	Silverio N, Goncalves A, Fonseca A. Cost analysis of several treatment sequences used for the treatment of relapsing-remitting multiple sclerosis in Portugal: The case for cladribine tablets. Value in Health. 2017;20(9):A721.
32	Chirikov V, Ma I, Joshi N, Patel D, Smith A, Giambrone C, et al. Cost-effectiveness of alemtuzumab in the treatment of relapsing forms of multiple sclerosis in the united states and societal spillover effects. Value in Health. 2017;20(9):A722.
33	Herring W, Zhang Y, Pearson I, Tempest M, Freudensprung U, Acosta C, et al. A cost-effectiveness analysis using real-world data from the MSBase Registry: Comparing natalizumab to fingolimod in patients with inadequate response to disease modifying therapies in relapsing-remitting multiple sclerosis in Scotland. Multiple Sclerosis Journal. 2017;23(3):341.
34	Adlard N, Brisbane F, Watson J, Bottomley C, Kroes M. A three month interim analysis of quality of life in patients with relapsing remitting multiple sclerosis in the UK: The Patient Reported Outcomes with Fingolimod in Local Experience (PROFILE) study. Multiple Sclerosis Journal. 2017;23(3):970.
35	Perumal J, Fox RJ, Balabanov R, Makh S, Dong Q, Balcer L, et al. Natalizumab is associated with stable or improved cognitive function, health-related quality of life, and work capacity in anti-JC virus seronegative patients with early relapsingremitting multiple sclerosis: A 2-year analysis of STRIVE. Multiple Sclerosis Journal. 2017;23(3):675.
36	Daigl M, Jhuti GS, McDougall F, Bennett I. Impact of disease activity measures on health utilities in PPMS. Value in Health. 2017;20(9):A727-A728.
37	Yang H, Duchesneau ED, Guerin A, Ma E, Thomas NP. Impact of ocrelizumab vs. interferon beta-1a in delaying the deterioration of patients' daily functions and associated costs in relapsing-remitting multiple sclerosis. Value in Health. 2017;20(9):A721.
38	Ziemssen T, Wang H, Zhang W, Thangavelu K, Melanson M, Hashemi L, et al. Impact of alemtuzumab on work capacity based upon evidence from the CARE-MS II study. Multiple Sclerosis Journal. 2017;23(3):902.
39	Ziemssen T, Albrecht H, Haas J, Klotz L, Lang M, Lassek C, et al. 5 years effectiveness of fingolimod in daily clinical practice: Results of the non-interventional study PANGAEA. Multiple Sclerosis Journal. 2017;23(3):372-373.
40	Rog D, Guo JD, Nucit A, Le Bagousse-Bego G, Chevli M, Chung L. Alemtuzumab is the most cost-effective option in comparison to available therapies in the treatment of RRMS from the UK NHS perspective. Value in Health. 2017;20(9):A723.
41	Taheri S, Yousefi N, Sahraian MA, Mehralian G. Cost-effectiveness analysis of alemtuzumab in comparison with natalizumab, intramuscular interferon beta-1a, subcutaneous interferon beta-1b, and fingolimod for the treatment of relapsing-remitting multiple sclerosis in Iran. Value in Health. 2017;20(9):A723.
42	Montgomery SM, Kusel J, Nicholas R, Adlard N. Costs and effectiveness of fingolimod versus alemtuzumab in the treatment of highly active relapsing-remitting multiple sclerosis in the UK: re-treatment, discount, and disutility. Journal of Medical Economics. 2017;20(9):962-973.
43	Melendez-Torres GJ, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J, et al. Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: Systematic review and economic evaluation. Health Technology Assessment. 2017;21(52).
44	Centonze D, Iannazzo S, Santoni L, Saleri C, Puma E, Giuliani L, et al. The economic profile of peginterferon beta-1a in the treatment of relapsing-remitting multiple sclerosis in Italy. Multiple Sclerosis and Demyelinating Disorders. 2017;2(1).
45	Johnson KM, Zhou H, Lin F, Ko JJ, Herrera V. Real-world adherence and persistence to oral disease-modifying therapies in multiple sclerosis patients over 1 year. Journal of Managed Care and Specialty Pharmacy. 2017;23(8):844-852.
46	Wickström A, Fagerström M, Wickström L, Granåsen G, Dahle C, Vrethem M, et al. The impact of adjusted work conditions and disease-modifying drugs on work ability in multiple sclerosis. Multiple Sclerosis. 2017;23(8):1137-1147.

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#	Reference
47	Dashputre AA, Kamal KM, Pawar G. Cost-effectiveness of peginterferon beta-1a and alemtuzumab in relapsing-remitting multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2017;23(6):666-676.
48	Lee A, Pike J, Edwards MR, Petrillo J, Waller J, Jones E. Quantifying the Benefits of Dimethyl Fumarate Over β Interferon and Glatiramer Acetate Therapies on Work Productivity Outcomes in MS Patients. Neurology and Therapy. 2017;6(1):79-90.
49	Montgomery SM, Maruszczak MJ, Slater D, Kusel J, Nicholas R, Adlard N. A discrete event simulation to model the cost-utility of fingolimod and natalizumab in rapidly evolving severe relapsing-remitting multiple sclerosis in the UK. Journal of Medical Economics. 2017;20(5):474-482.
50	Watson C, Gitlin M, Snyder S. Cost consequence analysis of sc peginterferon beta-1a every 2 weeks versus sc interferon beta-1atiw in patients with RRMS in The United States. Value in Health. 2017;20(5):A192.
51	Smith A, Hashemi L, Wandstrat T. Cost-utility analysis of alemtuzumab versus subcutaneous interferon beta-1a for the treatment of relapsing-remitting multiple sclerosis: Us payer perspective. Value in Health. 2017;20(5):A193.
52	Zimmermann M, Brouwer E, Tice JA, Seidner M, Loos A, Liu S, et al. Cost-utility of disease modifying therapies for relapsing-remitting multiple sclerosis. Value in Health. 2017;20(5):A193.
53	Ordonez JE. Cost-utility analysis of pegylated interferon beta-1a versus interferons beta-1a and beta-1b in patients with relapsing-remitting multiple sclerosis in Colombia. Value in Health. 2017;20(5):A193-A194.
54	Ordonez JE. Dimethyl fumarate versus fingolimod and teriflunomide for the treatment of relapsing-remitting multiple sclerosis in Colombia: A cost-utility analysis. Value in Health. 2017;20(5):A194.
55	Thomas N, Ma E, Yu EB. Economic implications of replacing interferon beta-1a with ocreli-zumab in relapsing multiple sclerosis. Value in Health. 2017;20(5):A191.
56	Alsop J, Medin J, Cornelissen C, Vormfelde SV, Ziemssen T. Two studies in one: A propensity-scorematched comparison of fingolimod versus interferons and glatiramer acetate using realworld data from the independent German studies, PANGAEA and PEARL. PLoS ONE. 2017;12(5).
57	Bargiela D, Bianchi M, Westover B, Healy B, De Jager P, Xia Z. Selection of first-line therapy in multiple sclerosis using risk-benefit decision analysis. Neurology. 2017;88(16).
58	Bozkaya D, Livingston T, Migliaccio-Walle K, Odom T. The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis. Journal of Medical Economics. 2017;20(3):297-302.
59	Hernandez L, Guo S, Toro-Diaz H, Carroll S, Syed Farooq SF. Peginterferon beta-1a versus other self-injectable disease-modifying therapies in the treatment of relapsing-remitting multiple sclerosis in Scotland: a cost-effectiveness analysis. Journal of Medical Economics. 2017;20(3):228-238.
60	Sawad AB, Seoane-Vazquez E, Rodriguez-Monguio R, Turkistani F. Cost-effectiveness of different strategies for treatment relapsing-remitting multiple sclerosis. Journal of Comparative Effectiveness Research. 2017;6(2):97-108.
61	Chirikov V, Ma I, Joshi N, Patel D, Smith A, Giambrone C, et al. Cost-effectiveness of alemtuzumab in the treatment of relapsing forms of multiple sclerosis in the United States. Journal of Managed Care and Specialty Pharmacy. 2017;23:S61.
62	Hua L, Hersh C, Morten P, Kusel J, Lin F, Cave J, et al. The impact of price reductions after loss of exclusivity in a cost-effectiveness analysis: Fingolimod versus intramuscularly administered interferon beta-1a for the treatment of relapsing-remitting multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2017;23:S62.
63	Molina M, Rodriguez E, Gonzalez A, Gonzalez L, Moreno F, Jimenez I, et al. Reasons for changing treatment to oral agents in multiple sclerosis. European Journal of Hospital Pharmacy. 2017;24:A125.
64	Moya-Carmona I, Dominguez-Rivas Y, Pedrosa-Ruiz M, Fernandez-Ovies JM. Economic impact of implementation of natalizumab use with extended interval dosing in patients with relapsing remitting multiple sclerosis. European Journal of Hospital Pharmacy. 2017;24:A43.
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186	Thomas N, Hurley D, Farr A, Lalla D. The impact of multiple sclerosis treatment persistence and adherence on emergency room visits and inpatient hospital stays. Journal of Managed Care and Specialty Pharmacy. 2016;22:S67-S68.
187	Nicholas J, Boster A, Yeh W, Garland R, Fay M, Iyer R, et al. Comparison of costs and health resource utilization in multiple sclerosis patients treated with disease-modifying therapies. Journal of Managed Care and Specialty Pharmacy. 2016;22:S68-S69.
188	Wu Y, Van Engen A, Tchoukouaha T, Rai G, Gandhi S. A cost analysis of drug-related monitoring requirements for glatiramer acetate and other multiple sclerosis disease-modifying therapies. Multiple Sclerosis. 2016;22(3):418.
189	Ogino M, Kawachi I, Otake K, Ohta H, Takeshima T, Iwasaki K, et al. Cost and treatment patterns for multiple sclerosis based on a health insurance claims database. Clinical Neurology. 2016;56:S385.
190	Livingston T, Fay M, Iyer R, Wells W, Pill MW. Quantifying differences in health care consumption for the management of multiple sclerosis within privately and publicly insured health care programs. Journal of Managed Care and Specialty Pharmacy. 2016;22(12):1385-1391.
191	Patel A, Carroll N. Dispensing channel used for specialty drugs and associated costs in medicare part D population. Journal of Managed Care and Specialty Pharmacy. 2015;21:S81-S82.
192	Phillips A, Edwards N, Locklear J. Cost-effectiveness of 44 mcg subcutaneous interferon beta-1a versus 30 mcg intramuscular interferon beta-1a using composite multiple sclerosis clinical endpoints. Journal of Managed Care and Specialty Pharmacy. 2015;21:S45-S46.
193	Franklin MA, Happe LE, Dillman R, Marshall LZ. Frequency and economic impact of comorbid cardiac conditions with multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2014;20(8):795-799.
194	Kobelt G, Thompson A, Berg J, Gannedahl M and Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. Multiple Sclerosis Journal. 2017, Vol. 23(8) 1123–1136

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#	Reference
195	Thompson A, Kobelt G, Berg, Capsa D, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe: Results for the United Kingdom. Multiple Sclerosis Journal. 2017, Vol. 23(2S) 204–216
196	Hawton AJ and Green C. Multiple sclerosis: relapses, resource use, and costs. The European Journal of Health Economics, 2016, vol. 17, issue 7, 875-884
197	Doesburg D, Mokkink W, Vennegoor A, Uitdehaag B and van Oosten B. Sick leave in early MS is associated with fatigue and relapse rate, not disability

b. a list of excluded references with rationale for eligibility (level 2) screening.

Response:

Table 15. List of excluded studies with rationale

#	Reference	Reason for Exclusion
1	Ginestal López RC. Efficiency of the new therapeutic options for the treatment of multiple sclerosis; a pharmacoeconomic review. Pharmacoeconomics - Spanish Research Articles. 2018;15(1-4):3-12.	Study type: SLR
2	Ziemssen T, Schulze Topphoff U, Fendji D. Interim analysis of the non-interventional study COPTIVITY assessing the alteration of activity in ambulatory patients with relapsing MS treated with COPAXONE® 40 mg tiw. European Journal of Neurology. 2018;25:136.	Outcomes: No outcomes presented in this abstract
3	Mékiès C, Heinzlef O, Jenny B, Ramelli AL, Clavelou P. Treatment satisfaction and quality of life in patients treated with fingolimod. Patient Preference and Adherence. 2018;12:899-907.	Outcomes: No relevant outcomes
4	Parente A, Sahlu I, Sutton BS, Petrilla A, Clark MA, Teigland C. Comparison of healthcare utilization by disease modifying therapy generation among individuals diagnosed with multiple sclerosis after one year of initiating therapy in the United States. Value in Health. 2018;21:S209-S210.	Outcomes: No outcomes presented in this abstract
5	Djambazov S, Slavchev G, Dineva T, Panayotov P, Vekov T. Budget impact analysis of cladribine tablets for treatment of patients with relapsing-remitting multiple sclerosis in Bulgaria. Value in Health. 2018;21:S205.	Study type: Budget impact model
6	Reyes S, Allen-Philbey K, Suarez S, Yildiz Ö, Turner B, Gnanapavan S, et al. The impact of socioeconomic status on treatment choice in patients with multiple sclerosis. Neurology. 2018;90(15).	Outcomes: No outcomes in this abstract
7	Isfort MC, Xia Z. Patterns and trends of healthcare utilization among people with multiple sclerosis in the age of disease-modifying modifying therapy. Multiple Sclerosis Journal. 2018;24(1):53-54.	Outcomes: No relevant outcomes
8	Oprea S, Negres S. Evolution in treatment of multiple sclerosis in a university hospital. International Journal of Clinical Pharmacy. 2018;40(1):279-280.	Outcomes: No relevant outcomes in this abstract
9	Álvarez Ayuso L, Rodríguez Marrodán B, Blasco Quílez MR, García-Merino JA, Sánchez Guerrero A. Economic impact of the new oral treatments for multiple sclerosis. Neurologia. 2018.	Other: Spanish article
10	Gaber T, Shippen C. Cladribine tablets and multiple sclerosis: NICE technology appraisal. Progress in Neurology and Psychiatry. 2018;22(1):5-6.	Study type: Review
11	Echave M, Oyagüez I, Casado Ruiz V, Ginestal R, Casado MÁ. Systematic review of studies of quality of life and/or work productivity in patients treated with natalizumab. Pharmacoeconomics - Spanish Research Articles. 2017;14(3-4):77-90.	Study type: SLR

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#	Reference	Reason for Exclusion
12	Vieira M, Li Y, Zhou H, Meng X, Wenxian Piao O, Kutz C, et al. Injectable disease-modifying therapies cycling versus switching to gilenya: A retrospective u.s. claims study of risk of ms-related relapses. Journal of Managed Care and Specialty Pharmacy. 2017;23:S53.	Outcomes: No relevant outcomes in this abstract
13	Ali ZK, Baker DE. Formulary drug review: Ocrelizumab. Hospital Pharmacy. 2017;52(9):599-606.	Study type: Formulary review
14	Afolabi D, Albor C, Altmann DR, Zalewski L, Baker D, Schmierer K. Cladribine tablets treating multiple sclerosis orally (CLARITY): An independent analysis of the quality of life data. Multiple Sclerosis Journal. 2017;23(3):423.	Outcomes: No relevant outcomes in this abstract
15	Landtblom AM, Guala D, Hau S, Jansson L, Martin C, Fredrikson S. RebiQoL: A telemedicine patient support program on health related quality of life and adherence in MS patients treated with Rebif. Multiple Sclerosis Journal. 2017;23(3):425.	Outcomes: No relevant outcomes in this abstract
16	Spelman T, Havrdova E, Horakova D, Trojano M, Lugaresi A, Izquierdo G, et al. A comparative-effectiveness analysis applying a 3 way propensity matching to real-world data from MSBase Registry in preparation for a cost effectiveness model: Patients switching within firstline agents or to natalizumab or fingolimod in active RRMS. Multiple Sclerosis Journal. 2017;23(3):395-397.	Outcomes: No relevant outcomes in this abstract
17	Zhang Y, Taylor B, Van Der Mei I. Patient-reported outcomes are worse for progressive-onset MS than relapse-onset MS, particularly early in the disease process. Multiple Sclerosis Journal. 2017;23(3):727.	Outcomes: No relevant outcomes in this abstract
18	Brown MG, Hicks V, Asbridge M, Murray TJ, Andreou P. Effectiveness, health outcomes and cost-effectiveness of first generation disease-modifying drugs in relapsing-onset multiple sclerosis: Nova Scotia evidence 1979-2010. Multiple Sclerosis Journal. 2017;23(3):360-361.	Outcomes: No relevant outcomes in this abstract
19	Leandersson A, Kagstrom S, Forsberg L, Hillert J, Nilsson P, Dahle C, et al. A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of fingolimod (IMSE 2). Multiple Sclerosis Journal. 2017;23(3):374-375.	Outcomes: No relevant outcomes in this abstract
20	Ziemssen T, Schulze-Topphoff U, Fendji D. Multicenter open-label non-interventional study assessing the alteration of activity in ambulatory patients with relapsing forms of MS (RMS) under treatment with COPAXONER 40 mg tiw-results of an interim analysis of the NIS COPTIVITY. Multiple Sclerosis Journal. 2017;23(3):679.	Outcomes: No relevant outcomes in this abstract
21	Guilleux A, Roux J, Leray E. Mood disorders and multiple sclerosis: A study based upon the French national health insurance databases. Multiple Sclerosis Journal. 2017;23(3):755.	Outcomes: No relevant outcomes in this abstract
22	Roux J, Grimaud O, Leray E. Care consumption of multiple sclerosis patients in France: An analysis of health insurance administrative databases using multichannel sequence analysis from 2007 to 2013. Multiple Sclerosis Journal. 2017;23(3):717.	Outcomes: No relevant outcomes in this abstract
23	Kieseier BC, Hyland M, Williams JR, De Moor C, Phillips GA, Rudick R. Treatment patterns of disease modifying therapies in MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions). Multiple Sclerosis Journal. 2017;23(3):951.	Outcomes: No relevant outcomes in this abstract
24	Cartier-Bechu C, Sivignon M, Petitjean A, Roze S, Pinguet J, Tehard B. How to address french health authority (HAS/CEESP) specific requirements in modelling relapsing-remitting multiple sclerosis in health-economic evaluation? modelling treatment sequences. Value in Health. 2017;20(9):A752.	Outcomes: No relevant outcomes in this abstract

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#	Reference	Reason for Exclusion
25	Stumpfe M, Redelsteins E, Sigel KO, Fischer J, Kausch U, Scholz E, et al. Defining areas of cognitive impairment in relapsingremitting multiple sclerosis (RRMS)-baseline analysis of a longitudinal multicenter study in 15 German practice centers. Multiple Sclerosis Journal. 2017;23(3):387-388.	Outcomes: No relevant outcomes in this abstract
26	Bargiela D, Bianchi MT, Westover MB, Chibnik LB, Healy BC, De Jager PL, et al. Selection of first-line therapy in multiple sclerosis using riskbenefit decision analysis. Multiple Sclerosis Journal. 2017;23(3):625.	Other: Duplicate of Bargiela (2016), ref ID 470
27	Schreiber H, Roßnagel F, Gößwein KH, Braune S, Bergmann A. Retrospective longitudinal analysis of cognition and clinicalbehavioral parameters (PRO) in relapsing-remitting multiple sclerosis (RRMS) patients treated with Teriflunomide - Results from a 12 month registry study in German practice centers. Multiple Sclerosis Journal. 2017;23(3):894.	Outcomes: No relevant outcomes in this abstract
28	Kagstrom S, Leandersson A, Forsberg L, Berglund A, Hillert J, Nilsson P, et al. Real-world longitudinal data of peginterferon beta-1a from a Swedish national post-marketing surveillance study (IMSE 6)-efficacy and safety profile. Multiple Sclerosis Journal. 2017;23(3):626-627.	Outcomes: No relevant outcomes in this abstract
29	Lux D, Zarkali A, Tredwell B, Marshall D, Beaumont J, Guck N, et al. Disease modifying therapies: Trending choices and the what's and why's to switching. Multiple Sclerosis Journal. 2017;23(3):664.	Population: outcomes only reported for rapidly-evolving severe MS in this abstract
30	Hincapie AL, Penm J, Burns CF. Factors associated with patient preferences for disease-modifying therapies in multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2017;23(8):822-830.	Outcomes: No relevant outcomes
31	Fernández O, Calleja-Hernández MA, Meca-Lallana J, Oreja-Guevara C, Polanco A, Pérez-Alcántara F. Estimate of the cost of multiple sclerosis in Spain by literature review. Expert Review of Pharmacoeconomics and Outcomes Research. 2017;17(4):321-333.	Study type: SLR
32	Alskaaabi M, Vaidya V, Mahashabde R. Cost effectiveness of oral agents compared with interferon-based therapy in relapsing-remitting multiple sclerosis saudi patients. Journal of the American Pharmacists Association. 2017;57(3).	Study type: Protocol
33	Edwards NC, Beckerman R, Phillips AL. Real-world evidence for disease-modifying drugs in multiple sclerosis: Trends in the literature. Value in Health. 2017;20(5):A189.	Study type: Abstract of a lit review. Results describe the characteristics of the papers included in the review
34	Martin A. Evidence map of cost-utility models in multiple sclerosis published since 1960. Value in Health. 2017;20(5):A194.	Study type: SLR
35	González RA, Margolin DH, Huang X, Wang H, Zhang W, Guo JD, et al. Improvements in quality of life over 6 years in patients with relapsing-remitting multiple sclerosis treated with alemtuzumab: Results from the CARE-MS II Extension Study. Neurology. 2017;88(16).	Outcomes: No relevant outcomes in this abstract
36	Ziemssen T, Albrecht H, Haas J, Klotz L, Lang M, Lassek C, et al. 5 years effectiveness of fingolimod in daily clinical practice: Results of the noninterventional study PANGAEA documenting RRMS patients treated with fingolimod in Germany. Neurology. 2017;88(16).	Outcomes: No relevant outcomes in this abstract
37	Bourdette D, Van Leuvin S, Johnston K, Lei M, Hartung D. Industry payments to neurologists who commonly prescribe repository corticotropin gel (H.P. Acthar). Neurology. 2017;88(16).	Outcomes: No relevant outcomes in this abstract

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#	Reference	Reason for Exclusion
38	Everage NJ, Prada C, Liu S, Balashov K, Macdonell R, Windsheimer J, et al. Safety and efficacy of delayed-release dimethyl fumarate in multiple sclerosis patients treated in routine medical practice: Interim analysis of ESTEEM. Neurology. 2017;88(16).	Outcomes: No relevant outcomes in this abstract
39	González RA, Guo JD, Wang H, Zhang W, Bury D, Melanson M, et al. Alemtuzumab improves patient-reported quality of life over 6 years in relapsing-remitting multiple sclerosis patients with highly active disease: Results from the CARE-MS II Extension Study. Neurology. 2017;88(16).	Outcomes: No relevant outcomes in this abstract
40	Jenny L, Ryan R, Michael A, Malin R, Signe H, Delphine B, et al. Clinical practice of analysis of anti-drug antibodies against interferon beta and natalizumab in multiple sclerosis patients in Europe: A descriptive study of test results. PLoS ONE. 2017;12(2).	Study type: Testing for anti-drug antibodies
41	Zaprutko T, Kopciuch D, Kus K, Merks P, Nowicka M, Augustyniak I, et al. Affordability of medicines in the European Union. PLoS ONE. 2017;12(2).	Outcomes: No relevant outcomes
42	ŠtouraČ P, Horáková D, Klímová E, TurČáni P. Ametyst-results of an observational phase IV clinical study evaluating the effect of intramuscular interferon beta-1a therapy in patients with clinically isolated syndrome or clinically definite multiple sclerosis. Ceska a Slovenska Neurologie a Neurochirurgie. 2017;80(6):660-665.	Other: Paper is not in English
43	Prosser C, Haas J, Wakeford C, Landsman-Blumberg P, Braun S. Relapse rates and healthcare resource use of therapy persistent and non-persistent multiple sclerosis patients in Germany-a real world analysis. Value in Health. 2016;19(7):A426.	Outcomes: No relevant outcomes in this abstract
44	Visintin E, Kanavos P. Criteria driving values assessments in multiple sclerosis medicines. Value in Health. 2016;19(7):A353.	Outcomes: No relevant outcomes in this abstract
45	Ashtari F, Toghianifar N, Zarkesh-Esfahani SH, Mansourian M. High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Neurological Research. 2016;38(10):888-892.	Outcomes: No relevant outcomes
46	Kantor D, Johnson K, Vieira M, Signorovitch J, Li N, Gao W, et al. Real-world persistence with fingolimod for the treatment of multiple sclerosis: A systematic review and meta-analysis. Journal of Managed Care and Specialty Pharmacy. 2016;22:S52.	Study type: Abstract of an SLR and MA
47	Bargiela D, Bianchi MT, Westover MB, Chibnik LB, Healy BC, De Jager PL, et al. Selection of first-line therapy in multiple sclerosis using risk-benefit decision analysis. Annals of Neurology. 2016;80:S63.	Other: Duplicate of ref ID 230
48	Lee LK, Wu Y, Cutter GR, Hobart JC, Flores NM, Carra AJ, et al. Psychometric evaluation of the medication satisfaction questionnaire (MSQ) to assess satisfaction with glatiramer acetate among patients with multiple sclerosis. Annals of Neurology. 2016;80:S137.	Outcomes: No relevant outcomes in this abstract
49	Stumpfe M, Redelstein E, Sigel KO, Fischer J, Kausch U, Scholz E, et al. Profiling cognitive deficits of patients with remitting relapsing multiple sclerosis (RRMS) in initial and later disease stages. Multiple Sclerosis. 2016;22:128-129.	Outcomes: EQ-5D data collected, but no results presented
50	Duddy M, Palace J, Lilford R, Bregenzer T, Lawton M, Zhu F, et al. The United Kingdom multiple sclerosis risk-sharing scheme: Final 10 year results. Multiple Sclerosis. 2016;22:74-75.	Outcomes: No results presented
51	Ziemssen T, Albrecht H, Haas J, Klotz L, Lang M, Lassek C, et al. 4 years PANGAEA: Effectiveness update of a 5 year noninterventional study on the daily use of fingolimod in Germany. Multiple Sclerosis. 2016;22:642-643.	Outcomes: No relevant outcomes presented

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#	Reference	Reason for Exclusion
52	Arroyo González R, Dive D, Dreyer M, Hupperts RMM, LaGanke C, Lycke J, et al. Improvements in quality of life over 5 years with alemtuzumab are associated with confirmed disability improvement in patients with active relapsing-remitting multiple sclerosis who had an inadequate response to prior therapy (CARE-MS II). Multiple Sclerosis. 2016;22:382-383.	Outcomes: No relevant outcomes presented
53	Bargiela D, Bianchi MT, Westover MB, Chibnik LB, Healy BC, De Jager PL, et al. Selection of first-line therapy in multiple sclerosis using risk benefit decision analysis. Multiple Sclerosis. 2016;22:350-351.	Other: Duplicate of ref ID 230
54	Ziemssen T, Faude U, Fendji D. COPAXONE® active registry-documentation of efficacy, tolerability and quality of life in outpatients with relapsing remitting multiple sclerosis (RRMS) treated with glatiramer acetate. Multiple Sclerosis. 2016;22:639-640.	Outcomes: No relevant outcomes presented
55	Everage NJ, Prada C, Liu S, Balashov K, Macdonell R, Windsheimer J, et al. Safety and effectiveness of delayed-release dimethyl fumarate in multiple sclerosis patients treated in routine medical practice: The first interim analysis of ESTEEM. Multiple Sclerosis. 2016;22:775-776.	Outcomes: No relevant outcomes presented
56	Haupts M, Faude U, Fendji D. Efficacy, tolerability, quality of life, and spasticity in outpatients with relapsing remitting multiple sclerosis (RRMS) treated with glatiramer acetate-results of an observational study. Multiple Sclerosis. 2016;22:814.	Outcomes: No relevant outcomes presented in this abstract
57	Kresa-Reahl K, Repovic P, Robertson D, Okwuokenye M, Meltzer L, Mendoza J. Clinical measures and impact on patient-reported outcomes of delayed-release dimethyl fumarate in relapsing multiple sclerosis patients after suboptimal response to glatiramer acetate: Analysis of the 12-month RESPOND study. Multiple Sclerosis. 2016;22:774.	Outcomes: No relevant outcomes presented in this abstract
58	Ruggeri M, Aiello A, D'Ausilio A, Di Brino E, Cottone S, Ghezzi A, et al. Evolution of the healthcare expenditure in Italy and effects of fingolimod increased prescribing in second line treatment of relapsing-remitting multiple sclerosis. Global and Regional Health Technology Assessment. 2016;3(3):125-133.	Other: Article in Italian
59	Chou CH, Lin TC, Cheng CL, Yang YHK. First-line disease modifying therapies in preventing multiple sclerosis relapse - A nationwide observational study in Taiwan. Pharmacoepidemiology and Drug Safety. 2016;25:580-581.	Outcomes: No relevant outcomes presented
60	Berenguer-Ruiz L, Sempere AP, Gimenez-Martinez J, Gabaldon-Torres L, Tahoces L, Sanchez-Perez R, et al. Rescue therapy using rituximab for multiple sclerosis. Clinical Neuropharmacology. 2016;39(4):178-181.	Outcomes: No relevant outcomes presented
61	Hatam N, Bastani P, Shahtaheri RS. Quality of life in relapsing-remitting multiple sclerosis patients receiving CinnoVex compared with Avonex. Journal of Research in Pharmacy Practice. 2016;5(3):181-185.	Outcomes: No relevant outcomes presented
62	Effat S, Azzam H, Shalash A, Elkatan S, Elrassas H. Self-reported quality of life of patients with multiple sclerosis with mild disability. Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2016;53(3):161-167.	Outcomes: No relevant outcomes presented
63	Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health: time matters in multiple sclerosis. Multiple Sclerosis and Related Disorders. 2016;9:S5-S48.	Study type: Consensus paper
64	Kuhelj R, Deol-Bhullar G, Garas M, Chin P, Hauser S, Montalban X. Open-label phase III extension studies to evaluate the long-term safety and efficacy of ocrelizumab in relapsing MS and primary progressive MS. European Journal of Neurology. 2016;23:200.	Outcomes: Trial currently ongoing, no results reported in the abstract

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#	Reference	Reason for Exclusion
65	Ziemssen T, Albrecht H, Haas J, Klotz L, Lang M, Lassek C, et al. 4 years PANGAEA: A 5-year non-interventional study of safety, effectiveness and pharmacoeconomic data for fingolimod patients in daily clinical practice-effectiveness update. European Journal of Neurology. 2016;23:417.	Outcomes: No relevant outcomes presented
66	Faude U, Ziemssen T. COPAXONE® active registry-documentation of efficacy, tolerability and quality of life in outpatients with relapsing remitting multiple sclerosis (RRMS) treated with glatiramer acetate. European Journal of Neurology. 2016;23:418.	Outcomes: No relevant outcomes presented in this abstract
67	Müller-Schubert A, Ziemssen T, Reichmann H, Kern R, Fendji D. Multicentre open-label non-interventional study (NIS) assessing the alteration of activity in ambulatory patients with relapsing forms of multiple sclerosis (RMS) under treatment with glatiramer aceta. European Journal of Neurology. 2016;23:418.	Outcomes: Results not presented in this abstract
68	Faude U, Fendji D, Haupts MR. Efficacy, tolerability, quality of life and spasticity in outpatients with relapsing remitting multiple sclerosis (RRMS) treated with glatiramer acetate-results of an observational study. European Journal of Neurology. 2016;23:814.	Outcomes: No relevant outcomes presented in this abstract
69	Hupperts RM, Vermersch P, Margolin DH, Thangavelu K, Arroyo Gonzalez R. Treatment-naiive patients with active relapsing-remitting multiple sclerosis demonstrate improved quality of life over 5 years with alemtuzumab related to disability improvement: CARE-MS I extension study. European Journal of Neurology. 2016;23:818.	Outcomes: No relevant outcomes presented in this abstract
70	Brownlee WJ, Ciccarelli O. All relapsing multiple sclerosis patients should be managed at a specialist clinic - YES. Multiple Sclerosis. 2016;22(7):873-875.	Outcomes: No relevant outcomes presented
71	Kresa-Reahl K, Repovic P, Robertson D, Okwuokenye M, Meltzer L, Mann M. Clinical effectiveness and impact on patient-reported outcomes of delayed-release dimethyl fumarate in relapsing multiple sclerosis patients after suboptimal response to glatiramer acetate: Six-month interim analysis of a prospective, multicenter, open-label, single-arm, observational study (RESPOND). Neurology. 2016;86(16).	Outcomes: No relevant outcomes presented in this abstract
72	Bierema C, Williamson E. JC virus antibody testing in the penn MS clinic-examining the utility and stability of the test. Neurology. 2016;86(16).	Study type: Serology
73	Sahai-Srivastava S, Wang SL, Ugurlu C, Amezcua L. Headaches in multiple sclerosis: Cross-sectional study of a multiethnic population. Clinical Neurology and Neurosurgery. 2016;143:71-75.	Outcomes: No relevant outcomes presented
74	Orefice NS, Alhouayek M, Carotenuto A, Montella S, Barbato F, Comelli A, et al. Oral Palmitoylethanolamide Treatment Is Associated with Reduced Cutaneous Adverse Effects of Interferon-β1a and Circulating Proinflammatory Cytokines in Relapsing–Remitting Multiple Sclerosis. Neurotherapeutics. 2016;13(2):428-438.	Outcomes: No relevant outcomes presented
75	Santoro M, Nociti V, De Fino C, Caprara A, Giordano R, Palomba N, et al. Depression in multiple sclerosis: Effect of brain derived neurotrophic factor Val66Met polymorphism and disease perception. European Journal of Neurology. 2016;23(3):630-640.	Outcomes: No relevant outcomes presented
76	Frisell T, Forsberg L, Nordin N, Kiesel C, Alfredsson L, Askling J, et al. Comparative analysis of first-year fingolimod and natalizumab drug discontinuation among Swedish patients with multiple sclerosis. Multiple Sclerosis Journal. 2016;22(1):85-93.	Outcomes: No relevant outcomes presented
77	Higuera L, Carlin CS, Anderson S. Adherence to disease-modifying therapies for multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2016;22(12):1394-1401.	Outcomes: No relevant outcomes presented

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#	Reference	Reason for Exclusion
78	Coles A, Giovannoni G, Moreau T, Havrdova E, Margolin D, Kasten L, et al. Alemtuzumab improves 3-year quality of life in CARE-MS II. Journal of Neurology, Neurosurgery and Psychiatry. 2015;86(11).	Outcomes: No relevant outcomes presented
79	Ko J, Navaratnam P, Friedman H, Herriott D, Nazareth T, Sasane R. Frequent prescriber preferences and insights regarding the use of oral disease-modifying therapies among patients with multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2015;21:S43.	Outcomes: No relevant outcomes presented.
80	Johnson K, Zhou H, Lin F, Ko J, Herrera V. Adherence and persistence to oral MS disease-modifying treatment in a real-world setting. Journal of Managed Care and Specialty Pharmacy. 2015;21:S44.	Outcomes: No relevant outcomes presented in this abstract
81	Bozkaya D, Livingston T, Migliaccio-Walle K, Mehta S, Odom T. The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis. Journal of Managed Care and Specialty Pharmacy. 2015;21:S42.	Outcomes: No relevant outcomes presented in this abstract
82	Dahdaleh D, Sharrack B. We can compare the relative efficacy of multiple sclerosis medications by examining the results of independent clinical trials: Yes. Multiple Sclerosis. 2015;21(1):35-36.	Study type: Commentary
83	Foley JF, Nair KV, Vollmer T, Stephenson JJ, Niecko T, Agarwal SS, et al. Long-term natalizumab treatment is associated with sustained improvements in quality of life in patients with multiple sclerosis. Patient Prefer Adherence. 2017;11:1035-1048.	Outcomes: No relevant outcomes presented
84	Huggett B. America's drug problem. Nat Biotechnol. 2016 Dec;34(12):1231-1241.	Study type: Narrative review
85	Ozakbas S, Cinar BP, Kosehasanogullari G, Kahraman T, Oz D, Kursun BB. Monthly methylprednisolone in combination with interferon beta or glatiramer acetate for relapsing-remitting multiple sclerosis: A multicentre, single-blind, prospective trial. Clin Neurol Neurosurg. 2017 Sep;160:69-72.	Outcomes: No relevant outcomes presented
86	Sater RA, Gudesblatt M, Kresa-Reahl K, Brandes DW, Sater P. NAPS-MS: Natalizumab Effects on Parameters of Sleep in Patients with Multiple Sclerosis. Int J MS Care. 2016 Jul-Aug;18(4):177-82.	Outcomes: No relevant outcomes presented
87	Sundgren M, Piehl F, Wahlin A, Brismar T. Cognitive function did not improve after initiation of natalizumab treatment in relapsing-remitting multiple sclerosis. A prospective one-year dual control group study. Mult Scler Relat Disord. 2016 Nov;10:36-43.	Outcomes: No relevant outcomes presented
88	Vormfelde SV, Ortler S, Ziemssen T. Multiple Sclerosis Therapy With Disease-Modifying Treatments in Germany: The PEARL (ProspEctive phArmacoeconomic cohoRt evaluation) Noninterventional Study Protocol. JMIR Res Protoc. 2016 Feb 4;5(1):e23.	Study type: Protocol
89	Efficacy of daclizumab beta vs intramuscular interferon beta-1a on patient-reported outcomes across patient demographic and disease activity subgroups in DECIDE. Multiple sclerosis journal. 2017;Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1):966-967.	Outcomes: No relevant outcomes presented
90	Yadav V, Marracci G, Kim E, Spain R, Cameron M, Overs S, et al. Low-fat, plant-based diet in multiple sclerosis: a randomized controlled trial. Multiple sclerosis and related disorders. 2016;9:80-90.	Outcomes: No relevant outcomes presented
91	Kingwell E, Leray E, Zhu F, Petkau J, Edan G, Oger J, et al. Beta-interferon and mortality in multiple sclerosis: a popu-lation-based international study. Multiple sclerosis journal. Conference: 3rd annual americas committee for treatment and research in multiple sclerosis forum, ACTRIMS 2018. United states. 2018;24(1 Supplement 1):122.	Outcomes: No relevant outcomes presented

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#	Reference	Reason for Exclusion
92	Papeix C, Lebrun-Frenay C, Leray E, Kobelt G, Visy JM, Coustans M, et al. Long-term efficacy, safety, tolerability and quality of life with fingolimod treatment in patients with multiple sclerosis in real-world settings in France: VIRGILE one-year results. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22:649-650.	Outcomes: No relevant outcomes presented in this abstract
93	De Seze J, Montalban X, McDougall F, Julian L, Sauter A, Deol-Bhullar G, et al. Patient-reported outcomes in the phase III double-blind, placebo-controlled ORATORIO study of ocrelizumab in primary progressive multiple sclerosis. Multiple sclerosis. Conference: 2017 americas committee for treatment and research in multiple sclerosis forum, ACTRIMS 2017. United states. 2017;23:84.	Outcomes: No relevant outcomes presented
94	Kingwell E, Leray E, Zhu F, Petkau J, Edan G, Oger J, et al. Beta-interferon and mortality in multiple sclerosis: a population- based international study. Multiple sclerosis journal. Conference: 7th joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 2017;23(3 Supplement 1):69-70.	Other: Duplicate of information in ref ID 819
95	Gold R, Khatri B, Edwards KR, Cavalier S, Rufi P, Brette S, et al. Impact of teriflunomide treatment on real-world quality of life in the Phase 4 Teri-PRO Study. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22:307-308.	Outcomes: No relevant outcomes presented
96	Wolinsky J, McDougall F, Lentz E, Deol-Bhullar G, Montalban X. Baseline assessment of fatigue and health-related quality of life in patients with primary progressive multiple sclerosis in the ORATORIO study. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22:676-677.	Outcomes: No relevant outcomes presented
97	Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. European journal of neurology. 23 (9) (pp 1482-1486), 2016. Date of publication: 01 sep 2016. 2016.	Outcomes: No relevant outcomes presented
98	Bertolotto A, Caldano M, Tortorella P, Annibali V, Capobianco M, Cottone S, et al. Non-interventional post-authorization safety study to prospectively evaluate the safety and tolerability profile of Rebif HSA-free scIFNbeta-1a in naive relapsing remitting multiple sclerosis subjects: STEP study. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22:681.	Outcomes: No relevant outcomes presented in this abstract
99	Herzog S, Shanahan M, Grimison P, Tran A, Wong N, Lintzeris N, et al. Systematic Review of the Costs and Benefits of Prescribed Cannabis-Based Medicines for the Management of Chronic Illness: Lessons from Multiple Sclerosis. PharmacoEconomics, 2018, vol. 36, issue 1, 67-78	Study type: SLR
100	Iannazzo S, Iliza AC and Perrault L. Disease-Modifying Therapies for Multiple Sclerosis: A Systematic Literature Review of Cost-Effectiveness Studies. PharmacoEconomics, 2018, vol. 36, issue 2, 189-204	Study type: SLR
101	Gyllensten H, Wiberg M, Alexanderson K, Norlund A, Friberg E, Hillert J, et al. Costs of illness of multiple sclerosis in Sweden: a population-based register study of people of working age. The European Journal of Health Economics, 2018, vol. 19, issue 3, 435-446	Population: Not separated by phenotype

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#	Reference	Reason for Exclusion
102	Hernandez L, O'Donnell M and Postma M. Modeling Approaches in Cost-Effectiveness Analysis of Disease-Modifying Therapies for Relapsing–Remitting Multiple Sclerosis: An Updated Systematic Review and Recommendations for Future Economic Evaluations. PharmacoEconomics, 2018, vol. 36, issue 10, 1223-1252	Study type: SLR
103	Webb EJD, Meads D, Eskyte I, King N, Dracup N, Chataway J. et al. A Systematic Review of Discrete-Choice Experiments and Conjoint Analysis Studies in People with Multiple Sclerosis.. The Patient: Patient-Centered Outcomes Research, 2018, vol. 11, issue 4, 391-402	Study type: SLR
104	Svendsen B, Grytten N, Bø L, Aarseth H, Smedal T and Myhr KM. The economic impact of multiple sclerosis to the patients and their families in Norway. The European Journal of Health Economics, 2018, vol. 19, issue 9, 1243-1257	Population: Not separated by phenotype
105	Kingdon CC, Bowman EW, Curran H, Nacul L and Lacerda EM. Functional Status and Well-Being in People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Compared with People with Multiple Sclerosis and Healthy Controls. Pharmacoecon Open. 2018 Dec;2(4):381-392	Outcomes: No relevant outcomes presented
106	Oliva J, Trapero-Bertran M, Peña-Longobardo LM and del Pozo-Rubio R. The Valuation of Informal Care in Cost-of-Illness Studies: A Systematic Review.. PharmacoEconomics, 2017, vol. 35, issue 3, 331-345	Study type: SLR
107	Montgomery S, Kusel J, Allen F and Adlard N. Paucity and Inconsistency: A Systematic Review and Critique of Budget Impact Analyses of Disease-Modifying Therapies for Multiple Sclerosis in the UK and the Implications for Policy in the UK. Applied Health Economics and Health Policy, October 2016, Volume 14, Issue 5, pp 545–558	Study type: SLR
108	Djambazov S, Vekov T. Cost-effectiveness analysis of alemtuzumab for the treatment of multiple sclerosis in Bulgaria, 2016. Value in Health. 2017;20(5):A193.	Study type: An abstract of SLR
109	Martin M, Campbell R, Jacob J. Reinvestment of biosimilar savings: What are the best options? Annals of the Rheumatic Diseases. 2018;77:326.	Outcomes: No relevant outcomes

B3. CS, Document B, sections B.3.1 and B.3.4.3. CS. Document C, Appendix H, section H.2. The company performed a systematic literature review for health-related quality of life.

a. Table 37 (Document B) reports a summary of 11 published studies on health-related quality of life. However, the data has not been used in the company submission or economic model. Please clarify what was included from the data found in the economic systematic literature review.

Response

As described in Document B, Section 3.1 The 11 published studies identified for health-related quality of life relate to those found in the latest update to the systematic literature review (i.e. between 1 February 2016 and 30 November 2018). This was part of a significantly broader systematic literature review where databases were searched back to 2003, with results used in the submission for TA320 and TA441. Only studies pertaining to this latest update (from 1 Feb 2016) were documented in this submission as agreed in the decision problem meeting for this appraisal with the ERG.

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From this update, only 2 studies were included in the company submission and economic model as a scenario analysis for health state costs (Thompson et al 2017, referred to as Burden of illness study) and utilities (Palace et al 2018, referenced as TA527, assessment group report). Studies identified for prior economic evaluations were used to validate the model structure and natural history data sources.

b. The company submission states that '*In line with the previous NICE technology appraisals, utility data from Orme et al.'s (2007)[78] study has been used to inform the patient utility values and data from Acaster et al. (2013)[180] were used to inform caregiver disutility values in the model in this submission*'. Please justify performing a systematic literature review if Orme et al. (2007) and Acaster et al. (2013) were intended to be the sources of evidence.

Response

We conducted an economic systematic literature review aligned with good practice for health economic evaluation and NICE methods guide 2013. As stated above (part a), the studies documented within the submission are from those identified in the latest update only (from 1 February 2016). The broader search dating back to 2003 did identify the studies from Orme et al (2007) and Acaster et al (2013) as referenced in TA320, TA441, TA492, TA527 and TA533.

c. Document C, section H.2. states that '*30 studies reporting health state utility estimates in patients with MS*' but section H.3. states that the '*results of the 29 identified utility studies are summarised*'. Please clarify the discrepancy.

Response

Upon review of utility extractions in CS, Document C, Appendix H, Section 2, Table 99, the extracted information for one utility study (Palace et al., 2018) was not incorporated into the table by error. Therefore, section H.3 should state 'results of the 30 identified utility studies are summarised', after addition of Palace et al. (2018) to the utility extraction table (Table 99). Please see Table 16 for the Palace et al. (2018) extraction.

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Table 16. Palace et al. (2018) to the utility extraction table

<table>
<tr><th>Author, Journal, Year (reference package ID)</th><th>Study Design, Setting, Country</th><th>Population, Treatments</th><th>Primary Objective of Study</th><th>Analytic Method Used</th><th>Utilities Reported</th><th>Conclusions</th></tr>
<tr>
<td>Palace et al. 2018, Journal of Neurology, Neurosurgery and Psychiatry (121)</td>
<td>Modelling of benefit outcomes. Two complementary analysis models were used: a multilevel model and a continuous Markov model. UK</td>
<td>Age: NR;
Sex: NR;
Sample size: 4,862;
Response rate: NR
Selection and recruitment: NR
Inclusion/exclusion criteria: patients with RRMS or SPMS fulfilling the Association of British Neurologists (ABN) 2001 criteria for treatment (EDSS ≤6.5; ≥18 years old; two relapses in the last two calendar years).
MS phenotype: RRMS and SPMS.
Number/timing of assessments: Ten-year follow-up planned</td>
<td>To compare the rate of disability worsening of patients treated with DMTs, with that in an untreated modelled comparator control group</td>
<td>Surveys of MS patients and an unpublished paper examined for the relation between EDSS and EQ-5D. Standard UK tariff was used (Dolan et al. 1995)</td>
<td>Utility values used for analysis, by EDSS score:
<table>
<tr><th>EDSS</th><th>EQ-5D (95% CI)</th></tr>
<tr><td>0</td><td>0.9248</td></tr>
<tr><td>1 or 1.5</td><td>0.7614</td></tr>
<tr><td>2 or 2.5</td><td>0.6741</td></tr>
<tr><td>3 or 3.5</td><td>0.5643</td></tr>
<tr><td>4 or 4.5</td><td>0.5643</td></tr>
<tr><td>5 or 5.5</td><td>0.4906</td></tr>
<tr><td>6 or 6.5</td><td>0.4453</td></tr>
<tr><td>7 or 7.5</td><td>0.2686</td></tr>
<tr><td>8 or 8.5</td><td>0.0076</td></tr>
<tr><td>9 or 9.5</td><td>-0.2304</td></tr>
</table>
Primary analysis outcomes: SPMS patients at baseline (n=4,862), average follow-up 8.7 years
<table>
<tr><th>Model</th><th>Utility, actual progression (95$ CI)</th><th>Utility, predicted progression (natural history) (95% CI)</th></tr>
<tr><td>Markov</td><td>0.122 (0.117 to 0.127)</td><td>0.161 (0.159 to 0.163)</td></tr>
<tr><td>Multilevel model</td><td>0.122 (0.117 to 0.127)</td><td>0.159 (0.156 to 0.162)</td></tr>
</table>
Subgroup of RRMS patients at baseline (n=4217), average follow-up 8.9 years
<table>
<tr><th>Model</th><th>Utility, actual progression (95$ CI)</th><th>Utility, predicted progression (natural history) (95% CI)</th></tr>
<tr><td>Markov</td><td>0.113 (0.108 to 0.119)</td><td>0.164 (0.163 to 0.166)</td></tr>
<tr><td>Multilevel model</td><td>0.113 (0.108 to 0.119)</td><td>0.150 (0.148 to 0.152)</td></tr>
</table>
</td>
<td>According to authors, “this study supports a beneficial effect on long-term disability with first-line MS disease-modifying treatments, which is clinically meaningful”.</td>
</tr>
</table>

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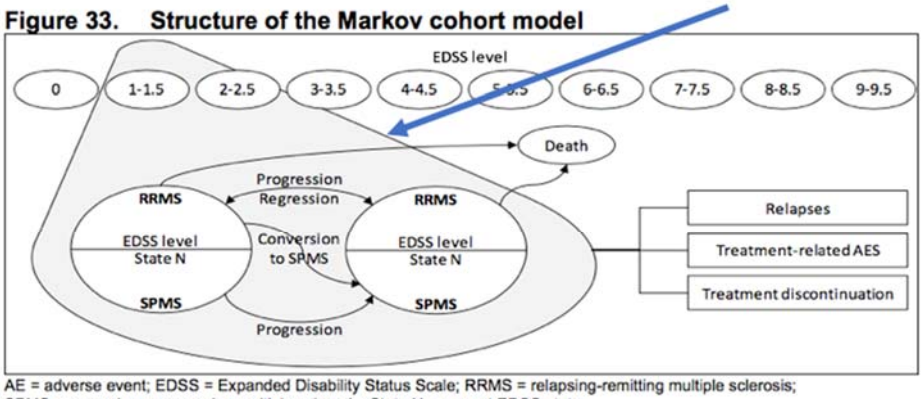
MODEL STRUCTURE

B4. CS, Document B, section B.3.2.2. Excel model 'ID1521_Pegiterferon Beta-1a for RRMS_CE Model_07 June 19 [ACIC]'. Figure 33 shows the model structure.

a. Please provide the interpretation of the large grey ovaloid (indicated by bold blue arrow). For example, please explain why it only encompasses EDSS states 1-1.5, 2-2.5, 3-3.5 but not the other EDSS states.

Figure 33. Structure of the Markov cohort model



AE = adverse event; EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis; State N = current EDSS state.
Note; ovals represent health states. Rectangles represent events that patients could experience at any time. Treatment-related AEs and treatment discontinuation could only occur for patients receiving treatment.

Response:

The grey ovaloid should be interpreted as a magnifier and represents an example of transitions that can occur within each of the EDSS health states. It is not specific to the EDSS levels encompassed by the ovaloid.

b. There is a similar diagram to Figure 33 in the Excel document in the 'Introduction' tab. However, there are some differences in presentation. Please clarify which of the following are correct:

   i. EDSS states in the Excel model (Introduction worksheet) 0, 0.5 to 1, 1.5 to 2 or Figure 33's EDSS levels 0, 1-1.5, 2-2.5, 3-3.5.

Response:

The EDSS banding as described in document B is correct (0, 1-1.5, 2-2.5, 3-3.5).

   ii. The recurring arrow for RRMS and SPMS is shown in the Excel model but not in Figure 33.

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Response:

In the excel model figure the recurring arrow represents relapses that occur as events within the RRMS & SPMS EDSS health states. This is captured by the right hand box in figure 33.

TRANSITION PROBABILITY MATRIX

B5. CS, Document B, section B.3.3.1.1. Table 28 shows the transition probability matrix based on the British Columbia natural history cohort. The matrix shows that there are probabilities of regressing to less severe EDSS levels. For example, there is a 0.8183 probability of remaining in EDSS 9-9.5 or regressing to less severe health states EDSS 6-6.5 (0.0018), EDSS 7-7.5 (0.0057) and EDSS 8-8.5 (0.1741). Please clarify what assumptions are being made about people who regress from a 'non-treatment' health state to an 'on-treatment' health state.

Response:

Regression from a 'non-treatment' health state to an 'on-treatment' health state is not possible within the model. The probabilities of regression are part of the natural history matrix; these regression probabilities are applied across all comparators and sub cohorts. Stopping rules for patients "on-treatment" can occur through progression beyond EDSS >7 (RRMS only), transitions to SPMS or all-cause discontinuation. No transition back to on-treatment can occur thereafter.

TREATMENT DISCONTINUATION

B6. PRIORITY QUESTION. CS, Document B, section B.3.3.2.1. Excel model 'ID1521_Pegiterferon Beta-1a for RRMS_CE Model_07 June 19 [ACIC]': There appears to be some inconsistencies in the all-cause discontinuation reported in Table 32 (Document B, p124) and the Excel model ('Treatment' worksheet). Please see table below. Please clarify which values are correct and should be used in the model.

Annual risk of treatment discontinuation (all-cause discontinuation)

Treatment	Document B (Table 32)	Excel model
Interferon Beta-1a 44µg	10.85%	10.53%
Glatiramer acetate 20mg	9.72%	11.02%
Generic glatiramer acetate 20mg	9.72%	11.02%
Alemtuzumab	2.46%	2.59%

Response:

The values presented in the model are the correct values and are aligned with the calculation presented in Document C, Table 122, p 464. The cited values in the table above for Cs, Document B, Section 3.3.2.1, Table 32, are transcription errors.

B7. PRIORITY QUESTION. CS, Document B, section B.3.3.2.1. CS, Document C, Appendix M, Table 121. Section B.3.3.2.1 states that '*The weights used to derive the treatment discontinuation for each disease-modifying therapy were based on sample size*

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from each trial included in the analysis. The weights used for each study in the derivation of the discontinuation risk are shown in Appendix M'.

a. Please outline the calculations undertaken to derive the weights used in the treatment discontinuation for each disease-modifying therapy.

Response:

The weights were derived from the number of patients evaluated in each of the studies included for a particular DMT. The respective weights per study are presented in Document C, Appendix M, Table 121, p 463, the underlying data are presented in Table 122, p 464. The study weight for each DMT is derived by dividing the number of patients evaluated in one study by the total patients evaluated for a particular DMT across all studies. Part b explores alternative options for weighting the studies.

b. Please clarify why the weights used to derive the treatment discontinuation for each disease-modifying therapy were based on sample size.

Response:

We acknowledge we should have weighted the studies including an element of follow-up time (by multiplying the number of patients evaluated with the mean or median follow-up time). The resulting annual discontinuation rates using follow-up time are presented in Table 17 alongside the base case (weighted by sample size alone) and a simple average. The annual discontinuation rates do not significantly differ across scenarios and are the same for some comparators when it is informed by one study or the mean follow-up time is the same for all included studies.

We assessed the impact of these scenario in the cost-effectiveness model with results comparatibe to PegIFNβ-1a not differing significantly versus the submitted base case analysis (Table 18).

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Table 17. Weighting all cause discontinuation risks

Treatment	Annual all-cause discontinuation risk			Sources
	Weighted by sample size (base case)	Weighted by person time	Simple average	
PegIFNβ-1a	15.56%	15.56%	15.56%	ADVANCE
IM IFNβ-1a 30	7.88%	8.27%	8.09%	Calabrese (2012), CombiRx, EVIDENCE, BRAVO, INCOMIN
IFNβ-1a 22	6.00%	6.00%	6.00%	PRISMS
IFNβ-1a 44	10.53%	9.74%	10.73%	Calabrese (2012), EVIDENCE, OPERA I & II, CARE MS I, CARE MS II, REGARD
IFNβ-1b	6.87%	7.54%	6.87%	IFNB MS Study, BEYOND, INCOMIN
GA 20	11.02%	8.05%	8.54%	BEYOND, CONFIRM, Copolymer 1 Study, REGARD, Bornstein
GA 40	8.91%	8.91%	8.91%	GALA
genGA 20	11.02%	8.05%	8.54%	Assumed equivalent to GA 20
genGA 40	8.91%	8.91%	8.91%	Assumed equivalent to GA 40
teriflunomide	18.57%	18.50%	18.12%	TOWER, TEMSO
DMF	18.01%	17.97%	18.01%	CONFIRM, DEFINE
alemtuzumab	2.59%	2.55%	2.59%	CARE MS I, CARE MS II
ocrelizumab	6.69%	6.69%	6.69%	OPERA I & II

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Table 18. Disconitnuation rate scenario analysis using CDP6M network and list prices

Scenario	pegIFNβ-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 22	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	ocrelizumab	alemtuzumab
Base case													
QALY	4.39	0.75	0.74	0.75	0.74	NA	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£273,641	-£11,423	-£14,035	-£8,701	-£11,033	NA	-£19,328	NA	-£20,557	-£23,796	-£34,865	-£66,027	-£1,250
ICER	-	-£15,291	-£19,086	-£11,647	-£15,004	NA	-£114,329	NA	-£44,272	-£39,846	-£78,516	£131,776	£1,155
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a less costly, less effective	pegIFNβ-1a less costly, less effective
Discontinuations - weighted by person time													
QALY	4.39	0.72	0.74	0.72	0.74	NA	0.14	NA	0.47	0.60	0.44	-0.50	-1.09
Costs	£273,641	-£14,907	-£14,037	-£11,776	-£11,035	NA	-£20,642	NA	-£19,888	-£23,887	-£34,947	-£66,027	-£1,165
ICER	-	-£20,572	-£19,090	-£16,252	-£15,008	NA	-£143,973	NA	-£42,130	-£40,051	-£78,841	£131,776	£1,071
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a less costly, less effective	pegIFNβ-1a less costly, less effective
Discontinuations - simple average													
QALY	4.39	0.73	0.74	0.73	0.74	NA	0.18	NA	0.47	0.59	0.44	-0.50	-1.08
Costs	£273,641	-£14,270	-£14,037	-£11,214	-£11,035	NA	-£19,001	NA	-£20,188	-£24,394	-£34,865	-£66,027	-£1,254
ICER	-	-£19,584	-£19,090	-£15,390	-£15,008	NA	-£108,265	NA	-£43,083	-£41,199	-£78,516	£131,776	£1,159
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a less costly, less effective	pegIFNβ-1a less costly, less effective

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B8. CS, Document B, section B.3.6.2. Table 45 provides the 'Key assumptions within the economic model'. It states that '*After treatment discontinuation, patients are assumed to follow the natural disease progression course*'. Please clarify the assumption(s) made when people discontinue treatment. For example, do people incur the annual cost of the disease-modifying therapy if they discontinue treatment at 3 months?

Response:

In the Markov traces, patients who discontinue treatment are removed from the 'on-treatment' sub-cohort at the beginning of each annual cycle, based on a discontinuation risk that is also annual. Once patients are moved to the 'off-treatment' sub-cohort they no longer accrue treatment (DMT) cost, and neither enjoy the treatment benefit (i.e. the delay on disease progression). Outcomes are calculated based on half-cycle corrected patients counts, except for the cases in which this was explicitly requested to be removed (alemtuzumab and ocrelizumab, due to their respective dosing schedules).

UTILITIES

B9. PRIORITY QUESTION. CS, Document B, section B.3.4.5. Table 40 provides the 'caregiver utility decrements by EDSS level stratified by RRMS versus SPMS'. Please outline the calculations undertaken to derive the caregiver utility decrements by EDSS level which were obtained from Acaster et al. (2013) for the base case.

Response:

Caregiver utility decrements were derived directly from the ID527 assessment group report (Table 29, p 213). These are the same values as used in the TA493 (committee papers p 64).

B10. PRIORITY QUESTION. CS, Document B, section B.3.4.5. Tables 39 and 40 provide utility values by EDSS level and disease phase (RRMS and SPMS) for no relapse and relapses, and utility decrements for caregivers respectively. Please clarify if age-related disutilities have been captured in the model.

Response:

Age-related disutilities have not been captured in the model submitted. Biogen cannot find any evidence of age-related disutilities been used in decision making for prior technology appraisals in multiple sclerosis including TA493, TA527 and TA533.

COSTS

B11. PRIORITY QUESTION. CS, Document B, section B.3.5.2.1. Table 43 provides 'Disease management costs by EDSS level (2016/2017 values)'. Please clarify if these costs are at 2016/17 values.

Response:

2016/2017 is a typographical error, this should read 2017/18 (inflated using the PSSRU 2017/18) as referenced in the preceding text to Table 43 in Document B, section 3.5.2.1.

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B12. PRIORITY QUESTION. CS, Document B, section B.3.5.1. Table 41 provides the 'Annual treatment-related costs for each treatment (2018 values)'. Please provide the unit cost for each disease modifying treatment that was used to derive the annual drug acquisition costs.

Response:

The annual drug acquisition costs were derived using the following unit costs (Table 19).

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Table 19. Posology, unit cost and annual costs for PegIFNβ-1a and included comparators

Drug	Dosage	Frequency per week	Strength	Pack size	Price per pack	Unit cost	Annual cost	Reference
PegIFNβ-1a 125 mcg	Week 0: 63mcg Week 2: 94 mcg Week 4+: 125mcg	0.5	125mcg	6	£1,962.00	£327.00	£8,502.00	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
PegIFNβ-1a 63 mcg & 94 mcg (Initiation pack)			1 x 63mcg 1 x 94mcg	2	£654.00	£327.00		
IM IFNβ-1a 30 mcg	30mcg weekly	1	30mcg	4	£654.00	£163.50	£8,502.00	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
SC IFNβ-1a initiation pack	Week 0-2: 8.8 mcg tiw	3	6x8.8mcg 6x22mcg	12	£552.19	£46.02	n/a	MIMS - June 2017
SC IFNβ-1a 22 mcg	Week 3-4: 22mcg tiw		22mcg	12	£613.52	£51.13	£7,975.76	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
SC IFNβ-1a 44 mcg	week 5+: 44mcg tiw		44mcg	12	£813.21	£67.77	£10,571.73	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
SC IFNβ-1b 250 mcg	Day 1,3,5: 62.5mcg Days 7,9,11: 125mcg Days 13,15,17: 187.5mcg Days 19+: 250mcg	3.5	250mcg	15	£596.63	£39.78	£7,239.11	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
Glatiramer Acetate 20mg	20mg daily	7	20mg	28	£513.95	£18.36	£6,681.35	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018

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Drug	Dosage	Frequency per week	Strength	Pack size	Price per pack	Unit cost	Annual cost	Reference
Glatiramer Acetate 40mg	40mg tiw	3	40mg	12	£513.95	£42.83	£6,681.35	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
genGA 20mcg (Brabrio)	20mcg daily	7	20mcg	28	£462.56	£16.52	£6,013.28	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
genGA 40mcg (Brabrio)	40mcg tiw	3	40mcg	12	£462.56	£38.80	£6,013.28	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
Teriflunomide	14mg Daily	7	14mg	28	£1,037.84	£37.07	£13,528.99	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
DMF	Week 1: 120mg Week 2+: 240mg	14	120mg	14	£343.00	£24.50	£17,848.75	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
			240mg	56	£1,373.00	£24.52		
Alemtuzumab	Year 1: 12mg for 5 days Year 2: 12mg for 3 days Year 3+: 12mg for 3 days	Yearly	12mg	1	£7,045.00	£7,045.00	Year 1: 35,225 Year 2: 21,135	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
Ocrelizumab	Week 0: 300mg Week 2: 300mg Week 2+: 600mg every 6 months	every 6 months	300mg	1	£4,790.00	£4,790.00	£19,160.00	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018

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PROBABILISTIC SENSITIVITY ANALYSES

B13. CS, Document B, section B.3.3.3.1, section B.3.3.3.3 and section B.3.8.1. Section B.3.8.1. states that '*To account for statistical uncertainties of multiple key parameters, probabilistic sensitivity analyses were performed by simultaneously varying ... log-normal distribution: rate ratios for the annualised relapse rates (ARRs) and confirmed disability progression (CDP) hazard ratios relative to placebo, ARRs by EDSS level, incidence of adverse events, rate ratio for MS mortality*'. However, Tables 34 and 36 report the credible intervals for the hazard ratio for CDP and rate ratio for ARR respectively. Please clarify whether the lognormal distributions were used for these inputs and not the posterior distributions.

Response:

Lognormal distributions were using for HR for confirmed disability progression at 3 and 6 months, please see "PSA inputs" or "parameters" worksheets in the excel model.

B14. CS, Document B, section B.3.8.1.

a. Please clarify the type of distributions being used in the probabilistic sensitivity analyses for the utility values for EDSS levels ≥8.

Response:

A beta distribution where the sampling uses the absolute value of the utility.

b. Please clarify the type of distributions being used in the probabilistic sensitivity analyses for caregiver utility decrements.

Response:

A beta distribution where the sampling uses the absolute value of the utility.

MISSING INFORMATION

B15. CS, Document C, Appendix J, sections J.1 and J.2. For Tables 102 and 103, please provide reference citations for the first row.

Response:

These results are derived from the submitted economic model which can be derived from the "all DMT results" worksheet by selecting either discounted or undiscounted outcomes.

Section C: Textual clarifications and additional points

C1. In Document B, please provide in text reference citations for the following:

a. Table 15 (Studies excluded from key analyses)

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b. Table 16 (Final inclusion in the mixed-treatment comparison for the overall relapsing-remitting multiple sclerosis population)

c. Section B.2.9.3.1 (Annualised relapse rate)

d. Section B.2.9.3.2 (Disability progression confirmed after 3 months [CDP3M])

e. Section B.2.9.3.3 (Disability progression after 6 months [CDP6M])

f. Section B.2.10.1 (Introduction)

Response:

Following the clarification teleconference on 9th July, Biogen and the ERG agreed to provide text reference citations lists and not to update the referencing within document B.

A full list of studies and citations for part a (table 15) and part b (table 16) along with citations can be found in document C, section 3.2, table 26 and have not been repeated here. Responses to part c through part f can be found in the table below (Table 20).

Table 20. Requested text citations

Query	Study	Citation
Section B.2.9.3.1 Annualised relapse rate network	ADVANCE	Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A, Advance Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014;13(7):657-65.
	BEYOND	O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, Hartung H-P, Jeffery D, Kappos L, Boateng F, Filippov V, Groth M, Knappertz V, Kraus C, Sandbrink R, Pohl C, Bogumil T, for the BEYOND Study Group. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study [Erratum appears in: Lancet Neurol 2011;10(2):115. Lancet Neurol 2009;8(11):981. Lancet Neurol 2012;11(1):27]. Lancet Neurol 2009;8(10):889-97.
	Bornstein 1987	Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E, Keilson M, Merriam A, Wassertheil-Smoller S, Spada V, Weiss W, Arnon R, Jacobsohn I, Teitelbaum D, Sela M. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med 1987;317(7):408-14.
	BRAVO	Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, Sasson N, Gilgun-Sherki Y, Arnold DL, BRAVO Study Group. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol 2014;261(4):773-83.
	Calabrese 2012	Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, Perini P, Gallo P. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler 2012;18(4):418-24.
	CAMMS223	CAMMS223 Trial Investigators, Coles AJ, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K, Tandon PK. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786-801.
	CARE MS I	Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA, CARE-MS I investigators. Alemtuzumab versus interferon beta 1a as first-

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Query	Study	Citation
		line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1819–28.
	CARE MS II	Henson LJ, Arnold DL, Canada M, Cohen JA, Coles AJ, Confavreux C, Fox EJ, Hartung H-P, Havrdova E, Selmaj K, Weiner HL, Miller TA, Twyman CL, Lake SL, Margolin DH, Panzara MA, Compston A. Durable effects of alemtuzumab on relapse rate over time in CARE-MS II. Paper presented at 27th Annual Meeting of the CMSC and the 5th Cooperative Meeting of the CMSC-ACTRIMS; 29 May-1 Jun 2013; Orlando: United States. 2013: DX38
	CombiRx	Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, Salter AR, Gustafson T, Wolinsky JS, CombiRx Investigators. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. Ann Neurol 2013;73(3):327-40.
	CONFIRM	Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Viglietta V, Dawson KT, CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087-97.
	Copolymer I	Johnson K, Brooks B, Cohen J, Ford C, Goldstein J, Lisak R, Myers L, Panitch H, Rose J, Schiffer R, Vollmer T, Weiner L, Wolinsky J. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45(7):1268-76.
	DEFINE	Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, Tornatore C, Sweetser MT, Yang M, Sheikh SI, Dawson KT, DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367(12):1098-107.
	EVIDENCE	Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, Monaghan E, Li D, Weinshenker B, EVIDENCE Study Group. EVidence of Interferon Dose-response: Europian North American Compartative Efficacy, University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59(10):1496-506.
	GALA	Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol 2013;73(6):705-13.
	IFNB MS	The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43(4):655-61.
		The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-lb in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995;45(7):1277-85.
	INCOMIN	Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, Montanari E, Zaffaroni M, Independent Comparison of Interferon (INCOMIN) Trial Study Group. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359(9316):1453-60.
	MSCRG	Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, Alam JJ, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Frederick E. Munschauer, Priore RL, Pullicino PM, Scherokman BJ, Weinstock-Guttman B, Whitham RH. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996;39(3):285-94.
	OPERA I	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S,

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Query	Study	Citation
		Chin P, Mairon N, Garren H, Kappos L, Opera I and Investigators OIC (2017). "Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 376(3): 221-234
	OPERA II	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L, Opera I and Investigators OIC (2017). "Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 376(3): 221-234
	REGARD	Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, Stubinski B, Uitdehaag BMJ, REGARD study group. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol 2008;7(10):903-14.
	TESMO	O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, Benzerdjeb H, Truffinet P, Wang L, Miller A, Freedman MS, for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365(14):1293-303.
	TENERE	Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, Olsson TP, Benamor M, Bauer D, Truffinet P, Church M, Miller AE, Wolinsky JS, Freedman MS, O'Connor P, TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler 2014;20(6):705-16.
CDP3M network	ADVANCE	Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A, Advance Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014;13(7):657-65.
	BEYOND	O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, Hartung H-P, Jeffery D, Kappos L, Boateng F, Filippov V, Groth M, Knappertz V, Kraus C, Sandbrink R, Pohl C, Bogumil T, for the BEYOND Study Group. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study [Erratum appears in: Lancet Neurol 2011;10(2):115. Lancet Neurol 2009;8(11):981. Lancet Neurol 2012;11(1):27]. Lancet Neurol 2009;8(10):889-97.
	BRAVO	Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, Sasson N, Gilgun-Sherki Y, Arnold DL, BRAVO Study Group. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol 2014;261(4):773-83.
	CAMMS223	CAMMS223 Trial Investigators, Coles AJ, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K, Tandon PK. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786-801.
	CONFIRM	Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Viglietta V, Dawson KT, CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087-97.
	DEFINE	Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, Tornatore C, Sweetser MT, Yang M, Sheikh SI, Dawson KT, DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367(12):1098-107.
	EVIDENCE	Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, Monaghan E, Li D, Weinshenker B, EVIDENCE Study Group. EVidence of Interferon Dose-response: Europian North American Compartative Efficacy, University of British Columbia MS/MRI Research Group. Randomized,

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Query	Study	Citation
		comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59(10):1496-506.
	OPERA I	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L, Opera I and Investigators OIC (2017). "Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 376(3): 221-234
	OPERA II	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L, Opera I and Investigators OIC (2017). "Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 376(3): 221-234
	PRISMS	Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group.[Erratum appears in Lancet 1999 Feb 20;353(9153):678]. Lancet 1998;352(9139):1498-504.
	TESMO	O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, Benzerdjeb H, Truffinet P, Wang L, Miller A, Freedman MS, for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365(14):1293-303.
	TOWER	Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, Wolinsky JS, Bagulho T, Delhay J-L, Dukovic D, Truffinet P, Kappos L, for the TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13(3):247-56.
CDP6M network	ADVANCE	Biogen Idec. 105MS301 Interim - TLGs. Year 1 trial results. 2013.
	BRAVO	Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, Sasson N, Gilgun-Sherki Y, Arnold DL, BRAVO Study Group. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. J Neurol 2014;261(4):773-83.
	CAMMS223	CAMMS223 Trial Investigators, Coles AJ, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K, Tandon PK. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008;359(17):1786-801.
	CARE MS-I	Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA, CARE-MS I investigators. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1819–28.
	CARE MS-II	Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung H-P, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DAS, CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380(9856):1829-39.
	CONFIRM	Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Viglietta V, Dawson KT, CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087-97.
	DEFINE	Biogen Idec Inc. Clinical study report. Full final. Study Number: 109MS301. A randomized, multicenter, double-blind, placebo-controlled, dose-comparison study to determine the efficacy and safety of BG00012 in subjects with relapsing-remitting multiple sclerosis. Cambridge, MA: Biogen Idec Inc, 2012

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Query	Study	Citation
	EVIDENCE	Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, Monaghan E, Li D, Weinshenker B, EVIDENCE Study Group. EVidence of Interferon Dose-response: Europian North American Compartative Efficacy, University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59(10):1496-506.
	OPERA I	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L, Opera I and Investigators OIC (2017). "Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 376(3): 221-234
	OPERA II	Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L, Opera I and Investigators OIC (2017). "Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis." New England Journal of Medicine 376(3): 221-234
	PRISMS	Wong SL, Aldrige J, Hettle R, Khurana IS, Siddiqui MK. Analysis of 6-month confirmed disability progression in RRMS patients treated with subcutaneous interferon beta-1a. Mult Scler J 2018;24(1 Suppl 1):32.
	TESMO	European Medicines Agency. Aubagio. EPAR - Assessment report. International Non-proprietary Name: teriflunomide. Procedure No. EMEA/H/C/002514/0000 [Internet]. London: European Medicines Agency, 2013 [accessed 18.5.17] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002514/WC500148684.pdf European Medicines Agency. Aubagio: EPAR - Product Information. Annex I. Summary of product characteristics [Internet]. London: European Medicines Agency, 2013 [accessed 1.4.15] Available from: https://www.ema.europa.eu/en/documents/product-information/aubagio-epar-product-information_en.pdf
	TOWER	European Medicines Agency. Aubagio. EPAR - Assessment report. International Non-proprietary Name: teriflunomide. Procedure No. EMEA/H/C/002514/0000 [Internet]. London: European Medicines Agency, 2013 [accessed 18.5.17] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002514/WC500148684.pdf European Medicines Agency. Aubagio: EPAR - Product Information. Annex I. Summary of product characteristics [Internet]. London: European Medicines Agency, 2013 [accessed 1.4.15] Available from: https://www.ema.europa.eu/en/documents/product-information/aubagio-epar-product-information_en.pdf
Introduction	ADVANCE	Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A, Advance Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol 2014;13(7):657-65.
	ATTAIN	Newsome SD, Scott TF, Arnold DL, Nelles G, Hung S, Cui Y, et al. Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. Ther Adv Neurol Disord. 2018;11:1756286418791143
	ALLOW	Naismith R, Hendin B, Wray S, You X, Sabatella G, Zambrano J, et al. ALLOW – a phase 3b trial characterising flu-like symptoms in patients switching to pegylated interferon beta-1a: interim analysis of all patients. Presented at the 31st Congress of the European Committee for Treatment

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Query	Study	Citation
		and Research in Multiple Sclerosis (ECTRIMS); October 2015. Barcelona, Spain.
	COMPARE	Hu X, Shang S, Nestorov I, Hasan J, Seddighzadeh A, Dawson K, et al. COMPARE: pharmacokinetic profiles of subcutaneous peginterferon beta-1a and subcutaneous interferon beta-1a over 2 weeks in healthy subjects. Br J Clin Pharmacol. 2016 Aug;82(2):380-8

C2. CS, Document B, section B.2.4. Section B.2.4 states '*Table 10 presents a summary of the statistical analysis and definition of study groups for the ADVANCE and ATTAIN trials*[11]'. However, the footnote in Table 10, cites reference 11, 124 and 128. Please clarify which citation is correct for the 'sample size, power calculation'.

Response

Reference 7 (Biogen Idec Inc. CSR: a multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of pegylated interferon beta-1a (BIIB017) in subjects with relapsing multiple sclerosis. 2013.) is also included in the footnote which is the correct source for the sample size & power calculation

C3. CS, Document B, section B.3.3.3.1. Table 34 reports the results of the network meta-analysis for CDP3M and CDP6M hazard ratio versus placebo. Please clarify why confidence intervals are reported for CDP3M (95% CI), while credible intervals are presented for CDP6M (95% CrI).

Response:

Typographical error, this should read as credible intervals for both CDP3M and CDP6M.

C4. CS, Document B, section B.3.8.2. Pages 165 to 166 report the impact of how sensitive the incremental cost-effectiveness ratios were to changes made to the lower and upper bound of the hazard ratios on disability progression using the 95% confidence intervals. Please clarify if these lower and upper bounds were 95% credible intervals.

Response:

Typographical error, these lower and upper bounds were 95% credible intervals

C5. CS, Document C, Appendix M. Excel model 'ID1521_Pegiterferon Beta-1a for RRMS_CE Model_07 June 19 [ACIC]'. Table 124 (Document C) includes the adverse event 'Pneumonia/urinary tract infection' but the Excel model states 'Pneumonia/URT'. Please clarify whether URT refers to urinary tract infection or upper respiratory tract infection.

Response:

Typographical error, this should read "upper respiratory tract infection".

C6. CS, Document C, section L.3.1.3. Please provide the source and citation of the text '*patients experienced an event rate 0.256 after approximately 12 months of follow-up compared with an event rate of 0.397 for patients in the placebo arm*' (p438).

NICE National Institute for Health and Care Excellence

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London
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Response:

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

These data are also reported in document B, section 2.6.1, table 11, p49.

C7. CS, Document C. Please provide a contents page for the appendices in Document C and its sub-sections.

Response:

A contents page has been added to document C and reuploaded to NICE DOCs

NICE National Institute for Health and Care Excellence

Patient organisation submission

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis ID1521

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.

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Information on completing this submission

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Multiple Sclerosis Society (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 a leading patient organisation representing the over 100,000 people living with MS in the UK. We are a registered charity and receive no government subsidy, we are funded by charitable fundraising through individual donations, philanthropic donors and legacies.
4b. 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 prepared this submission utilising our extensive networks and communication channels that keep us in touch daily with people living with MS and those affected by the condition. The case studies represented here were gathered from members of our MS Research Network; a network that connects researchers, academics and people with MS who want to hear about the latest advancements in medical research and find out how to get in involved in clinical trials, of which the MS Society is a major funder. Subsequent to our call for case studies to the MS Research Network, we interviewed people who responded and have ensured that there are diverse experiences represented. The

	responded included individuals currently using peginterferon beta-1a and responding well as well as and people who had used it and switched to another treatment. We need this in order to demonstrate a rounded picture of its benefits.
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 a neurological condition that affects the brain and spinal cord. It is unpredictable, highly individualised and is often painful and exhausting to live with. Its symptoms are often invisible and people living with MS are often negatively impacted by a relatively poor public understanding of the condition and its symptoms. Most people living with MS (approximately 80%) live with its relapsing-remitting form, which is characterised by periods of intense disease activity called 'relapses' that coincides with an increase in severity of symptoms, such as loss of mobility, fatigue and other motor or muscle impairments, including temporary or long-lasting blindness, which is followed by periods where symptoms reduce or stop completely. As the range of symptoms above demonstrates, the condition is highly variable and complex so that for some patients there is little meaningful difference between living with a relapsing form of MS and a progressive form of the disease. Common less visible symptoms include but are not limited to: - low mood - fatigue - depression - cognitive difficulties - neuralgia and other forms of neuropathic pain

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	People with MS regularly tell us through the MS Society's national surveys that they experience an inconsistency in standard of care in the NHS, whether it be in diagnosis, treatment or what support services are available. This inconsistency seems to be dependent on a few factors, namely: - which nurse specialist, GP, consultant neurologist a patient sees regularly - which NHS Trust manages their care; and, - which area of the UK they live in. We know for instance that when we last conducted a national survey of people with MS in 2016, only 56% of people who could benefit from a disease modifying therapy (DMT) were taking one. This was up from 40% in 2013 but is significantly lower than the MS Society's goal of 70% by 2019 *('Is Access to Treatment Still a Lottery?*' MS Society, 2016). The results of our updated survey will be published in 2020 ('*My MS MY Needs*' MS Society, forthcoming). In the same survey in 2016 we found that access to a DMT was highly dependent on receiving timely support from MS specialists. The survey found of the 1 in 10 respondents that had not seen an MS nurse or neurologist in the past year, just 12% were taking a disease modifying therapy compared to 73% of those who had seen an MS nurse of neurologist in the past year. With no national standards of care for MS services and without a national clinical director for neurological services in the NHS, this variation may not be surprising. However, the effect this has on receiving adequate and timely clinical interventions means that patients do not always

	receive the right treatment at the right time and receive conflicting advice about managing symptoms. Lack of standards for clinicians to be monitored and benchmarked against is a source frustration for clinicians and service users alike and is the cause of significant barriers to improving services. The variation in experience that results is a significant cause distress for people with MS and their carers, especially when someone moves local authority or CCG area, where services may be delivered differently. The MS Society Helpline receives daily calls referring to the complexity of MS services. People commonly tell us they spend time 'battling' services to get the right treatment for them due to the highly individualised nature of the condition. This is a waste of time that patients and carers could be spending better managing the impact of the condition. One individual highlighted that this experience is notable when compared with treatment experienced outside the UK. One individual noted that in Singapore they had contact with consultant neurologists much more regularly and received MRI scans every 6-months to check on the progression of the disease. In the Netherlands, they had more frequent contact with nurse specialists than they now do in the UK.
8. Is there an unmet need for patients with this condition?	In absence of a cure, the main unmet need comes in the form of effective treatments to reduce the severity and impact of the disease for people living with progressive forms of the disease. There are also significant unmet care needs for people living with MS, both due to inconsistency in primary and secondary care, and in common with other disabling conditions, significant problems receiving social care support. Specifically, in a 2016 survey focusing on the MS community's social care needs, we found that 1 in 3 people with MS that need help getting dressed, fed and washed were not getting the essential care and support they needed (*'My MS My Needs'* MS Society, 2016).

	Remaining in employment is also of critical importance. We know that within 10 years of diagnosis, around 50% of people with MS will have left employment, with all the associated financial, social and psychological consequences. We also know that those who are not in and looking for work due to their MS lose almost 20 working years on average. Cost effectiveness calculations by NICE and other government agencies do not take account of the burden of loss of work on the individual, but particularly do not account for the impact it has on carers having to give up work in order to support those they care for.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Clinical trials have demonstrated the effectiveness of peginterferon beta-1a compared to placebo and confirmed that it has a similar efficacy to other beta interferons. Peginterferon beta-1a and other beta interferons are currently the only effective treatments for people secondary progressive who still have significant relapses. As mentioned, we spoke to a small sample of people who have taken peginterferon beta-1a and are responding well, and also those who stopped using peginterferon due to side effects. The advantages of peginterferon that patients clearly demonstrated were that it is: - easy to administer through individual injection - easy to store at home via refrigeration - allowed them to manage flu-like side effects better and any other side effects can be managed effectively with generic treatments like ibuprofen and paracetamol - can be delivered at home if needed - time efficient due to longer intervals. The allowed one individual we spoke to avoid necrosis, which when on a daily dose treatment appeared on sites around the leg, which were embarrassing and made physical activities more difficult.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Three individuals experienced severe side effects including neuralgia from using peginterferon beta-1a. One individual said that the side effects were intolerable and led to them to refusing to be treated with any other DMT.
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.	Peginterferon beta-1a is likely to be a preferred treatment option for people who are risk adverse and have a relatively low level of MS activity. In line with the MS Trust, we would not expect peginterferon to be used for very active relapsing remitting MS (also known as rapidly evolving severe MS or highly active despite previous treatment) for which more effective treatments would be used (fingolimod, natalizumab, cladribine, ocrelizumab, alemtuzumab).

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Women are three times more likely to be diagnosed with MS than men, therefore any reduction in treatment options would have a direct and disproportionate impact on women and a double impact on women living with disabilities. All the patients we spoke to for the purposes of this appraisal were women, one of whom was a single mother of three who was a part time student. When approached to be interviewed, the Society offered to nominate her to appear at the technology appraisal meeting. Due to the distance to travel (she lives in the North East of England) and her caring responsibilities she felt that she would be unable to participate. If meetings were held remotely via video call she would have felt more able to participate. This is an important issue to consider as it is patients like her that are commonly unrepresented in decision-making forums such as single technology appraisals.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This is a well-established treatment that services have the capacity to continue to administer, which in the context of significant financial constraints in the health system currently is important to consider.

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • Patient choice when it comes to treatments is paramount for people with MS. Any reduction in choice is likely to lead to significant distress for people currently using and responding well to peginterferon beta-1a. • Peginterferon beta-1a is an effective treatment option for people who depend on its ease of administration and ready access. • Peginterferon beta-1a offers an effective treatment option that has a reduced impact on stretched services due to it being self-administered and it being able to be stored at home. • Peginterferon beta-1a has a good safety profile. • Peginterferon beta-1a offers a treatment option for those with less severe active disease and benefits most of its users due to increased intervals between injections compared to other beta interferons.

Thank you for your time.

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Patient organisation submission

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis ID1521

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- 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. 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 MS: coping with the impact of diagnosis, coping with physical, emotional and financial consequences of MS and making difficult decisions about treatment choices. To gain further insight into the experience of people taking peginterferon, we interviewed people who are currently taking this drug. We also reviewed feedback on peginterferon in survey data collected between 20 December 2017 and 10 January 2018 in response to the Appraisal Consultation Document for TA527.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well and not taken account of in cost effectiveness calculations. MS is sometimes mild, frequently relapsing remitting, but often progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity. Good management of MS can be a huge challenge to health professionals because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers. Approximately 80% of people with MS will have relapsing remitting MS (RRMS). MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms. Many of these invisible symptoms are sensitive areas and can be difficult to recognise or talk about, putting an extra burden on a person with MS to deal with on their own. Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect

	financial burden, both for the individual, their family and the state. They can have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends. In a cash-strapped NHS, the reality is that services to support people coping with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. For example, a caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS. Research evidence supports the treatment of people with relapsing remitting MS with disease modifying drugs (DMDs) early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that if people with MS continue to have relapses while on therapy, this should prompt a discussion about switching treatments. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; signs of MS activity trigger a treatment review and escalation to an alternative disease modifying drug is considered. A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing forms of MS.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	MS care involves a mix of clinical management of symptoms, responsive services to manage relapses and other acute deteriorations, therapies including physiotherapy and occupational therapy, tailored, evidence based information, support for effective self-management and, for those with RRMS, access to the range of DMDs and support to make the choice that is right for their condition, their lifestyle and their treatment goals. The majority of people with RRMS are eager to start treatment with one of the DMDs and

	aware of the importance of starting treatment soon after diagnosis. A number of DMDs are available for relapsing remitting MS: • beta interferons • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • ocrelizumab • cladribine • natalizumab • alemtuzumab It is not possible to say which of these treatments are preferred; the widening range of DMDs gives greater scope for personalised treatments. If MS remains active despite taking one of the DMDs there is more potential to switch to a treatment with a different mechanism of action. Different responses to DMDs from one person to another are not easily captured in clinical trial data but are important to address in clinical practice. Through different aspects of our work with people affected by MS, we are aware that a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, as is evidence of their effect on the underlying course of the condition and their impact on disease progression. Other issues will also be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD.

	Beta interferon drugs are well established treatments for relapsing remitting multiple sclerosis, having been prescribed on the NHS since 2002. Consequently, the risk/benefit profile is very well known by both neurologists and people with MS. For those people with a more cautious approach to treatments, this wealth of experience means that the beta interferon drugs continue to represent a preferred first-line choice. However, presently available beta interferon drugs require self-injecting once to four times each week. Self-injecting can be painful and can lead to skin reactions and complications at injection sites so a treatment which reduces injection frequency would allow more time for the skin to recover. One of the more common side effects of the beta interferon drugs is flu-like symptoms such as headache, muscle ache and stiffness, chills or fever which occur following injection. For some people, flu-like side effects can be severe and have a significant impact on work and family commitments. A treatment which reduces injection frequency would provide more opportunity to limit the impact of these side effects by allowing greater flexibility in the timing of injection.
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. 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 trials have demonstrated the effectiveness of peginterferon compared to placebo and confirmed that it has a similar efficacy to other beta interferons. Peginterferon has been prescribed as an NHS treatment since 2015; despite the introduction of oral treatments and treatments with a greater efficacy it has continued to be a popular option for people with RRMS. To gain further insight into the experience of people taking peginterferon, we interviewed people who are currently taking this drug. We also reviewed feedback on peginterferon in survey data collected between 20 December 2017 and 10 January 2018 in response to the Appraisal Consultation Document for TA527. As noted above, the majority people with RRMS wish to start treatment with one of the DMDs soon after diagnosis in order to reduce relapse rates and 'silent' MS activity as well as delay long term disability. For some people, after discussion with MS neurologists and MS specialist nurses, beta interferons are the preferred treatment because they are well established and have a very low risk of serious side effects. Overwhelmingly, fortnightly administration was the most important factor influencing people's choice of peginterferon over other self-injected DMDs. People identified a number of advantages that this offered: • allowed them to manage timing of flu-like side effects and minimise the impact of this side effect on work and family commitments • longer interval between using an injection site allows more time for injection reactions to resolve • improved adherence – several people commented that it was easier to remember a fortnightly injection than to remember to take oral medications once or twice daily • less frequent dosing means less frequent reminder of MS, making it easier to cope with the emotional and psychological impact of MS • one person who travels a lot on business noted that injection packs can be bulky, so packing one or two doses needed for a business trip was much more convenient than packing sufficient for daily dosing

	Peginterferon's pre-filled pen-style injector was described as being very easy to use, which is particularly important for people with manual dexterity, visual or cognitive problems. One person chose peginterferon over the other beta interferons because the incidence of neutralising antibodies is lower[1], making it less likely to lose efficacy over time. They had identified this difference through their own in-depth research, highlighting the importance people place on making decisions about choosing a DMD. While some people had chosen peginterferon as their first option, others had started with one of the other DMDs. A number had originally chosen Avonex (interferon beta 1a, weekly injection) because they preferred the lower frequency of injections, then later switched to peginterferon for the even lower injection frequency. Others switched from Avonex to peginterferon because peginterferon's subcutaneous injection suited them better than Avonex's intramuscular injection. In addition, some people switched to peginterferon after experiencing intolerable side effects on oral treatments. An advantage noted by several people was the fact that, while peginterferon is normally stored in the fridge, it can be kept at room temperature for up to 28 days (compared to 7 or 14 days for other beta interferons), making it very practical when travelling. Finally, one of the people interviewed described how initially they had felt unhappy about injecting peginterferon, but now see this in a more positive light and feel empowered by it, recognising that it is part of their strategy to manage their MS.

[1] White JT, Newsome SD, Kieseier BC, et al. Incidence, characterization, and clinical impact analysis of peginterferon beta1a immunogenicity in patients with multiple sclerosis in the ADVANCE trial. Ther Adv Neurol Dis 2016; 9(4): 239-249. https://www.ncbi.nlm.nih.gov/pubmed/27366230

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	People identified a few disadvantages, but also explained how these had been resolved. One person initially experienced painful injections, but this was avoided by improving injection technique with help from the Biogen support nurse. Several people described the development of a big red patch over several days at the injection site which takes some time to fade, however this was cosmetic only, and did not lead to discomfort. In common with the other beta interferons, peginterferon causes a flu-like side effect. All the people we spoke to found that this lessened over time and were able to do their injection at a time when this side effect had minimal impact. Other measures such as drinking plenty of water the day before injection and taking paracetamol or ibuprofen before the injection also reduced flu-like side effects. One individual who switched from weekly Avonex to fortnightly peginterferon found the flu-like side effect more severe, which they felt was the result of taking a larger amount of beta interferon in a single injection. They had a difficult transition between the two drugs and after four months were offered the opportunity to go back to Avonex, but side effects began to improve and they have now been taking peginterferon for two years.
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.	Peginterferon is likely to be a preferred treatment option for people who are risk adverse and have a relatively low level of MS activity. For this group, fortnightly injection offers minimal treatment burden and a more easily manageable side effect burden. We would not expect peginterferon to be used for very active relapsing remitting MS (also known as rapidly evolving severe MS or highly active despite previous treatment) for which more effective treatments would be used (fingolimod, natalizumab, cladribine, ocrelizumab, alemtuzumab).

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.
Other issues	
13. Are there any other issues that you would like the committee to consider?	The committee is in the unusual position of appraising a drug which has been prescribed by the NHS since 2015. Peginterferon is an established treatment with well-defined safety profile. MS teams are very experienced with this agent; there is a wealth of published research and clinical experience confirming its general safety; there are well-established services to initiate and monitor treatment. Despite the availability of alternative treatments, peginterferon along with other beta interferons and glatiramer acetate continue to be prescribed widely. Although it is now an established product, compared to other beta interferons and glatiramer acetate, peginterferon should be considered innovative. Pegylation extends circulating half-life and therefore reduces injection frequency, making it an attractive option for patients. Extensive real-world experience of DMDs has confirmed that at an individual patient level, different products suit different individuals. There are significant differences between the DMDs in terms of ease of use, dosing schedules, storage, side effects, safety during pregnancy and tolerability. The availability of a range of treatment options accommodates the widest possible range of patient and clinician preferences, enhances patient adherence and, consequently, clinical effectiveness.

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: Peginterferon beta-1a offers the security of an established treatment combined with a less frequent (fortnightly) dosing regimen. • At least comparable efficacy at reducing relapse rates compared to current beta interferon drugs • Consequent avoidance of residual disability • Established drug with well-known risk/benefit profile • Less frequent injection frequency compared to presently available beta interferon drugs which enables people to better plan their injections around work and other commitments • Improved quality of life, reduced steroid administration and fewer hospital admissions (resulting from lower relapse rate)

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis ID1521

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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.

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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.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To reduce clinical relapses associated with relapsing-remitting (RR) multiple sclerosis (MS) and slow clinical disability progression.

or prevent progression or disability.)	
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 of relative relapse rate compared to best supportive care. Relative reduction in confirmed disability progression compared to best supportive care is more difficult to ascertain due to the longer term nature of data needed to determine this in comparison to relapse rates.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes in a wider sense there is a need in RR MS for 'safe'/low risk therapies which have efficacy and are well tolerated. This technology in part meets this unmet need in some people in that it has good long-term safety (as demonstrated by similar technology – beta interferons) but also due to its lower injection frequency (fortnightly) and lower rate of formation of neutralising antibodies compared to other beta interferons potentially means it may in some people be better tolerated and more efficacious.
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 RR MS is using disease modifying therapies (DMT) or which this technology is one.
• Are any clinical guidelines used in the treatment of the	ABN Guidelines published in 2017 in Practical Neurology

condition, and if so, which?	NHSE Treatment algorithm for DMT in RR MS. 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 differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	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-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. 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 therapy option to a relatively small number of people with RR MS who prefer on the grounds of safety or convenience an infrequent injection therapy with minimal systemic immune suppression. It is likely to represent a niche area but still valuable for those people on the therapy who have no other DMT options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it would be used as laid out in the current NHSE treatment algorithm.
• How does healthcare resource use differ between the technology and current care?	It should not have any impact as this technology is similarly used and priced to other beta interferon preparations.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As above – mainly in a small group of people who prefer from a safety and/or convenience aspect an infrequent injection therapy with minimal systemic immunosuppression. Increasingly all DMTs are prescribed through neuroscience centres or designated prescribing centres as agreed with NHSE.
• 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 adds to our clinical options but take up has been in a small number of people as there are several other choices available to most people with RR MS. In those who have taken up the technology it has proved to be a valuable therapy.
• Do you expect the technology to increase length of life more than current care?	Equivalent to other beta interferon technologies.
• Do you expect the technology to increase health-related quality of life more than current care?	Equivalent to other beta interferon technologies but the less frequent injections may add to this.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per NHSE Treatment algorithm
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.)	No impact as similar therapies available already and this technology is not expected to have a large uptake amongst people with MS.

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 per current NHSE Treatment Algorithm. No additional testing necessary.
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	Yes. The additional pegylation of the beta-interferon molecule allows for less frequent injections and a significantly lower rate of neutralising antibody formation which may improve compliance, tolerance and potentially some possible improvement in efficacy.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No it offers a possibly improved method of delivery of a pre-existing molecule.
• Does the use of the technology address any particular unmet need of the patient population?	Yes in a relatively small group of people with MS who are not able to tolerate other DMTs or have significant concern regarding safety of other DMTs which may suppress systemic immune activity.
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 injectable DMTs may cause skin bruising or itching and occasional localised infection. Beta interferons can cause in up to 50% of people who take them 'flu-like symptoms' usually on the day of injection. Usually the medications are well tolerated.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	Outcomes of efficacy – relative relapse rate, disability progression, MRI activity, evidence of impaired tolerance compared to equivalent DMTs. Yes this was measured in appropriate clinical trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MRI markers of inflammatory action were used as is standard for clinical trials in this area. They are not full surrogate outcome measures but have a relationship with treatment efficacy.
• 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	No.

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	Equivalent.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None known.
22b. Consider whether these issues are different from issues with current care and why.	n/a

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

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

- Fewer injections
- Good safety profile
- Equivalent efficacy to similar available DMTs
- Niche/low take-up by patients
- Possible better tolerance than other beta-interferons

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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

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.....

Charlotte Brown

Plegridy

Personal Statement

I was officially diagnosed with RRMS in 2012 although I had my first relapse in 2007. My mum was diagnosed with PPMS when I was a child and I have watched her deteriorate. She is now fully chair bound and has only limited use of her hands. I have been very lucky with symptoms and have none day to day – just some brought on by exercise. My relapses have lasted between 6 weeks and 6 months and have been sensory/visual.

I was first offered DMDs in 2016 when I started taking Tecfidera. Initially I had no side effects from this and it seemed like the perfect treatment but about 3 months in I developed an allergy to sulphites/sulphates and one of the ingredients in the Tecfidera tablet in SLS (Sodium Lauryl Sulphate) so I was unable to continue this treatment.

I began plegridy at the end of 2016 and have been taking it ever since. I do suffer from the achy/flu like side effects sometimes but generally if I am well hydrated these can be kept at bay with ibuprofen and taking it easy. I am a busy mum and foster mum and so neither taking plegridy nor the side effects interfere with my very busy day to day life. The main advantage for me of plegridy is that it is only fortnightly and so I am not constantly reminded of the diagnosis I have – especially having seen my mum suffer so. I am able to live life as normal – I can take my medication at home and after my children have gone to bed so it doesn't remind them either.

The physical impact of MS and DMDs is relatively easy to measure and record but the mental toil it takes is massive and as I am lucky enough not to be reminded everyday by symptoms I am thankful to be able to take a treatment that enables me to live a normal life and not have to remember what the future might hold (until someone finds a cure of course!!.)

Title: *Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (ID1521)*

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Contributions of authors
Peter Auguste (Research Fellow) and Vijith Gunasekera (Clinical Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Oliver Putt (Academic Foundation Year Doctor) and Farah Kidy (Academic Clinical Research Fellow) provided the clinical summary; Amy Grove (Assistant Professor) co-ordinated and conducted the critique of the clinical effectiveness evidence and co-ordinated the project and the report; Mubarak Patel (Research Assistant) reviewed and critiqued the statistics and undertook any additional analyses; Jacoby Patterson (Senior Researcher) and Wendy Knerr (Senior Researcher) conducted the critique of clinical effectiveness evidence; Chris Stinton (Senior Research Fellow) critiqued the mixed treatment comparisons. Sam Johnson (Information Specialist) and Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Harpal Aujla (Clinical Research Fellow) reviewed and critiqued the company submission, (Olga Ciccarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Honorary Clinical Research Fellow) reviewed and critiqued the company submission and advised of the clinical and cost-effectiveness critique,

Aileen Clarke (Professor) reviewed and critiqued the company submission, clinical and cost-effectiveness evidence and report.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

ABN	Association of British Neurologists
AE	Adverse events
ALT	Alanine aminotransferase
ARR	Annualised relapse rate
CDP	Confirmed disability progression
CDP3/6/12M	Confirmed disability progression 3/6/12 months
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CrL	Credible interval
CS	Company submission
CSR	Clinical study report
DMTs	Disease modifying therapies
EDSS	Expanded disability status scale
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol five dimensions
ERG	Evidence review group
GA	Glatiramer acetate
Gd	Gadolinium
Gd+	Gadolinium-enhancing
HCHS	Hospital and community health service
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IFNs	Interferons
IFNβ	Interferon beta
IM	Intramuscular
ITT	Intention to treat
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KM	Kaplan-Meier
LOCF	Last observation carried forward
LY	Life year
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MRI	Magnetic resonance imaging
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NEDA	No evidence of disease activity
NHS	National health system
NHSEED	NHS's economic evaluation database
NICE	The National Institute for Health and Care Excellence
ONS	UK Office for national statistics
OR	Odds ratio

PASAT3	Paced audio serial addition test 3
PAS	Patient access scheme
PEG	Polyethylene glycol
pegIFNβ-1a	Peginterferon beta-1a
PICOS	Population, intervention, comparator, outcome, study design
PML	Progressive multifocal leukoencephalopathy
PRMS	Progressive relapsing multiple sclerosis
PSA	Probabilistic sensitivity analysis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSS	Person social service
PSSRU	Personal social services research unit
QALYs	Quality adjusted life years
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RCT	Randomised controlled trial
RoB	Risk of bias
RR	Rate ratio
RRMS	Relapsing remitting multiple sclerosis
RSS	Risk sharing scheme
SAE	Serious adverse events
SC	Subcutaneous
SE	Standard error
SD	Standard deviation
SDMT	Symbol digit modalities test
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
SUCRA	Surface under the cumulative ranking curve
VTF	Visual function test
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submission (CS) decision problem matches the intervention and outcomes described in the NICE final scope[1], as displayed in Table 1.

The CS decision problem differs from the NICE scope[1] for the population and comparators.

-The NICE final scope[1] addresses people with RRMS, which is consistent with the marketing authorisation

-The CS decision problem is restricted to exclude subpopulations of patients with highly active or rapidly evolving severe RRMS. The ERG consider this appropriate as it is unlikely that pegIFNβ-1a would be used in these subgroups in clinical practice

-The NICE final scope states that "*People who could not tolerate previous treatment*" should be considered as a subgroup if the evidence allows.[1] However, the CS decision problem states that "*most clinical trials generally have exposure to previous disease modifying therapies (DMTs) within a specified time frame (or any exposure at all) as an exclusion criterion*"

-The comparators in the CS decision problem differ from the NICE scope[1] because they exclude those interventions which are indicated for patients with highly active or rapidly evolving severe RRMS (i.e., cladribine, natalizumab, fingolimod).

The CS provides no evidence of the effectiveness or cost-effectiveness of Peginterferon beta-1a (pegIFNβ-1a) to the population including highly active or rapidly evolving severe RRMS.

Table 1. ERG comparison of NICE[1] and CS decision problem

	NICE	CS	ERG comment
Population	People with relapsing-remitting multiple sclerosis (RRMS)	People with RRMS that is not highly active or rapidly evolving severe	The ERG consider the exclusion of these subpopulations to to be appropriate
Intervention	Peginterferon beta-1a	As per scope	-
Comparator	For people with RRMS: • alemtuzumab • dimethyl fumarate	The comparators are for people with RRMS that is not highly active or	The ERG consider the exclusion of interventions which are

	• teriflunomide • beta interferon • glatiramer acetate • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with rapidly-evolving severe relapsing–remitting multiple sclerosis: • alemtuzumab • cladribine • natalizumab • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) For people with highly active relapsing–remitting multiple sclerosis despite previous treatment: • alemtuzumab • fingolimod • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	rapidly evolving severe. •Alemtuzumab •Dimethyl fumarate •Teriflunomide •IFNβ •Glatiramer acetate •Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	listed in the NICE scope to be appropriate as they align to the exclusion of the highly active or rapidly evolving severe subpopulations
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom from disease activity (for example lesions on magnetic resonance imaging [MRI] scans) • mortality • adverse effects of treatment • health-related quality of life	As per scope. The CS Document B Table 1 states some outcomes (severity of relapse, symptoms, and freedom from disease activity) could not be assessed in a mixed treatment comparison (MTC) due to lack of comparative data or heterogenous definitions or scales	The ERG consider this restriction in outcomes assessment to be non-ideal however, recognise that it is a limitation of the evidence available

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence in the CS comes from a single randomised controlled trial (RCT), the ADVANCE trial of pegIFNβ-1a in people with RRMS.[2] The trial was an international, randomised phase III double-blind parallel-group, placebo-controlled study (1 year [year 2 patients were blinded only to treatment frequency]) which included 26 countries from India, Northern America, Western Europe, Eastern Europe and the 'rest of world'. The ADVANCE trial was designed to evaluate the effectiveness of pegIFN-β-1a (125 μg subcutaneous [SC] every 2 weeks) compared with placebo. A beneficial effect was found for relapse outcomes, disability progression and freedom from disease activity for patients with RRMS. For health related quality of life (HRQoL) measures, 125 μg of SC pegIFN-β-1a every 2 weeks was not different from placebo. Relapse severity outcomes were not reported. Groups were not significantly different with respect to mortality. 1516 patients were randomised and 1512 patients entered the trial:

- In year 1, patients received SC injections with pre-filled syringes of placebo (n=500), pegIFNβ-1a at a dose of 125 μg once every 2 weeks (n=512), or pegIFNβ-1a 125 μg once every 4 weeks (n=500). A total of 456 placebo patients and 438 pegIFNβ-1a 125 μg once every 2 weeks completed year 1. Treatment every 4 weeks is not included in the marketing authorisation, this is not discussed in detail in the CS and will not be described in this report
- At the end of 48 weeks, the 456 patients in the placebo group were randomly re-assigned to pegIFNβ-1a 125 μg every 2 weeks (n=228) or 4 weeks (n=228). Of these, 196 patients completed year 2 in the every 2 week group (200 in the 4 week group).

Pre-specified primary outcome (intention to treat [ITT]) population):

- The primary endpoint was annualised relapse rate (ARR) at week 48, based on number of relapses. At week 48, the ARR rate was 0.397 relapses per patient-year (95% Confidence Internal [CI], 0.328, 0.481) in the placebo group and 0.256 (95% CI, 0.206, 0.318) in the pegIFNβ-1a every 2 weeks group.

Secondary outcomes (ITT population):

- The secondary efficacy endpoints were the number of new or newly enlarging hyperintense lesions at 1 year, proportion of patients who relapsed, and proportion of patients with disability progression at 48 weeks which is reported in the CS as continuing disability progression (CDP) at 3 and 6 months (CDP3M and CDP6M)

- Patients treated with pegIFNβ-1a every 2 weeks had fewer new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks than patients in the placebo group (3.6 9 [5% CI, 3.1, 4.2] versus 10.9 [95% CI, 9.6, 12. 5]). The CS reported the adjusted lesion mean ratio as 0.33 (95% CI, 0.27,0.40; P < 0.0001) for pegIFNβ-1a every 2 weeks versus placebo. Lesions were significantly smaller for those patients taking pegIFNβ-1a compared to placebo (P <0.0001)
- The proportion of patients with a relapse at 48 weeks was 0.291 (Standard error [SE], 0.0206) in the placebo group, 0.187 (SE, 0.0178) in the every 2 week group (Hazard Ratio [HR], 0.61 [95% CI, 0.47,0.80] P=0.0003)
- Disability progression at 48 weeks was 0.105 (SE, 0.0142) in the placebo group and 0.068 (SE, 0.0119) in the intervention group (HR, 0.62 [95% CI, 0.40,0.97] P=0.0383). The CS reports that the pegIFNβ-1a every 2 week group significantly reduced the risk of CDP3M at year 1 by 38% compared with placebo (estimated proportion of patients who progressed for every 2 week versus placebo: 0.068 versus 0.105), resulting in an HR of 0.62 (95% CI, 0.40,0.97 P=0.0383)

  In year 2, patients receiving pegIFNβ-1a every 2 weeks significantly reduced the CDP3M over 2 years by 37% when compared with delayed treatment (HR, 0.63 [95% CI, 0.43,0.94] P=0.0223)
- Post hoc analysis demonstrated that pegIFNβ-1a every 2 weeks significantly reduced the risk of CDP6M at year 1 compared with placebo by 54%, resulting in an HR of 0.46 (95% CI, 0.26, 0.81, P=0.0069)
- In year 2, early initiation of pegIFNβ-1a every 2 weeks significantly reduced the risk of CDP6M by 41% compared with delayed treatment (estimated proportion of patients who progressed every 2 weeks versus delayed treatment: 0.077 versus 0.119), resulting in an HR of 0.59 (95% CI, 0.38,0.90 P=0.0137).[2]

The CS also draws upon the ATTAIN study, which is a 2-year extension study of ADVANCE.[3] Patients in ATTAIN received the same dosing regimen that they had received in year 2 of ADVANCE. ATTAIN was not used to populate the economic model but is included in the CS as it provides supplementary evidence for the long-term efficacy and safety profiles of pegIFNβ-1a.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The Evidence Review Group (ERG) have the following concerns about ADVANCE,[2] the sole source of randomised comparative evidence for the value of pegIFNβ-1a:

- ADVANCE was conducted across 26 countries. The majority were from Eastern Europe (69%), followed by India (11%) and Western Europe (8%). Only 14 patients were enrolled from the UK. It is unclear if these populations, or the care they receive, are representative of the care currently provided or likely to be received in the UK

- Patient withdrawal was uneven across arms. The 1-year placebo-controlled treatment period was followed by a second year of treatment, during which all patients initially allocated to placebo were re-randomised to receive either pegIFNβ-1a every 2 weeks (n=228) or every 4 weeks (n=228); total 456 (i.e., 91.2% of the original placebo group). The patients who received pegIFNβ-1a every 2 weeks or every 4 weeks in year 1 remained on their assigned treatment regimen in year 2 (every 2 weeks, n=438/512 [85.5%]; every 4 weeks, n = 438/500 [87.6%]). This represents differential drop-out between the placebo (n=44) and pegIFNβ-1a every 2 week group (n=74) by the end of year 1 of ADVANCE (14.5% from the every 2 week group, and 8.8% from the placebo arm, in year 1[2]). Withdrawal of consent was the most common reason for discontinuing study treatment

- The proportion of patients who discontinued study treatment or withdrew in the first 48 weeks due to adverse events (AE) was also lower in the placebo group compared with the intervention group. In the every 2 week arm, n=25 discontinued due to an AE and n=25 withdrew due to an AE; in the placebo arm the figures were n=7 and n=6, respectively

- The rates of AE were generally similar between treatment and placebo, with the exception of treatment-related AE: 90% of the pegIFNβ-1a (2-week) group had at least 1 compared to only 53% of the placebo group.

Further important issues:

- The systematic literature review methods were appropriate when checked. The ERG noted some discrepancies in quality appraisal of studies included in the mixed treatment comparisons (MTC)
- The MTC results seem appropriate. The ERG performed a comparison of trials and studies included in the analysis for ARR, CDP3 and CDP6M outcomes between the CS MTC and those performed in a previous technology appraisal, ID527[4] and noted some minor discrepancies

- There was little information on which to examine consistency in the MTCs. The results of the tests of potential inconsistency which were presented appear to be appropriate
- Transitivity in the MTCs included in the CS is unclear, there is some evidence to suggest that the assumption of transitivity has been violated. The ERG note systematic differences between studies in the disease duration of the patient populations, study publication dates, age inclusion criteria, MS diagnostic criteria, EDSS cut-off criteria, follow-up time between studies and lack of detail regarding previous relapses/treatments
- It was difficult to assess heterogeneity of patient characteristics and the clinical similarity of study populations was often unclear. Studies were included despite heterogeneity and the acceptability of this is unclear, however it appears to be appropriate to avoid the use of arbitrary cuts off points
- The methods of statistical analysis for the MTCs presented in the CS is appropriate.

1.3 Summary of cost-effectiveness submitted evidence by the company

The submission received by the ERG included: 1) a systematic review of economic evaluations, and studies that reported resource use and costs, or HRQoL for the management of people with RRMS and 2) an electronic version of the company's *de novo* Markov model programmed in Microsoft Excel.

The search for cost-effectiveness analyses identified 66 studies (1 February 2016 and May 2019). Of these, 12 were undertaken in the UK, of which two (Hernadez et al., 2017[5] and Melendez-Torres et al., 2017[6]) studies were undertaken in England, with both studies comparing pegIFNβ-1a with other DMTs. Some study characteristics and results were reported for these studies. The search strategy also identified 29 studies reporting HRQoL. Of these, 11 studies reported utility values by EDSS level, of which two studies (Kobelt et al., 2017[7] and Thompson et al., 2017[8]) included participants from the UK. Both studies included the same participants and reported the same utility values by EDSS. However, for consistency, the company used the utility values obtained from Orme et al., (2007)[9] which included participants from the UK. Both studies included the same participants and reported the same utility values by EDSS.

Biogen Idec used a Markov model to assess the cost-effectiveness of pegINFβ-1a 125µg compared to other DMTs for treating people with RRMS. The company's illustrative model structure comprised EDSS health states for people with RRMS and secondary progressive MS

(SPMS), and those experiencing relapses, treatment-related AE and treatment discontinuations. From all health states there was a risk of death.

The model starts with a hypothetical cohort of people aged 36 years, distributed across RRMS EDSS levels 0 to 4.5, reflecting the mean age and distribution of the participants in the ADVANCE trial. Disease progression for people with RRMS was based on transition probabilities derived from the British Columbia natural history cohort. On progression to SPMS, natural history progression was based on transition probabilities derived from the London, Ontario cohort. In each cycle, people may have experienced relapses, treatment-related AE or discontinued treatment, all of which are captured in separate health states.

Treatment effects were assumed to delay disease progression of RRMS and reduce the frequency of relapses. Information about treatment effect was based on the company's MTC. Information on utilities were based on information from Orme et al. (2007),[9] which were derived from utility values from the UK MS survey. Caregivers utility decrements were based on information obtained from Acaster et al., (2013).[113] Disutility values for people who experienced AE associated with each DMT were obtained from various sources. Age- and gender-specific all-cause mortality rates for a UK general population were derived from the UK Office for National Statistics (ONS) data, and adjusted using the mortality rates obtained from Pokorski et al., (1997).[11] Information about resource use and unit costs were obtained from various published sources.

The analysis was undertaken from the National Health Service (NHS) and Personal Social Service (PSS) perspective, with the main outcomes life-years (LY) and quality-adjusted life-years (QALYs) gained over a 50-year time horizon. The company's base-case results were presented as an incremental cost-effectiveness ratio (ICER), expressed as cost per QALYs gained. Both costs and effects were discounted at 3.5% per annum. A number of deterministic one-way sensitivity analyses and scenario analyses were undertaken, as well as probabilistic sensitivity analysis (PSA) based on the outcome cost per QALY only.

Base-case results showed that treatment with pegINFβ-1a 125µg dominated all comparators except treatment with alemtuzumab 12mg. Alemtuzumab 12mg when compared to SC pegINFβ-1a 125µg was more costly and more effective, with an ICER of approximately £1200 per QALY gained. Base-case results were robust across all scenario analyses undertaken. Results for the PSA

showed that at a willingness-to-pay (WTP) threshold for a QALY, pegINFβ-1a 125µg had a 0.17 probability of being cost-effective when compared to alemtuzumab 12mg. In comparison to all other comparators pegINFβ-1a 125µg had probabilities >0.85 of being cost-effective.

1.4 Summary of the ERG's critique of cost-effectiveness evidence submitted

Whilst the ERG consider the economic model structure to be appropriate, we have some concerns that relate to some of the model inputs.

Interpolated disease-specific relative risk obtained from Pokorski et al., (1997)[11]

The ERG agrees that there is an increased risk of mortality compared to the general population. Mortality multipliers applied to some EDSS levels might have been over- or underestimated. For example, people with EDSS 0, it is assumed that there is a 1.6 increased risk of mortality compared to the general population. Conversely, the interpolated value for EDSS 0 assumes that there is no increased risk of mortality compared to the general population. The ERG considers the interpolated values to better reflect the increased risk of mortality compared to the general population.

Caregivers utility decrements obtained from Gani et al., (2008)[10]

Caregivers utility decrements for EDSS 5-5.5 and 6-6.5 appear to be higher compared to the utility decrements for more severe EDSS levels. However, we would expect the caregivers' utility decrements to increase as EDSS levels rise.

All-cause discontinuation risk using a parity of 5% per annum

RCTs may not be the best way to capture real-life tolerability/discontinuations. First, RCTs can be considered artificial, with highly selected/motivated participants. Second, there may be various non-clinical reasons for discontinuation. Third, limited long-term follow-up. Given the limitations, the ERG considers it more appropriate to use estimates from post-marketing surveillance/real life clinical studies (e.g., Risk sharing scheme [RSS]), as these can provide better rates for discontinuation.

A parity of 5% per annum was used in a previous assessment, which was based on evidence from the RSS. The ERG acknowledges that some of the DMTs (pegIFNβ-1a, teriflunomide, alemtuzumab, dimethyl fumerate, and ocrelizumab) included in the economic analysis were not included in the RSS. The ERGs preference would be to use 5% per annum for the older DMTs

and another estimate for newer DMTs. However, given the paucity of real-life studies following up people on newer DMTs, we assumed that the discontinuation rate is the same for the newer DMTs. The ERG clinical advisor suggested that there is no good reason why the annual all-cause discontinuation for pegIFNβ-1a is higher compared to other interferons (IFNs).

RRMS relapse frequency from the ID527[4] assessment Melendez-Torres et al., (2017)[6]
Values used in the company's base-case show that there is a steady decrease in the annual relapse rates, where in some more severe EDSS states the annual relapse rates were slightly higher than less severe EDSS states. The ERG clinical advisors suggested that they would expect there to be gradual decrease in the annual relapse frequency. The ERG considered the values reported in ID527 assessment, which is based on the British Columbia cohort to be more appropriate.

SPMS relapse frequency from the ID527[4] assessment Melendez-Torres et al., (2017)[6]
People with SPMS are characterised by increasing disability commonly without relapses; though some people continue to experience relapses. We considered that some of the values used in the company's base-case are likely to overestimate the annual relapse rate. For example, the annual relapse rate for people with EDSS 3-3.5 SPMS) is 0.875, which is higher than EDSS 2-2.5 (SPMS) with a value of 0.4650. This suggests that people in EDSS 3-3.5 health state experience more relapses than people in EDSS 2-2.5. Furthermore, the annual relapse rate for people in EDSS 3-3.5 (SPMS) is more frequent than people in the corresponding health state but with RRMS (0.720). The ERG considered the ID527[4] assessment values to be more appropriate because the relapse rates decrease as EDSS levels increase and the annual relapse rates in people with SPMS are less than the relapse rates for people with RRMS.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

The company's systematic literature review methods were appropriate and the MTC results seem appropriate. The appraisal of the single pivotal trial submitted as evidence for effectiveness of pegINFβ-1a was satisfactory.

The company's model is logical and it depicts the natural history for people living with RRMS, with an appropriate cycle length of one year to capture any changes in the disease progression. In general, the process of identifying and justifying the choice of key model inputs were transparent. The economic analysis conforms to the NICE reference case in that the perspective, discount, and the lifetime horizon was considered to be long enough to capture the costs and benefits of pegIFNβ-1a and other DMTs. The assumptions made in order to have a workable model were plausible, and the economic model submitted allowed for a range of scenario analyses to be undertaken.

1.5.2 Weaknesses and areas of uncertainty

The ERG were concerned about ADVANCE,[2] as the sole source of randomised comparative evidence for the value of pegIFNβ-1a because only 14 patients were enrolled from the UK, therefore the generalisability to a UK population is unclear. There was uneven withdrawal across trial arms by the end of year 1 ADVANCE (14.5% from the every 2 week group, and 8.8% from the placebo arm) which represents differential drop-out between the placebo (n=44) and pegIFNβ-1a every 2 week group (n=74) by the end of year 1, in year 1[2]). The proportion of patients who discontinued study treatment or withdrew in the first 48 weeks due to AE was also lower in the placebo group compared with the intervention group (every 2 week n=25 discontinued due to an AE and n=25 withdrew due to an AE; in the placebo arm the figures were n=7 and n=6, respectively). Finally, treatment-related AE were 90% of the pegIFNβ-1a (every 2 week) group experiencing 1 event compared to 53% of the placebo group. Overall, these concerns may mean that the results obtained in ADVANCE could potentially be biased, and therefore need to be interpreted with caution. The ERG consider the differential drop-out might introduce bias, as there are potential differences in characteristics of subjects who dropped out, compared to the subjects who remained in the study. However, the ERG are not able to confirm the differences due to lack of data.

The ERG noted some discrepancies in quality appraisal of studies included in the MTC, and in the inclusion of trials and studies included in the analysis for ARR, CDP3 and CDP6M outcomes between the CS MTC and those performed in ID527[4]. There was little information on which to examine consistency of the MTCs, and transitivity of the MTCs included in the CS is unclear, there is some evidence to suggest that the assumption of transitivity has been violated.

There was evidence of lack of critical appraisal of the economic evidence identified by the systematic review. For example, the company undertook a systematic review of the HRQoL evidence and identified 11 studies that reported results by EDSS score. However, there was not adequate discussion/justification about why the evidence was not appropriate for the economic model. The company further stated that for consistency and in line with other technology appraisals it was more appropriate to use those by Orme et al., (2007).[9] The ERG have highlighted areas of uncertainty: 1) An annualised discontinuation rate, as the rate of discontinuations may change over time (for example, early higher rate of discontinuations due to adverse effects/tolerability, then plateau, then later increase due to progression to SPMS or inactive MS), 2) Long-term all-cause discontinuation of newer DMTs obtained from a real-world setting, 3) the impact of treatment switching to other lines of DMTs. The model assumes that people do not receive other DMTs when they discontinued treatment and 4) whether there is evidence to support treatment waning.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.6.1 Exploratory analyses related to cost-effectiveness

The ERG made some amendments to the company's base-case model inputs. In general, the company's base-case results were robust to making each individual change while holding all other input parameters constant. The ERG's preferred base-case consists of making the following changes simultaneously:

- Interpolated disease-specific relative risk obtained from Pokorski et al., (1997)[11]
- Caregivers utility decrements obtained from Gani et al., (2008)[10]
- All-cause discontinuation risk using a parity of 5% per annum
- RRMS relapse frequency from the ID527[4] assessment (Melendez-Torres et al., 2017)[6]
- SPMS relapse frequency from the ID527[4] assessment (Melendez-Torres et al., 2017)[6]

Under the ERGs preferred assumptions, and taking the list price for each DMT, the results showed that alemtuzumab dominated all strategies by being the least costly and most effective treatment strategy. Results from the PSA show that at a willingness-to-pay threshold of £20,000 per QALY, there was a 0.28 probability that pegIFNβ-1a was cost-effective when compared to alemtuzumab.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

2.1.1 Disease overview

The CS provides a good disease overview and describes the underlying health condition with emphasis on its types, prevalence, symptoms and risk factors. The CS correctly states that disease onset is due to complex interactions between environmental and genetic factors. It describes smoking, adolescent obesity, and the Epstein-Barr virus as associated with an increased risk of developing multiple sclerosis (MS) (CS Document B, pg.18) however, it should be noted that this is not an exhaustive list. The ERG notes that Vitamin D deficiency has been shown to have an impact on disease activity and progression.[12, 13]

2.1.1.1 Types of MS

The CS provides a succinct and accurate definition of the three main types of MS. It states that RRMS affects 85% of newly diagnosed patients (this is taken from the 2008 WHO Multiple Sclerosis Atlas).[14] The ERG notes that this document was updated in 2013, however, the update does not state any change in the given statistics.[15]

2.1.1.2 Epidemiology

MS is described in the CS as one of "*the leading cause(s) of non-traumatic [central nervous system] CNS morbidity and mortality in young and middle-aged adults*" which generally manifests itself between the ages of 25 and 35 (CS Document B, B.1.3.1.2 pg.18). A review of literature revealed that the peak incidence for MS in the UK occurs between 40 and 50 years of age.[16] In Document B, B.1.3.1.2, the CS references a significant amount of data from the MS Trust website that does not cite any peer reviewed publications (CS Document B, reference ID29). Therefore, the values may underestimate the number of people living with MS in the UK. A study completed in 2010 estimated that 126,669 people in the UK were living with MS and 6,003 with new diagnoses in a year.[16] This is currently the most comprehensive study regarding the prevalence and incidence of MS across the UK. The MS society produced an estimate in 2018 using data from the Mackenzie paper[16]and extrapolating forward suggested that there are over 110,830 people with MS in the UK, and that each year around 5,190 people are newly diagnosed with the condition.[17] The CS states that patients with MS require expensive support throughout life, this is valid.[7]

2.1.1.1 Pathophysiology

The CS summarises the pathophysiology of MS which is not well understood. It focuses on the intrinsic model hypothesis which suggests that initiation of the immune cascade occurs within the CNS, but tends to neglect to discuss the extrinsic model.[18] The CS also mentions the role of T-helper cells in the pathogenesis of MS, however fails to mention that newer studies suggest that B cells have a larger role than previously thought.[19]

2.1.1.2 Presentation

Clinical symptoms

The ERG note that the CS has discussed a range of symptoms experienced by patients with MS (CS Document B, pg.19). However the ERG note that the CS does not describe some of the most common presenting symptoms including:[15]

- Sensory (40%)
- Motor (39%)
- Fatigue (30%)
- Visual (30%)
- Balance (24%)
- Sexual (20%)
- Urinary (17%)
- Pain (15%)
- Cognitive (10%)

The ERG also note that the CS states: "*Later in the disease course, cognitive problems are the most common symptoms affecting 40%-70% of patients with MS*" (Document B, B.1.3.1.4 pg.19). The document that is referenced for this statistic does not state that cognitive problems are the most common.[15] And other literature also suggests that fatigue or limb disability are more common, however it should be noted that symptoms can be dependent on age, gender, disease progression as well as disease severity.[20]

Imaging features

The CS provides a reasonable description of the main MRI sequences used for MS (2012).[21] The ERG note that there are now newer, more complex, imaging sequences allowing better insights into pathophysiology and improved specificity for diagnosis.[22] For example, the use of double inversion recovery or phase sensitive inversion recovery may be beneficial in the detection of cortical lesions.

2.1.1.3 Diagnostic criteria

The CS states the use of the McDonald criteria for diagnosis of RRMS and acknowledges the 2017 update.[19] However, the ERG note that the criteria provided in CS Document B, page 20 are for the 2005 McDonald criteria. The McDonald criteria incorporate MRI into the diagnostic assessment that focuses on neurological history, examination and a variety of paraclinical laboratory examinations.[19]

2.1.2 Prognosis and disease monitoring

The ERG were unable to verify the value that 50-60% of patients develop SPMS within 15-20 years (CS Document B, pg.20) however, it is widely accepted that untreated patients with RRMS will develop SPMS.[23]

Risk factors for disease progression

The ERG believe the CS offers a good summary for risk factors (CS Document B, pg.20) however, it again neglects to comment on Vitamin D as previously mentioned. Table 3 (CS Document B pg.21-23) provides a summary of different outcome measures however it should be noted that it is not conclusive.[24, 25]

Measurement of disability

As described in the CS, the EDSS can be used to measure disease progression (CS Document B, pg.24). The EDSS does have limitations, including being scored by a clinician thus at risk of subjective bias, it is also argued by some professionals that the scale is non-linear.[26] The citation provided (54, 55 from CS Document B) does not deliver detailed information which is available elsewhere.[26, 27] The ERG would like to clarify that the eight domains are as follows:

1. Pyramidal
2. Cerebellar

3. Brainstem
4. Sensory
5. Bowel and bladder function
6. Visual function
7. Cerebral function
8. Other

Disability progression

The CS describes disability progression citing papers with patient populations from the West of France which can be considered equivalent to the UK in terms of population characteristics.[28] The CS summary of disease progression with relation to relapses is valid (CS Document B, pg.24), however, the ERG are concerned that some statistics are incorrectly presented. An example would include "*42% of patients experiencing a permanent residual deficit of ≥ 0.5 EDSS points following a relapse*" (CS Document B, pg.24). The cited paper states that 42% of patients had a residual deficit of at least 0.5 EDDS units at an average of 64 days, the paper proceeds to state that there is a suggestion of permanence.[29] The summary regarding ongoing MRI activity on disability progression is reasonable.

2.1.3 Burden of MS

The ERG consider that the CS description of the impact of MS on the patient and care giver are appropriate (CS Document B, B.1.3.2 pg.25). The ERG note that the CS states "*Patients with MS have worse QoL scores than patients with epilepsy, diabetes, recent myocardial infarction, and hypertension*" (CS Document B, pg25). However, the ERG note that scores for MS patients are lower in some domains (physical functioning, role limitations-physical, energy, and social function) when compared to epilepsy patients however are equal in other domains (emotional wellbeing, and role limitations-emotional).[30] The ERG consider the assumptions around the societal and healthcare burden of MS are reasonable.

2.2 Critique of company's overview of current service provision

The CS is focussed on DMTs which are the main treatments for patients with RRMS. Current service provision and a significant portion of the NICE MS guidelines (CS Document B,

B.1.3.3.2 pg.28) describe the management of symptoms associated with MS (such as fatigue and spasticity) and with the management of relapses.

The CS has appropriately raised the issue of complexity with treatment choice as the number of available DMTs increases. The UK Association of British Neurology (ABN) guidelines (2015)[31] outlines the range of DMTs which are available in order to meet the clinical and individual needs for each patient. The ABN divides DMTs into two categories, drugs of moderate or of high efficacy (CS Document, B B.1.3.3.2 pg.29). Alternatives to pegIFNβ-1a which are currently available in the NHS are outlined in Figure 2 (CS Document B, pg.30). The CS provides a general summary about interferons on page 32 (Document B, pg.32) which the ERG consider to be accurate.

The CS highlights the importance of shared decision making which involves identification of goals, benefits and risks of treatments. The CS notes that "*most patients require a change in therapy over the course of their disease, and achieving treatment goals requires careful planning*" (CS Document B, pg.27). However, indications for stopping and starting treatment are not fully described. The NHS England treatment algorithm for MS DMTs suggests that treatment should be initiated only in those who are ambulant and have no evidence of non-relapsing disease.[32] Stopping criteria for the current drug include intolerability, ineffectiveness, developing secondary progressive disease or the inability to walk.[32]

The CS (Document B, pg.30) presents a summary of the NHS England treatment algorithm. The ERG note some differences in the summary presented in the CS and the updated 2019 algorithm:[32]

- Ocrelizumab is offered as an alternative to alemtuzumab wherever the latter appears in the algorithm
- In order to be eligible for treatment, patients with a single clinical episode must satisfy the McDonald diagnostic criteria
- Glatiramer acetate (GA) is a first-line and alternative first-line treatment option for patients with RRMS (one relapse in two years) or a single clinical episode satisfying the McDonald diagnostic criteria
- For patients with RRMS with one relapse in the last two years, no treatment is not a preferred option

- There is a difference in the recommendation between interferon beta 1a and 1b with the latter only appearing in the "*2 significant relapses in 2 years*" pathway
- Natalizumab only appears in the "*rapidly evolving severe MS*" pathway.

The ERG clinical expert states that the NHS England treatment algorithm included in the CS "*mostly*" provides an appropriate reflection of clinical practice. However, they note that "*some patients with 2 relapses in 2 years opt for no treatment because of doubt over reduction in long term disability/prevention of secondary progression with 1st line DMTs*". The ERG clinical expert also notes that "*some clinicians would be nervous of using highly active agents in sequence i.e., changing from natalizumab to alemtuzumab to cladbribine (in any order) because do not know the long term toxicity*".

The CS highlights the differential effect of DMTs on disability. The ABN recommendations suggest that the relationship between relapse rate, DMTs and disability is complex.[31] However, there is a consensus that DMTs do not affect the development of disability where this is unrelated to relapses.[31]

The ERG note the association between reduced treatment adherence and poor outcomes including more frequent and severe relapses, increased health system use, poorer mental health and lower employment prospects is summarised in the literature.[33-39] However, since these are all cross-sectional studies a causal relationship cannot be assumed.

The CS describes issues of poor patient compliance and adherence with interferons (Document B B.1.3.3.5 pg.32). In a large MS database study, Fox et al., (2013) found that patients were significantly more likely to stop the once daily SC GA than either weekly IFNβ-1a (P=0.0007) or alternate day IFNβ-1b (P=0.0010).[39] However, there was no significant difference between weekly intramuscular (IM), three times a week SC or alternate day SC interferon beta (IFNβ) regimens. This would suggest that the relationship between frequency of dosing and adherence is not linear and may be mediated by drug effects or type of injection.

Furthermore, specific to injections, anxiety and dependency on others have been noted as barriers to treatment compliance.[40] Several additional groups of barriers to treatment adherence have been identified. Perceived lack of efficacy was the most common reason given for treatment cessation in a large MS database.[39] In multivariable analysis of questionnaires completed by patients and

health professionals, ease of injection (odds ratio [OR] 1.47 [95% CI, 1.15,1.87]), satisfaction with treatment (OR 1.54, [95%,CI, 1.20,1.98]), being treated at an MS centre (OR 1.36, [95% CI, 1.09,1.71]), having had a discussion about adherence (OR 1.54 [95% CI, 1.14,2.10]) and excellent family support (OR 1.33 [95% CI, 1.06,1.67]) were all significantly associated with treatment adherence.[36] However, a causal relationship cannot be assumed between frequency of injections and adherence.

The potential advantages of pegylation on pharmacodynamics, thermal stability and immunogenicity are described in detail in the CS (Document B, B.1.3.4.1 and B.1.3.4.1 pg.33). The ERG consider these to be appropriate.[41] The CS reports "*36% reduction in annualised relapse rate (ARR) rate ratio (RR) 0.644 (95% CI 0.500 - 0.831)*" in the first year of treatment with pegIFNβ-1a (CS Document B, pg.34) and suggests that this is not dissimilar to drugs which NICE has included in first-line recommendations for RRMS.[4] The CS proposes potential benefits of pegIFNβ-1a compared with other IFNs and GA including:

- PegIFNβ-1a has a prolonged circulation time in comparison to other IFNs and GA, which results in reduced frequency of administration (every 2 week dose)
- PegIFNβ-1a does not require cold chain and can be kept at room temperature for 30 days
- Pegylation can decrease drug immunogenicity by shielding antigenic determinants, which may result in a lower incidence of neutralising antibodies. This could potentially have an impact on efficacy.[41, 42] (CS Document B, B.1.3.4.2 pg.33).

The CS state that "*no equity issues are foreseen*" (Document B, B.1.4 pg.33). The ERG consider this to be appropriate.

3 Critique of company's definition of decision problem

3.1 Population

The CS population differs in part from the final NICE scope.[1] The final scope defined the population as "*people with relapsing-remitting multiple sclerosis*".[1] The population in the CS decision problem (CS Document B, Table 1 pg.13) had RRMS but excluded subpopulations of patients with highly active or rapidly evolving severe RRMS.

Highly active subpopulations were defined as patients who "*have disease activity despite previous treatment*" (CS Document B, Table 1 pg.13). High disease activity was defined as "*failure to respond to at least 1 year of treatment with a DMT and either, ≥ 1 relapse in the previous year with either ≥ 9 T2 lesions and/or ≥ 1 Gd+ lesion, or unchanged or increased relapse rate, or ongoing severe relapse compared with the previous year*".[43] The CS states that there are "*limited data available to assess the efficacy of pegIFNβ-1a in the highly active subgroup*" (CS Document B, Table 1 pg13). Rapidly evolving severe RRMS subpopulations were defined "*as one or more disabling relapses in 1 year, and with ≥ 1 (Gadolinium) Gd+ lesion or a significant increase in T2 lesion load compared with a previous recent MRI*".[43] The company state that pegIFNβ-1a should not be assessed in this subpopulation as it is "*highly unlikely to be used in this population in clinical practice*" (CS Document B, Table 1 pg.14). The ERG clinical advisors agreed with the subpopulation restrictions, and suggest that there are more effective options in these scenarios.

The company suggest that the subpopulations were excluded for consistency with the current recommendations within the NHS England DMT algorithm for first-line therapy, and for consistency with the exclusion criterion (previous treatment with IFN for more than 4 weeks) in the included pivotal trial (CS Document B, Table 1 pg.13). The ERG's clinical advisor confirmed that the NHS England DMT algorithm presented in CS Figure 2 (CS Document B, pg.30) is a mostly accurate description of NHS clinical practice (see Section 2.2) and that the exclusion criteria of the pivotal trial are reasonable. The clinical evidence submitted by the company (ADVANCE)[2] matches the patient population described in the CS decision problem.

The European Public Assessment Report (EPAR) states that "*Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis*".[44] The company reported that

"*the [Committee for Medicinal Products for Human Use] CHMP considered lack of data in patients with high disease activity*" (CS Document B, Table 1 pg.13). The ERG note that the lack of data reflects the exclusion criteria of the pivotal trial.

Overall, the ERG considers the exclusion of highly active and rapidly evolving severe subgroups populations of RRMS to be appropriate.

3.2 Intervention

The intervention in the decision problem is pegylated interferon β-1a (pegIFNβ-1a) which matches the NICE final scope.[1] The company provides a description of the technology and the mechanism of action of pegIFNβ-1a (CS Document B, pg.17) which the ERG confirm is consistent with the summary of product characteristics (SmPC).

Pegylated interferon β-1a is a medication administered SC using a prefilled syringe/autoinjector. The recommended dosage is 125 µg administered SC every two weeks by self-injection. In pegIFN-β -1a, polyethylene glycol (PEG) is added to the N-terminus of beta-interferfon-1a, allowing for less frequent administration.[4] The company report that although the mechanism of action of pegIFNβ-1a is not fully understood, it is thought to reduce disease activity in MS by a similar mechanism to that of non-pegIFNβ-1a. In that, it binds to the type I interfon receptor on the surface of cells which leads to regulation of interfon-responsive gene expression.[44]

3.3 Comparators

The comparators described in the company decision problem are partially consistent with the NICE final scope.[1]

The CS decision problem matches the NICE final scope for patients with RRMS. The comparators are: alemtuzumab, dimethyl fumarate, geriflunomide, IFNβ, GA and ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable). The ERG's clinical advisor confirmed these comparators are appropriate, but stated that some patients with two relapses in two years may opt for no treatment, and this circumstance is not considered in the NHS England: treatment algorithm for MS DMTs.[32]

The comparators in CS decision problem differ from the NICE final scope due to the exclusion of people with rapidly evolving serve RRMS and highly active RRMS despite previous treatment. Therefore, the following treatments for rapidly evolving severe RRMS; (cladribine, natalizumab); and for highly active RRMS (fingolimod); are not included in the CS decision problem.

The comparators included in the company decision problem align to the population included in the NICE final scope, as outlined above in Section 3.1. The ERG considers the exclusion of highly active and rapidly evolving severe RRMS comparators appropriate.

3.4 Outcomes

The outcomes in the company decision problem match the NICE final scope.[1] These include; relapse rate, severity of relapse, disability (e.g., EDSS [reported as CDP3/6/12]) symptoms of MS (such as fatigue, cognition and visual disturbance), freedom from disease activity (e.g., lesions on MRI scans), mortality, adverse effects of treatment and HRQoL. The ERG provide a critique of outcomes where possible in the clinical effectiveness review (see Section 4.2.6).

The company state that "*some outcomes (severity of relapse, symptoms, and freedom from disease activity) could not be assessed in the CS MTC due to lack of comparative data or heterogenous definitions or scales*" (CS Document B, Table 1 p15). Please see Section 4.3.1.4 for more detail. The ERG consider this restriction in outcomes assessment to be non-ideal however, recognise that it is a limitation of the evidence available.

3.5 Other relevant factors

The European Medicine Agency issued a marketing authorisation (17th July 2014) for the use of pegIFNβ-1a in the treatment of adults with RRMS.[44]

The ERG note that the EPAR states "*The safety and efficacy of Plegridy in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials*".[44]

The company note that there is no Patient Access Scheme (PAS) in place.

The NICE final scope states that the following subgroup should be considered if the evidence allows; "*People who could not tolerate previous treatment*".[1] The CS decision problem states that "*Due to lack of evidence this subgroup is not included in the submission*" (CS Document B, Table 1 pg16). The company suggest that this subgroup is relevant in clinical practice, which the ERG clinical advisors have confirmed. However, the CS continues "*most clinical trials generally have exposure to previous DMTs within a specified time frame (or any exposure at all) as an exclusion criterion*" (CS Document B, Table 1 pg16). As described in Section 3.4 the ERG considers the exclusion of "*people who could not tolerate previous treatment*" as appropriate due to lack of evidence. In this appraisal, 83% of subjects in the pivotal trial (ADVANCE) were MS treatment-naive and the remaining 17% had previously discontinued treatments.[2]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of reviews

The CS undertook two systematic reviews of evidence which are relevant to the company's decision problem; a systematic literature review (SLR) that evaluated clinical effectiveness evidence, and an SLR of cost-effectiveness evidence.

The SLR which evaluated clinical effectiveness of pegIFNβ-1a in adult patients with RRMS was presented in CS Document B, page 36; and the ERG critique is provided below. The processes (methods and number of reviewers) for study selection and data extraction were described in the CS and appear to be appropriate. Table 2Table 2 provides the ERG quality assessment of the CS clinical effectiveness SLR. Overall, the ERG consider the chance of systematic error in the clinical effectiveness SLR to be low.

Table 2. Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Eligibility criteria were reported for the systematic review, however, there are inconsistencies in the reporting of the numbers of included studies which appear to be related to the numbers of hits in the searches and update searches (rather than the number of included studies) (see Section 4.1.1).
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes. However, ERG judgements differ for some items in the MTC (see Section 4.3.1.1)
4. Is sufficient detail of the individual studies presented?	Yes. Details of the RCTs of the intervention and comparators were described in sufficient detail. The company assessed the quality of the included trial (ADVANCE);[2] the ERG generally agreed with the company's assessment although there were some differences in judgements (see Section 4.1.4).
5. Are the primary studies summarised appropriately?	Yes. Results for the pivotal RCT (ADVANCE) and 2-year follow up study (ATTAIN) are presented in tabular and narrative form in the CS Document B, page 36-46. Other trials included in the synthesis were not reported in detail. However, following clarification (clarification question A8) study details of studies included in the systematic review were provided.

The submitted evidence is generally consistent with the company decision problem defined in the CS.

4.1.1 Searches

Literature searches were conducted as part of a wider review for treatment of either RRMS or SPMS and for approved treatments or treatments expected to be approved in the future (CS Document C, D.1.2). The CS differs from the NICE scope[1] and reference case as it focuses on RRMS and excludes highly active MS or rapidly-evolving severe subpopulations (see Section 3.1 2). Only DMT's with a positive reimbursement decision by NICE for patients with RRMS that was not highly active or rapidly evolving sever were included in the MTC (CS Document C, D.1.2), therefore natalizumab, daclizumab, fingolimod and cladribine were excluded. Daclizumab was initially included in the SLR but it was withdrawn during the SLR. The MTC identified studies for pegIFNβ-1a and relevant comparators (CS Document C, D.1.2). This found 32 studies (561 papers) of which five studies were excluded because they could not be incorporated into any analyses, leaving 27 studies in the MTC (CS Document B, Table 16 pg.69).

The SLR reported in CS Document B, Section B.2.1 and CS Appendix Document C, D1.1 searched a comprehensive range of databases and trial registries. The ERG consider an appropriate range of natural language and thesaurus search terms were used to search for the disease and all relevant interventions as identified by the scope[1] and were combined using the relevant syntax. The original searches were run in October 2014, with seven subsequent update searches performed up to December 2018. There were two typographical errors in reporting actual search dates, but confirmation was received in the clarification response (A1) that the final searches were conducted in December 2018. There were no language or age limits. The searches were as follows:

- Separate, rapid appraisal searches identified systematic reviews, protocols, HTAs and guidelines via the CDSR, DARE, HTA, NIHR, Prospero, NICE, CADTH and KSR Evidence databases
- Database searches were conducted in Medline, Embase and PubMed using a recognised RCT search filter. This may have missed systematic reviews and meta-analyses, which can be a source of primary studies. PubMed was searched to retrieve non Medline papers but no MeSH terms were used in the PubMed search. The presentation of the Web of Science search was not clear, but the strategy appears reasonable. The search was limited to the SCI database, excluding the conference proceedings databases
- Trial databases were used to identify completed and ongoing trials
- Conferences were searched via Embase and Northern Light Life Sciences Conference abstracts (OVID).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram Figure 1 (CS Document C, Appendix D, pg.37) contains discrepancies in the reported search results. The ERG noted a discrepancy in the search number (n=30,866) presented in Figure 1 compared to the combined number of results for the individual searches (n=29,865 not including the references for previous Biogen MTCs ([n=118] and handsearching [n=12]) listed in Tables 1 to 21 (CS Document C, Appendix D). The ERG queried the discrepancy during the clarification stage. However, the ERG consider these to not be resolved by the clarification response (A2). The additional tables provided (Table 1 and Table 2, clarification response A2) record the search numbers of the updated searches, which indicate that the search numbers recorded are cumulative. For the rapid appraisal searches and the trial databases, the final cumulative number is less than the de-duplicated number reported in the PRISMA diagram. The ERG conclude that differences may be due to the difficulties in running complex searches and update searches in these databases. Rapid searches record retrieved in December 2018 reported as 395 whilst 461 reported in PRISMA. For the Trial databases, 1997 references were retrieved in December 2018 but 2296 reported in PRISMA. In addition, 45 SmPCs and EPARs were reported in the PRISMA but only 39 listed in the recorded search run in December 2018 (26 SmPCs and 13 EPARs).

4.1.2 Inclusion criteria

Eligibility criteria for the CS SLR are stated in CS Document C, page 30 Table 22, described in PICOS format. Table 3 compares the CS PICOS and the ERG summary of study selection criteria. Study inclusion was not limited by language or publication date. The ERG consider this to be appropriate.

Table 3. Study selection criteria

Domain	Inclusion criteria	ERG comment
Population	*CS Document C, page 30 Table 22 states the population is "Adults (≥ 18 years) with a confirmed diagnosis of rapidly evolving severe (RES) or relapsing/remitting multiple sclerosis (RRMS)".*	The ERG note that the literature searches for this review were conducted as part of a wider programme of research on treatments for either RRMS or SPMS (CS Document B, pg.27). All EU-approved treatments or treatments expected to be approved in the near future in either CIS, RRMS or SPMS were identified. Only studies including RRMS patients were included in this CS SLR. The ERG consider this appropriate as it aligns to the CS

		decision problem.
	The CS reports on CS Document C, page 30 "In some studies, the patient population was composed predominantly of patients with one type of MS but may have included a small proportion of patients with other types of MS."	The ERG notes that the CS does not provide citations for these studies. The response to the clarification A8 (Table 7, pg.27) states that the proportion of patients with SPMS was not stated in BEYOND, Bornstein 1987 and Crentsil 2012, while O'Connor 2006 specified 11.5-13.1% SPMS between the treatment groups, TEMSO 3.3-6.1%, TENERE 0-0.9% and TOWER 1% SPMS.
	The CS states that the SLR "allowed the inclusion of studies where ≥ 85% of the patient population were classified as RRMS in all treatment arms".[45] *The CS notes that this was the recommended cut off in the IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) methods guide.*	The ERG found that the threshold reported in the cited recommendations of the IQWiG was actually 80% rather than 85%. However, the reported percentages of the populations with RRMS in the included studies was ≥85% for all the studies.[45]
Intervention	*Polyethylene Glycolated Interferon beta-1a (pegIFNβ-1a, Plegridy®) is listed as the intervention in CS Document C, Table 22 page 30.*	-
Comparator(s)	*There were nine comparators including standard care (11 separate medicines including placebo)* • *Alemtuzumab (Lemtrada®)* • *Ocrelizumab* • *Dimethyl fumarate (Tecfidera®)* • *Teriflunomide (Aubagio®)* • *Interferon beta-1a (IFNβ-1a, Avonex®)* • *IFNβ-1a 22 mcg or 44 mcg (Rebif®)* • *IFNβ-1b (Betaferon®, Betaseron®, Extavia®)* • *Glatiramer acetate (Copaxone®)* • *Standard care (± placebo)*	The CS (Document C, D.1.2 pg.29) states that "*Only disease-modifying therapies (DMTs) with a positive reimbursement decision by NICE for patients with RRMS that was not highly active or RES were included in the mixed-treatment comparison (MTC*)" and that "*only DMTs that were used at European Medicines Agency (EMA)–approved doses were included*". The ERG consider this to be appropriate as it is in line with the CS decision problem.
Outcomes	*Clinical outcomes were reported as efficacy, tolerability and safety outcomes.*	The ERG consider these to be appropriate, but note the discrepancy to the outcomes listed in the NICE

	Efficacy outcomes: • *ARR* • *Severity of relapse (e.g., proportion of patients with relapses requiring hospitalisation)* • *CDP sustained for 3 months* • *CDP sustained for 6 months* • *CDP sustained for 12 months* • *Symptoms of MS, including cognition, fatigue and visual disturbance* • *Freedom from disease activity, e.g., No Evidence of Disease Activity (NEDA)* • *Quality-of-Life: SF-36, Global VAS, MSIS* *Tolerability Outcomes:* • *Discontinuations due to any cause* • *Discontinuations due to AEs* *Safety outcomes:* • *Any Adverse Events (AE)* • *Any Serious Adverse Events (SAE)* • *Mortality*	decision problem. Discrepancies include the following: • EDSS is not listed as an outcome, (disability is reported as CDP3/6/12) • HRQoL is not listed as an outcome, (Quality-of-Life: SF-36, Global VAS, MSIS is reported) • Tolerability outcomes and SAEs were not listed in the NICE decision problem.
Study design(s)	*The CS SLR included published or unpublished prospective RCTs.*	The ERG note that the CS Document C, D.1.1 page 4 report electronic databases and grey literature sources, including trial registries and conference abstracts, were searched and updated. The ERG found no further information on seeking unpublished material (e.g., contacting authors).

The CS Document B, page 67 states that "*The selection of studies for inclusion in the final MTC was conducted in two stages. In the first stage studies were selected for inclusion in the systematic review based on the PICOS criteria [listed in Table 3]. These studies were then considered for inclusion in the analysis based on the similarity criteria (trials should be similar for moderators of relative treatment effect)".* The ERG note that the CS SLR did not exclude any studies based on clinical heterogeneity, but the CS state that "*there was some heterogeneity between studies*", (CS Document B, pg.67). Heterogeneity is discussed further in Section 4.4.1.

The CS provides a PRISMA flowchart for the systematic review (CS Document C, Appendix D Figure 1 pg.37) which provides numbers included and excluded at each stage. Reasons for exclusions are reported in CS Document C Appendix D, Table 29 for those assessed at full text assessment. List of excluded studies is reported in CS Document C Appendix D, Table 30. The ERG inspected the lists of included and excluded studies (Document C Table 26 and Table 30) and although the reasons for exclusion of studies by the ERG were not always identical to those given by the CS, the same studies were classified as included or excluded. Therefore, the ERG consider the excluded studies appropriate according to the criteria presented in Table 3. Additional references were provided by the company in response to clarification question A3.

4.1.3 Critique of data extraction

The CS Document C, page 31 states that "*Forms for data extraction were individually designed and piloted using Microsoft Excel 2010. Data extraction was performed by two reviewers independently. Any discrepancies were resolved through discussion or through consultation with a third reviewer."* The ERG consider this approach acceptable.

The ERG note that data were extracted for relevant outcomes (CS Document C, Table 22 pg.30). However, as described in Table 3 the outcomes listed in the SLR inclusion criteria differ slightly from those stated in the NICE decision problem, for example "*disability (for example, expanded disability status scale [EDSS])"* is reported as CDP3/6/12 in the CS.[1]

4.1.4 Quality assessment

The company provided a quality assessment of the ADVANCE[2] trial using the Cochrane risk of Bias (RoB) tool for RCTs, not the NICE checklist, (a quality appraisal of the comparator trials was done for the MTC and is reported separately, see Section 4.3.1.1). The quality assessment of the ADVANCE trial was reported in CS Document C, Table 24 page 31, although the ERG note that this was not the same as the one supplied in the Biogen Data Extraction excel spreadsheet dated August 2018 (CS Reference pack C).

The company assessed the ADVANCE study as having a low RoB on all measures (CS Document C, Appendix D, Table 24, pg.31), in contrast to the previous network meta-analysis conducted by Melendez-Torres et al, 2017 (for TA ID527[4]) which noted a high RoB related to blinding, incomplete outcome data (due to differential attrition between arms) and 'other' RoB because the study was conducted by the drug manufacturer.[6]

The ERG conducted a quality assessment of the ADVANCE^2 trial using the Cochrane RoB tool and the NICE criteria. These are compared to the quality assessment conducted by the company in Table 4. Overall, the ERG consider the RoB for ADVANCE^2 to be unclear.

Table 4. ERG assessment of trial quality using Cochrane RoB and NICE checklist

RoB item	CS RoB	CS Comment	ERG judgement	ERG rationale
Randomisation	*Low*	*Randomisation used a centralised IXRS and was stratified by site. At randomisation, the IXRS was to assign a unique 6-digit subject identification number to each subject.*	Low	Agree. Randomisation was done by a centralised interactive voice response and web system, stratified by site
Allocation concealment	*Low*	*Randomisation was done by a centralised interactive voice response and web system, stratified by site.*	Low	Agree. Performed using a centralised interactive voice/web response system.
Are participants blinded?	*Low*	*All study management and site personnel, investigators, and patients were masked to treatment assignment. Appropriate matched placebo medication was used.*	Unclear	Disagree. The level of side effects - namely injection site reactions – may have introduced a risk of bias related to blinding of participants, particularly as injection sites were not covered. However, the ERG note that this critique often occurs in drug trials of this type
Are caregivers blinded?	*Low*	*All study management and site personnel, investigators, and patients were masked to treatment assignment.*	Unclear	Disagree. The level of side effects - namely injection site reactions – may have introduced a risk of bias related to blinding of caregivers particularly as injection sites were not covered. However, the ERG note that this critique often occurs in drug trials of this type
Blinding of assessors	*Low*	*All study management and site personnel, investigators, and patients were masked to treatment assignment. Central MRI reading centre by an assessor masked to treatment allocation.*	Unclear	Disagree. The level of side effects - namely injection site reactions – may have introduced a risk of bias related to blinding of assessors, particularly as injection sites were not covered. However, the ERG note that this critique often occurs in drug trials of this type

RoB item	CS RoB	CS Comment	ERG judgement	ERG rationale
Incomplete outcome data	*Low*	*The ITT population for year 1 included all randomised patients who received at least one dose of study drug, only 4 patients were excluded, low risk.*	Low for Year 1	Agree. At baseline: 500 placebo patients; 512 pegIFN beta-1a every 2 weeks and 500 pegIFN beta-1a every 4 weeks. 1332/1512 (88%) patients completed Year 1 of study and continued with active treatment in Year 2 (patients receiving placebo in Year 1 re-randomized to pegIFN beta-1a every 2 or 4 weeks at Week 48). Completed Year 2: pegIFN beta-1a every 2 weeks, 391/438 (89%), pegIFN beta-1a every 4 weeks, 411/438 (94%), and delayed treatment 396/456 (87%); total completing year 2: 1198 of the original 1512 (79%).[46]
	High risk	*The analysis population for year 2 included only those patients who completed year 1 of the study, high risk.*	High risk	Agree: The analysis population for year 2 included only those patients who completed year 1 of the study.
Selective reporting	*Low*	*All specified outcomes were reported.*	Low	Agree. Note, the CS reported all outcomes relevant to the economic evaluation (or specified in the NICE scope[1]), but did not report data on all outcomes measured in the trial as reported in the trial publication[2] and the CSR (pg.77, 80, 82).
Other biases	*Low*	*No other apparent sources of bias.*	High	Disagree. The study was funded by the drug manufacturer. There was differential drop-out between the placebo and every 2 week intervention group by the end of year 1. In placebo: 44 discontinued, in the intervention group (every 2 week) 74 discontinued).
Overall risk of bias	*Unclear*	*N/A*	Unclear	N/A

NICE checklist item	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Yes	As above
Was the concealment of treatment allocation adequate?	Yes	As above
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	The ERG note that the placebo group is marginally numerically (but not statistically) less severe than the intervention group, therefore the differential works in the direction of the null hypothesis.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Uncertain	As above
Were there any unexpected imbalances in drop-outs between groups?	Yes	There was a differential drop-out between the placebo and every 2 week group by the end of year 1 (456/500 versus 438/512, P=0.005)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	As above

RoB item	CS RoB	CS Comment	ERG judgement	ERG rationale
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?			Yes in year 1	As above
ITT = intent to treat; IXRS = Interactive Voice/Web Response System; MRI = magnetic resonance imaging; N/A = not applicable; RoB = risk of bias.				

4.1.5 Evidence Synthesis

A narrative review was provided (CS Document B, B.2.3.1 pg.39) of the single included trial (pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study: NCT00906399)[2] for the direct evidence for the placebo-controlled double-blind period of 1 year. Where possible the ERG has checked key data presented in the CS against those in the CSR provided by the company for this appraisal, and the trial publication[2] and found several differences.

The CS does not provide details on reasons for withdrawal of consent in ADVANCE. The ERG found no comparison of baseline characteristics between completers and subjects who dropped out in any documents provided as part of the CS. While the CSR reports the number of participants who 'withdrew consent' and details of 'other' reasons for withdrawal (CSR, 10.1.2 pg.126), this was a combined figure for both years 1 and 2, with reference to appendices that were not submitted in the CS reference pack. This appendices were requested from the company, and subsequently provided at clarification in response to clarification question A16. The ERG reviewed the CSR appendices regarding drop-outs, however the ERG failed to identify any further information about the characteristics of subjects who dropped out or completed the trial (see Section 4.2.3 for further discussion).

In addition, the CS does not report how missing data from drop-outs were dealt with; (these data are reported in the trial report[2]) or the differential drop-out between the placebo and every 2 week group by the end of year 1. The ERG are concerned that the results obtained in ADVANCE could potentially be biased due to these issues, and therefore need to be interpreted with caution.

ATTAIN extension study

In addition the CS reports on ATTAIN (Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN: NCT01332019)[3] which is an

extension of ADVANCE, where subjects received the same dosing regimen that they received in year 2 of ADVANCE. ATTAIN is described in detail in CS Document B, page 44-46. In Table 6 (CS Document B, pg.41) the ADVANCE efficacy endpoints are described, ATTAIN endpoints are listed in CS Document B, Table 8 page 45. Results are mainly presented in figures and as HRs between groups for both ADVANCE and ATTAIN. The CS states that the ATTAIN study was not used to inform the economic model (CS pg.38) but "*was included as supplementary evidence for long-term efficacy and safety*" (in CS sections B.2.2 to B.2.6). Therefore, ATTAIN is assessed separately in the ERG report.

Summary

As only one trial was included, no meta-analysis was conducted in the CS. The CS SLR identified 27 studies that were eligible for inclusion in indirect and mixed treatment comparisons of at least one outcome. See Section 4.4 for critique of the indirect and mixed treatment comparisons.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Evidence for the clinical effectiveness on pegIFNβ-1a is presented from a single pivotal RCT,[2] which is described in the CS (Document B, B.2.3.1 pg.39) and for which CSRs were provided by the company. Neither the company nor the ERG identified any other relevant RCTs that meet the NICE decision problem. The CS provides summary information about the trial design, intervention, population, patient numbers (e.g., how many were eligible, randomised, allocated and dropped out), outcomes and statistical analyses.

4.2.1 Conduct of the trial

The ADVANCE trial was a phase 3, double-blind, multi-centre, placebo-controlled RCT sponsored by the company (Biogen Idec.), which lasted 1 year (48 weeks).[2] After year 1 of the trial, patients in the placebo group were re-randomised to receive treatment (CS Document C, Figure 2, pg.140) reproduced in Figure 1).

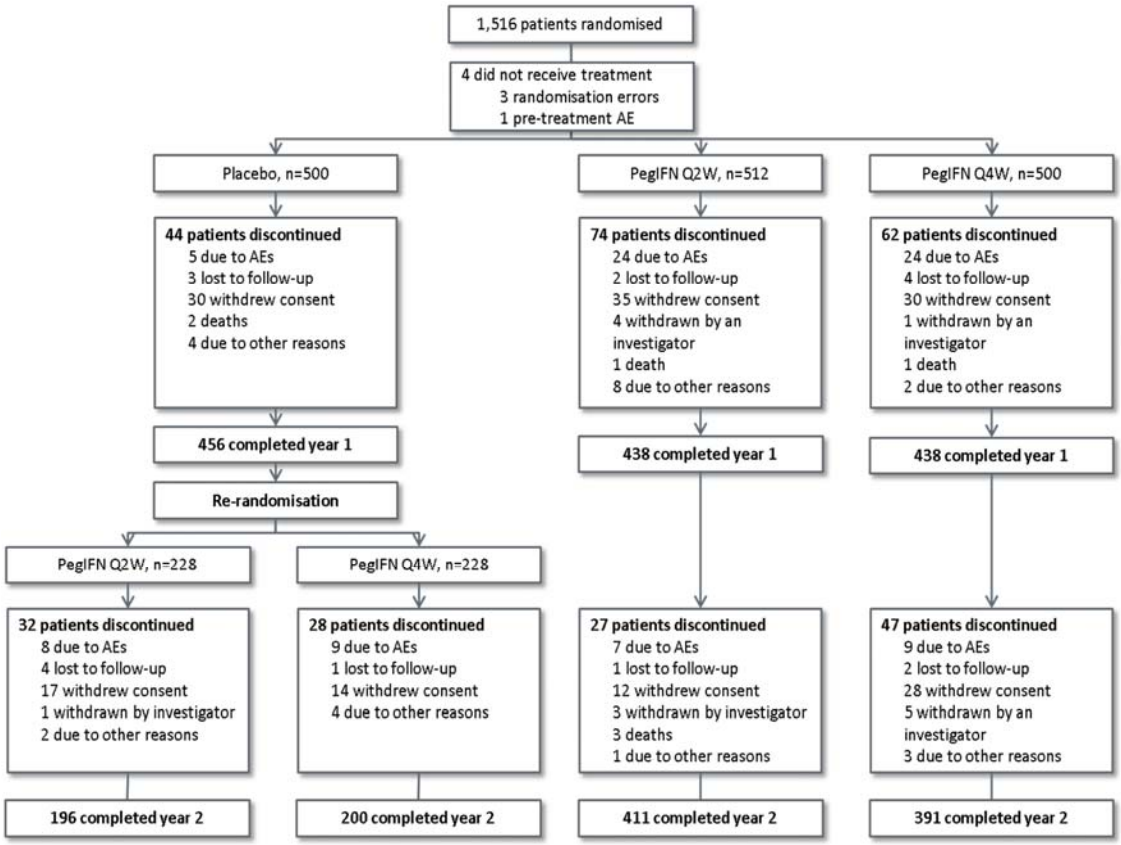

Figure 1. Patient disposition in ADVANCE reproduce from Document C Figure 2

Summary details of the ADVANCE trial were provided in the CS (Document B, B.2.3.1) and in CS Document C, Appendices D, E and F. In addition, the trial is reported in a number of peer review publications[2, 47], the NCT and a CSR which was provided to the ERG for this appraisal.

4.2.2 Randomisation

ADVANCE was designed to investigate the use of SC pegIFNβ-1a in people with RRMS. Participants were assigned randomly in a 1:1:1 ratio to receive an injection of either pegIFNβ-1a 125 mcg every 2 weeks (Q2W) or every 4 weeks (Q4W), or placebo, for a double-blind controlled period of 48 weeks.[2] The company reports (CS Document B, Table 7 pg.42) that only the 2-week dosage is currently licensed and is therefore the focus of the CS. The ERG confirm that pegIFNβ-1a 125 mcg every 2 weeks is the licensed dose, and therefore also the focus of ERG report.

The CS does not report the dates when randomisation took place nor of the study period. A previous meta-analysis reports the study period as June 2009 to November 2011.[6] The CSR notes the study cut-off date was [redacted] (year 1, after which placebo patients received the treatment).

The key inclusion criteria are reported in the CS Table 6 (CS Document B, pg.40) and CSR (2013, pg.53). In summary, these were age 18-65 years; confirmed diagnosis of RRMS as defined by McDonald criteria 1 through 4; EDSS score 0.0-5.0; at least 2 medically documented relapses within the last 3 years with at least 1 of these in the last 12 months prior to randomisation; and ability and willingness to practice effective contraception during the study and for 3 months after the last dose of study treatment (where appropriate). The ERG note that in the pegIFNβ-1a 2-week group, the EDSS score for 1 participant exceeded the upper limit of 5 specified in the protocol (CS Document B, pg.41).

Relapse within 50 days prior to randomisation and/or not stabilised from a previous relapse, primary progressive, secondary-progressive, or progressive relapsing MS, known allergy to any component of the pegIFNβ-1a formulation and history of hypersensitivity or intolerance to paracetamol, ibuprofen, naproxen, or aspirin were all key medical exclusion criteria. In addition, participants were excluded if they had undergone prior treatment with interferon that exceeded 4 weeks, and they had to have discontinued interferon treatment 6 months prior to the first day of the study. Previous treatment with pegIFNβ-1a, total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, fingolimod, any therapeutic monoclonal antibody (including natalizumab), or GA within 4 weeks prior to randomisation would also result in exclusion from the study. Additional exclusion criteria were listed on pages 53-55 of the CSR. The ERG clinical expert considers these exclusion criteria to be reasonable.

A flow-chart of participants through the ADVANCE trial was presented in CS Document C Appendix D (D.4, Figure 2, pg.140): 1516 were randomised and 1512 received at least one dose of the assigned treatment (>99%). Of the 4 participants who did not receive at least one dose, 3 were due to randomisation error and 1 to an AE prior to first dose. Of those randomised, 500 were assigned to receive pegIFNβ-1a every 4 weeks, 512 were assigned to receive it every 2 weeks, and 500 were assigned to placebo (see Figure 1).

4.2.3 Patient withdrawals

The ERG calculated trial attrition from the Q2W treatment arm to be 14.5% (n=74/512) and from the placebo arm, 8.8% (n=44/500), based on data from the trial publication (Figure 1 pg.4).[2]

Reasons for withdrawals were similar in the two treatment groups, primarily withdrawal of consent (accounting for about half of withdrawals, based on ERG calculations) and AE (accounting for around one-third of withdrawals)(See Calabresi et al., 2014 Figure 1[2]) (see Table 5). Drop-out from the placebo arm was overwhelmingly due to withdrawal of consent. Withdrawal from the study was more likely within the first [redacted] of the trial, but was [redacted] (CSR Table 76, pg.420).

The 1-year placebo-controlled treatment period was followed by a second year of treatment, during which all patients initially allocated to placebo were re-randomised to receive either pegIFNβ-1a Q2W (n=228) or Q4W (n=228); total 456 (i.e., 91.2% of the original placebo group), while patients who received pegIFNβ-1a Q2W or Q4W in year 1 remained on their assigned treatment regimen in year 2 (Q2W, n=438/512 [85.5%]; Q4W, n=438/500 [87.6%]) (CS Document B, pg.40).

The ERG considers that there is a differential drop-out between the placebo and Q2W groups by the end of year 1 (placebo 456/500 versus Q2W 438/512, P=0.005). Therefore, the year 2 population is no longer an ITT population (due to drop-out and re-randomisation). This differential drop-out was discussed in the published article of the ADVANCE study,[2] where authors state that "*The proportion of patients who discontinued study treatment or withdrew in the first 48 weeks was slightly lower in the placebo group compared with the intervention groups, as a result of differences in adverse events*".[2] However, this is not reported in the CS. The information was requested during clarification (A16), and although supplementary CSR appendices were provided by the company, the ERG were unable to compare characteristics of completers and drop-outs for ADVANCE. The data which was submitted by the company in response to clarification A16 did not display demographic data for drop-outs. The ERG consider the differential drop-out might introduce bias, as there are potential differences in characteristics of subjects who dropped out, compared to the subjects who remained in the study. However, the ERG are not able to confirm the differences due to lack of data.

The CS did not report the numbers of participants in the treatment or control groups in year 1 of ADVANCE who withdrew consent or gave 'other' reasons for withdrawal. This was reported in the CSR, including numbers who withdrew due to relapse or lack of effect (CSR, 10.1.2, p126), as a combined figure for both years 1 and 2, with reference to appendices that were not submitted in the reference pack. The trial publication (Calabresi et al., 2014, Figure 1) stated the number of participants in each group during year 1 who discontinued: 74 in the Q2W arm and 44 in the placebo arm, with the majority of discontinuations in the Q2W group due to AE (n=24) and withdrawal of consent (n=35), in the placebo arm due to withdrawal of consent (n=30) (see Table 5).[2]

Table 5. Differential drop-out between the placebo and Q2W groups by the end of year 1

Discontinuation cause	Placebo	pegIFNβ-1a every 2 weeks
AE	5	24
Influenza-like illness	-	4
Lost to follow up	3	2
Withdrew consent	30	35
Investigator decision	-	4
Death	2	1
Other	4	8
Total	44	74

In year 1, n=25 participants discontinued study treatment due to AE and n=25 withdrew from the study due to AE in the Q2W treatment arm; in the placebo arm the figures were n=7 and n=6, respectively (CSR, Table 42, pg.258).

Further details of the reasons why participants 'withdrew consent' and details of 'other' reasons for withdrawal were requested by the ERG during clarification (question A16) and provided by the company (CSR appendices 16.2.1 and 16.2.7) as combined figures for ADVANCE and ATTAIN. Based on Table 3 in CSR Appendix 16.2.1, the most common reason for withdrawal from the Q2W arm over both years was 'unspecified'.

4.2.4 Missing data

The trial publication reports: "*Data after patients switched to alternative multiple sclerosis drugs were deemed missing; all missing data were imputed on the basis of previous visit data assuming a constant rate of lesion development. 18 participants in the placebo group, 23 in the every 4 weeks group, and 18 in the every 2 weeks group had imputed data*."[2] Based on ERG calculations, data were imputed for 3.6% of the Q2W and placebo arms (3.5% and 3.6% respectively).

The ERG note that CS Document B, does not discuss missing data. In CS Document C (pg.35), the company states that missing values were calculated from the available data. In the CSR for ADVANCE, section 9.7.2.2, page 94, it states "*These missing MRI data were imputed up to Week 48, regardless of reasons, using the principle of constant rate of lesion development and the method of last observation carried forward (LOCF)",* only for the T2 Hyprintense Lesions, which is the same as stated the trial publication (see Calabresi et al., 2014, footnotes Table 2).[2] The ERG could not locate details on imputation for ARRs or disability progression.

4.2.5 Dosage

The trial publication states that dose escalation (titration) took place over the first four weeks of treatment for participants assigned to receive pegIFNβ-1a, to allay influenza-like symptoms, with a starting dose of 63 μg, 94 μg at week 2 and the target dose of 125 μg from week 4 onward. After the 4-week titration, injection of either pegIFNβ-1a or placebo was delivered every two weeks to all participants, with participants assigned to receive pegIFNβ-1a every 4 weeks given alternate injections of placebo and pegIFNβ-1a.[2] Placebo was a matched diluent, given with a matched pre-filled syringe.[2]

Treatment compliance was calculated by the number of doses a subject received divided by the number of injections the subject was expected to take, (and) was greater than 99% across treatment groups. The ERG confirmed with the clinical expert that this was an appropriate way to measure and report compliance.

4.2.6 Outcomes

The outcomes reported in the CS for ADVANCE generally matched the NICE final scope[1] and company decision problem (see Section 3.4). The ERG note that ADVANCE reported CDP3M and CDP6M (post-hoc analysis) as measures of disability progression. In CS Document B, Table 6, (pg.41) the company states for secondary efficacy outcomes: "*CDP3M at 1 year, and post hoc analysis of CDP6M at 6 months that was defined as a ≥ 1.0-point increase on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 3 or 6 months, or a ≥ 1.5-point increase on the EDSS from baseline EDSS = 0.0 that was sustained for 3 or 6 months."*

The CS provides a list of the primary and some secondary efficacy outcomes in CS Document B, Table 6 page 198 (further description in CS Document B Table 3, and CSR 9.5.2.1 pgs.77-80). The ERG have provided a brief overview of these outcomes in Table 6.

The company reports that the primary outcome was ARR at 1 year. Secondary outcomes were the proportion of patients relapsed at 1 year; number of relapses requiring IV steroid use; number of MS-related hospitalisations; progression of disability as measured by both the EDSS and the Multiple Sclerosis Functional Composite (MSFC); visual function measured by the Visual Function Test (VFT); cognitive changes measured by the Symbol Digit Modalities Test (SDMT). These endpoints were analysed at the end of treatment year.

The CS Document B, Table 3 (Outcome measures commonly used in MS studies, pg.21) states "*EDSS… does not capture cognitive disability*". However, page 24 of the CS states "*EDSS is the standard measure used in clinical practice (as well as economic evaluation models) to measure disease progression in MS*", due to the ability to measure delay in disability progression of MS, it was clinically relevant. Although EDSS is not directly reported in the CS SLR, the ERG consider the inclusion of EDSS important for the assessment of cost-effectiveness.

The ERG note that the trial results for outcome measures are reported in section CS Document B B.2.6.1 (pg.48-51) and in CS Document C Appendix L, section L.2. The CS reports data for the primary outcome (ARR at 1 year) and five of the secondary/tertiary outcomes (proportion of patients relapsed at 1 year, number of relapses requiring IV steroid use, number of MS-related hospitalisations, progression of disability as measured by EDSS, number of new or newly enlarging T2 hyperintense lesions at 1 year), all of which showed a positive effect compared to placebo. The CS provides data for progression of disability as measured by MSFC, visual function measured by the VFT and cognitive changes measured by the SDMT in Document C Table 106 page 430.

Table 6. CS reported outcomes and ERG comments

CS outcome	In line with NICE Scope.[1]	ERG comment
Year 1 (ADVANCE trial)		
Primary outcome (CS Document B Table 3, 6)		
ARR at 1 year (week 48)	Yes (relapse rate)	Standard key outcome. This indicates the number of relapses a patient would expect to have on average every year. Differences in the annualised relapse rate are measured as a rate ratio, which suggests the percentage difference in rate between two groups. A rate ratio of 0.75 in group 1 compared with group 2 means that group 1 has 25% fewer relapses than group 2. In MS, an improvement of one drug over another would be represented by a rate ratio of < 1.[6]
Secondary outcomes (CS Document B Table 3, 6 and CSR 9.5.2.1 pgs.77 and 80)		
Proportion of patients relapsed at 1 year and 2 years	Yes (relapse rate)	Standard
Number of relapses requiring IV steroid use	Yes (severity of relapse)	Additional
Number of MS-related hospitalisations	Yes (symptoms of MS)	Additional
Disability progression (CDP3M and CDP6M) defined as a ≥ 1.0-point increase on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 3 or 6 months, or a ≥ 1.5-point increase on the EDSS from baseline EDSS = 0.0 that was sustained for 3 or 6 months	Yes (disability)	Standard key outcome. The CS Document B Table 3 includes EDSS, CDP and MSFC as scales of disability progression. ADVANCE reported CDP. Time to disability progression indicates how quickly a patient would expect to have disability progression compared with another patient. This is measured as a HR. A HR of < 1 in group 1 compared with group 2 means that group 1 will take longer to have disability progression. In MS, an improvement of one drug over another would be represented by a HR of <1.[6] Many trials require that an initial sign of disability progression be confirmed at a repeat visit 3 (or 6) months later. Thus, time to disability progression confirmed at 3 months is the time to disability progression when that disability progression has been subsequently confirmed 3 months after the visit when progression was first detected. Similarly, time to disability progression confirmed at 6 months is the time to progression when that progression has been subsequently confirmed 6 months after the visit when it was first detected.[6]

Disability progression: Multiple Sclerosis Functional Composite	Yes (disability)	Additional
Visual function: Visual Function Test	Yes (disability)	Additional
Cognitive changes (Symbol Digit Modalities Test, SDMT)	Yes (disability)	Additional
Paced Audio Serial Addition Test 3 (PASAT 3)	Yes (disability progression)	Additional
Tertiary (MRI) outcomes (CS Document B Table 3, 6 and CSR 9.5.2.1 pgs.77 and 80)		
Mean number of new or newly enlarging T2 hyperintense lesions and Gd+ lesions	Yes (freedom from disease activity)	Standard
New T1 hypointense lesions	Yes (freedom from disease activity)	Additional
New active lesions (the sum of gadolinium-enhancing plus non-enhancing new or newly enlarging T2 hyperintense lesions)	Yes (freedom from disease activity)	Additional
Volume of new or newly enlarging T2 hyperintense, gadolinium-enhancing, and T1 hypointense lesions	Yes (freedom from disease activity)	Additional
Brain atrophy	Yes (freedom from disease activity)	Additional
Magnetisation transfer ratio	Yes (freedom from disease activity)	Additional
Year 2 (ATTAIN extension trial CS Document B Table 6)		
ARR	Yes (relapse rate)	Standard key outcome. As above
Proportion of patients relapsed	Yes (relapse rate)	Additional
Disability progression	Yes (disability)	Additional
Mean number of new or newly enlarging T2 hyperintense lesions and Gd+ lesions	Yes (freedom from disease progression)	Additional

ARR = annualised relapse rate; CDP3M = confirmed disability progression sustained at 3 months; CDP6M = confirmed disability progression sustained at 6 months EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium enhancing; MRI = magnetic resonance imaging; McDonald criteria 1-4 = see Section **Error! Reference source not found.**; MS = multiple sclerosis; pegIFNβ-1a = pegylated interferon; Q2W = every 2 weeks; Q4W = every 4 weeks; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneou.

Note: Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting ≥ 24 hours, and accompanied by new objective neurological findings upon examination by a neurologist. Relapses were required to be confirmed by an independent committee consisting of 8 blinded neurologists with expertise in MS (3 neurologists were voting members, with 1 substitute member at any one time). New or recurrent neurologic symptoms that occurred < 30 days following the onset of a protocol-defined relapse were considered part of the same relapse (i.e., if 2 relapses had onset days that were ≤ 29 days apart, they were counted only as 1 relapse, and the onset date used in the analysis was the onset date of the first relapse).[2]

The ERG did not locate any information regarding 'Time to Sustained Progression of Disability' assessed using the Paced Auditory Serial Addition Test (PASAT 3), which was an outcome that

was measured in the ADVANCE trial. However, the CSR (section 11.2.3.1.7.) reports: "[redacted]

The company's interpretation of outcome data and effectiveness is appropriate, but it is unclear why they have not reported data for all outcomes included in the CSR (as described in the RoB see Table 4).

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

Statistical analyses are summarised in CS Document B, Table 10 (pg.46).

4.2.7.1 Trial statistics for ADVANCE

Primary outcome

The pre-specified primary end point in the trial was defined as "t*he annual relapse rate (ARR) of relapsing-remitting multiple sclerosis (RMSS) at week 48, based on the number of relapses, from the point of baseline*".[2] The efficacy analysis was completed on the ITT population which was defined as all subjects randomly assigned to received study treatment (pegIFNβ-1a or placebo).[2]

The null hypothesis was that treatment with pegIFNβ-1a would not result in a statistically significant reduction in ARR at 48 weeks, compared with placebo. The alternate hypothesis was that treatment with pegIFNβ-1a would result in a statistically significant reduction in ARR at 48 weeks, compared with placebo. Statistical tests were two-sided, with an overall type 1 error of 0.05.

According to Table 10 in the CS (Document B, Table 10 pg.47), "*The primary end point was analysed using negative binomial regression, adjusted for baseline EDSS score (< 4 vs. ≥ 4), baseline age (< 40 vs. ≥ 40 years), and baseline relapse rate (number of relapses in 3 years prior to study entry divided by 3). A sequential closed testing procedure was used to control the type I error rate. For the primary end point, the pegIFNβ-1a Q2W group was compared with placebo; if the difference between the pegIFNβ-1a Q2W group vs. placebo was statistically significant (P ≤ 0.05), the comparison of pegIFNβ-1a Q4W group vs. placebo could also be performed and considered statistically significant if P ≤ 0.05; however, if statistical significance was not*

achieved with the pegIFNβ-1a Q2W group vs. placebo, the comparison of the pegIFNβ-1a Q4W group vs. placebo was not considered statistically significant, regardless of P value."

The Kaplan-Meier (KM) plot for the primary outcome in the ADVANCE study is shown in Figure 2 of the trial publication (Calabresi et al., 2014 Time to first relapse over 48 weeks), and Figure 3 of the trial publication shows the Time to Disability Progression over 48 weeks KM plot.[2] The ERG consider this analysis to be appropriate for these outcomes. See Section 4.2.10 for primary results of ADVANCE.

Potential shortcomings in estimating the primary outcomes

The analysis (up to 48 weeks; placebo=500, Q2W=512, [Q4W=500]) did not include any imputation of missing data of the primary outcome ARR, or disability progression, but rather defined study duration of withdrawals depending on when a patient withdrew from the study: "*If patients withdrew from the study or switched to an alternative MS medication before 1 year, the total number of days was defined as the number of days from the date of the first dose to the last date on study or last date prior to the switch*", see Table 10, page 47 of CS. Therefore, after 48 weeks, 1332 patients completed ADVANCE (456, 438, 438 respectively).[2] The ERG assessed these calculations and are satisfied they are a true representation.

Censoring was defined as, "*Relapses that occurred after patients received any alternative approved MS treatments such as chronic immunosuppressant therapy or other immunomodulatory treatments were excluded from the analyses of relapse rate, and the patient's time on study was censored at the time the alternative MS medication was started*" (in Table 10 of CS, pg.47). As this was a time-to-event analysis (time to first relapse over 48 weeks) based on pegIFNβ-1a, other MS medication may affect the time to first relapse, so the ERG considers this approach as appropriate.

Five sensitivity analyses (three prespecified and two post-hoc) of ARR at year 1 were performed; these differed from the primary analysis by using:

- The per protocol population (prespecified)
- Poisson regression model (prespecified)
- All relapses recorded on the unscheduled relapse assessment CRF (prespecified)
- Protocol-defined objective relapses recorded on the unscheduled relapse assessment CRF (post hoc)
- Baseline Gd+ lesion (presence vs. absence) as a covariate in the model (post-hoc)

The ERG considers these sensitivity analyses as appropriate.

Section B.2.6.1 of the CS states: "*Five sensitivity analyses (three prespecified and two post-hoc) of the ARR at year 1 were performed as described in Table 10 in section B.2.4. The results of all five analyses were consistent with the primary efficacy results, showing that pegIFNβ-1a Q2W resulted in statistically significant reductions in the ARR compared with placebo, ranging from 33.8% to 38%*", compared to the 35.6% reduction in the ITT population. The ERG consider this analysis to be appropriate for these outcomes.

Secondary and tertiary outcomes

The secondary efficacy endpoints were the number of new or newly enlarging hyper-intense lesions on T2-weighted images (relative to baseline MRI), proportion of patients who relapsed, and the proportion of patients with disability progression at 48 weeks. The tertiary pre-specified MRI endpoints at 48 weeks were the number of gadolinium-enhancing lesions, new T1 hypointense lesions, and new active lesions (sum of gadolinium-enhancing plus non-enhancing new or newly enlarging T1 hyperintense, gadolium-enhancing, and T1 hypo-intense lesions, brain atrophy, and magnetisation transfer ratio.[2] See Section 4.2.10 for secondary and tertiary results of ADVANCE.

Potential shortcomings in estimating the secondary and tertiary outcomes

The ERG considers the post-hoc analysis of CDP6M at one year appropriate as it is a secondary efficacy outcome over the course of the ATTAIN study (up to 240 weeks). However, the ERG note that 1,076 patients took part in the ATTAIN study, of whom 376 received continuous pegIFNβ-1a Q2W and 171 received delayed treatment with pegIFNβ-1a Q2W (CS Document B, pg.45). Therefore, the total Q2W at the beginning of ATTAIN was 547. The ARR values for year 5 of ATTAIN were based on smaller samples (pegIFNβ-1a Q2W was 185) (CS Document C, pg.425), i.e., by year five this number represents only 33.8% of the Q2W group, so there is potentially a high risk of bias by year five due to large drop-out.

4.2.7.2 Trial statistics for ATTAIN

The pre-specified primary end points in the trial were: the incidence of AE, SAE, discontinuations of study treatment due to an AE, and laboratory abnormalities. The secondary endpoints included MS relapse outcomes, MRI outcomes, disability outcomes, and

immunogenicity, adjusting for baseline EDSS score (<4.0 versus ≥4.0), baseline relapse rate, and age (<40 versus ≥40). Mean number of gadolinium-enhancing (Gd+) lesions, new/newly enlarging T2 lesions, and new T1 hypointense lesions were evaluated in each study year by pegIFNβ-1a dosing frequency in the ATTAIN population.

The efficacy analysis was completed on the study population which was defined as all patients who received at least one dose of treatment while enrolled in ATTAIN. The population includes all subjects who entered ATTAIN and received at least 1 dose of study treatment.[3] This is compared to the ITT of ADVANCE which states that the ITT population was defined as all subjects who were randomised and received at least 1 dose of study treatment (pegIFNβ-1a or placebo).[2] As in ADVANCE, the two treatment groups were patients given pegIFNβ-1a injections every 2 weeks, and the other every 4 weeks.

The null hypothesis was the incidence of AEs, SAEs, discontinuations of study treatment due to an AE, and laboratory abnormalities were constant across the treatment groups. The alternate hypothesis was the treatment with pegIFNβ-1a injections every 2 weeks would result in a statistically significant reduction in the incidence of AEs, SAEs, discontinuations of study treatment due to an AE, and laboratory abnormalities compared to pegIFNβ-1a injections every 4 weeks. Statistical tests were two-sided, with an overall type 1 error of 0.05.

According to Table 10 of the CS (Document B, pg.46) , all summary analyses of AEs were based on the principle of treatment emergence. In a given data set, an event was considered to be treatment emergent if it had an onset date on or after the date of first study treatment, or if it was present before the start of study treatment and subsequently worsened. In general, AEs were analysed based on incidence, defined as the proportion of patients who had at least one occurrence of an event out of the number of patients in the relevant safety analysis population. The ERG consider this analysis to be appropriate for these outcomes.

4.2.8 Subgroups

The company reports 12 pre-planned subgroups (CS, Table 6, pg.41 and Document B pg.41) which were not included in the NICE final scope. The NICE final scope[1] listed one additional subgroup (people who could not tolerate previous treatment) which was not reported in the CS.

- ARR between patients who withdrew before the end of year 1 and those who completed year 1.
- Baseline EDSS (EDSS < 4.0 vs. EDSS ≥ 4.0)
- Age at baseline (< 40 vs. ≥ 40 years)*
- Sex*
- Region
- Baseline weight*
- Baseline number of relapses in the 3 years prior to study entry
- Time since most recent pre-study relapse (months) (≤ 4 vs. > 4 months
- Baseline McDonald criteria
- Prior MS treatment
- Baseline Gd+ lesions*
- Baseline T2 lesion volume

In CS Document B, footnote to Table 6 also states, however, that "*Due to the number of outcomes and subgroups, only those which were felt to be relevant will be presented. Therefore, results for those subgroups marked with an asterisk (*) will not be presented*". The ERG note that there was no definition provided of what the company "*felt to be relevant*". Yet the subgroup results presented for ARR for ADVANCE (CS Document B, pg.59) did not include ARR between patients who withdrew before the end of year 1 and those who completed year 1, or region (both specified for inclusion), but did include Baseline Gd+ lesions(*) (specified not to be presented).

Results for the subgroups of patients who withdrew before the end of year 1 versus those who completed year 1, could not be located by the ERG in CS Document C (Table 32 summary of subgroup analyses of ADVANCE at 1 year). The ERG consider that data for subgroups who withdrew before the end of year 1 might not be captured if the participants dropped out. However, the ERG note that the other subgroup data add up to the original numbers randomised, so it is assumed therefore that the data from subjects who dropped out are included. The CS Document B, page 47 states that in ADVANCE, "*If patients withdrew from the study or switched to an alternative MS medication before 1 year, the total number of days was defined as the number of days from the date of the first dose to the last date on study or last date prior to the switch*". The ERG interprets this as data were included but censored, however the ERG note that this is not clearly stated in the CS.

4.2.9 Baseline characteristics

The ERG generated Table 7 to summarise the key baseline characteristics of the trial ITT populations for ADVANCE year 1 (randomised population), and for the population included in year 2. The ERG consider that there were no meaningful differences at baseline in demographic or disease characteristics between participants receiving pegIFNβ-1a (at 2 or 4 week intervals) and those in the placebo arm in the ADVANCE trial.

During clarification the ERG requested information on the patient characteristics at the start and completion of both ADVANCE and ATTAIN (clarification question A4); the data provided is reflected in Table 7. The only substantial difference between the ADVANCE and ATTAIN trials was for race: in the former, nearly three-quarters (around 70%) of participants were white, while for ATTAIN the company reports just over one-third (34-40%) were white and race was not reported for half of the study participants. The CS reports data on race for ADVANCE but not for ATTAIN, and there is no explanation for the missing data on race.

Table 7. Baseline characteristics of ITT population[a]

	ADVANCE							ATTAIN	
	Year 1			Year 2					
Characteristics	pegIFNβ-1a Q2W n=512	pegIFNβ-1a Q4W n=500	Placebo n=500	Continuous pegIFNβ-1a Q2W n=376	Delayed pegIFNβ-1a Q2W n=171	Continuous pegIFNβ-1a Q4W n=354	Delayed pegIFNβ-1a Q4W n=175	Continuous pegIFNβ-1a Q2W n = 376	Continuous pegIFNβ-1a Q4W n=354
Age, mean (SD)	36.9 (9.8)	36.4 (9.9)	36.6 (9.8)	39 (9.73)	38.2 (9.27)	38.1 (9.91)	38.2 (10.06)	39.0 (9.73)	38.1 (9.91)
Sex, % female	71	70	72	74	74	71	73	72	71
Race, % White	81	82	82	35	40	34	38	NA	NA
Years since onset of MS symptoms, mean (SD) Median	6.9 (6.61) 5.0	6.5 (6.07) 4.0	6.3 (6.28) 4.0	--	--	--	--	8.5 (6.27)	8.1 (6.11)
Years since diagnosis, mean (SD) median	4.0 (5.09) 2.0	3.4 (4.36) 1.0	3.5 (4.63) 2.0	5.7 (4.99) --	5.3 (4.8) --	5.2 (4.46) --	5.4 (4.03) --	NA	NA
EDSS, mean (SD) < 4, % >= 4, %	2.47 (1.25) 83 17	2.48 (1.24) 83 17	2.44 (1.18) 86 14	2.43 (1.27) 83 17	2.3 (1.19) 88 12	2.35 (1.18) 86 14	2.38 (1.08) 90 10	2.39 (1.34)	2.41 (1.37) [n=352]
Relapses in previous year, mean (SD)	1.6 (0.7)	1.5 (0.6)	1.6 (0.7)	1.6 (0.69)	1.5 (0.65)	1.5 (0.61)	1.6 (0.68)	NA	NA
Relapses in previous 3 years, mean (SD)	2.6 (1.0)	2.5 (0.8)	2.6 (1.0)	2.6 (1.01)	2.5 (1.04)	2.4 (0.67)	2.5 (0.83)	NA	NA
Number of lesions, mean (SD) T2	48.7 (36.83)	51.4 (35.99)	50.6 (36.65)	50.2 (38.33)	50.9 (34.93)	50.9 (36.01)	48.3 (34.68)	5.8 (12.23) [n=374]	14.8 (23.39) [n=353]

T1	27.8 (28.05)	29.6 (30.84)	28.1 (29.5) [CS reports SD=29.5, [redacted]]	29.1 (28.98)	26 (25.08)	29 (31.06)	26.3 (25.85)	29.1 (28.98)	29 (31.06)
GD+	1.2 (3.44)	1.8 (5.38)	1.6 (3.81)	1.3 (3.65)	1.3 (3.54)	1.9 (5.74)	1.6 (3.36)	0.2 (1.18) [n=375]	0.6 (1.74) [n=353]

[a] Data for ADVANCE are from the CS, Table 7, p42; all other ADVANCE data are from tables provided by the company in response to clarification question A4. Greyed out = Q4
[b] Data for ATTAIN are from CS Table 9 pg. 45.

The CS (Document B, pg.41) reports that 14 patients from the UK were included in the trial; the CSR specifies [redacted] (CSR pg.405). The ERG did not consider this to be reflective of adult patients with RRMS in the UK and requested clarification on why the company suggested it was generalisable. In response to clarification question A5 the company suggested "*most patients were from Eastern Europe*". The company suggested that "*Subgroup analysis by region has been performed for ADVANCE and suggests that the efficacy of pegIFNβ-1a is broadly similar across all populations, regardless of region.*" The ERG suggest that there is a difference in efficacy between the three regions with [redacted], the UK population were included in region 1. [redacted] was provided in response to clarification question A7. It shows that there is no statistically significant benefit for patients receiving pegIFNβ-1a in [redacted] but no analysis of interaction were presented to confirm a subgroup effect.

[redacted]

In clarification response A5, the company go on to state that "*baseline characteristics from other comparator studies relevant to this appraisal*" do not "*significantly differ*". The ERG suggests that there is potential variation geographically in outcomes and potentially in accompanying clinical practice, treatment physiotherapy and standards of care regimes.

4.2.10 Primary and secondary clinical and MRI results for ADVANCE

The primary and secondary clinical and MRI results for the pivotal trial were reported in the trial publication.[2] The results of ADVANCE have been reproduced by the ERG in Table 8 for completeness.

Table 8. Primary and secondary clinical and MRI results for ADVANCE[2]

	Placebo group (n=500)	**Peginterferon beta-1a 125 µg every 2 weeks group (n=512)**
Annualised relapse rate at 48 weeks		
Annualised relapse rate (95% CI)*	0.397 (0.328-0.481)	0.256 (0.206-0.318)
Rate ratio (vs placebo; 95% CI)	..	0.644 (0.500-0.831)
p value (vs placebo)	..	0.0007
Proportion of patients with a relapse at 48 weeks		
N	142	90
Estimated proportion relapsed (SE)	0.291 (0.0206)	0.187 (0.0178)
Hazard ratio vs pleace (95% CI)	..	0.61 (0.47-0.80)
p value (vs placebo)	..	0.0003
Disability progression at 48 weeks		
N	50	31
Estimated proportion with disability progression (SE)	0.105 (0.0142)	0.068 (0.0119)
HR vs placebo (95% CI)	..	0.62 (0.40-0.97)
P value (vs placebo)	..	0.0383
New or newly enlarging T2-weighted hyperintense lesions at 48 weeks		
Number of patients evaluated	476	457
Adjusted mean number of lesions (95% CI)	10.9 (9.6-12.5)	3.6 (3.1-4.2)
Lesion mean ratio (95% CI)	..	0.33 (0.27-0.40)
p value (vs placebo)	..	< 0.0001

EDSS=Expanded Disability Status Scale. Peginterferon=pegylated interferon. *Based on negative binomial regression; adjusted for baseline EDSS (<4 vs ≥4), baseline relapse rate, and age (<40 vs ≥40). †Based on Cox proportional hazards model, adjusted for baseline EDSS (<4 vs ≥4), age (<40 vs ≥40), baseline relapse rate, and baseline gadolinium-enhancing lesions (presence vs absence). ‡Defined as ≥1·0 point increase on the EDSS from a baseline EDSS ≥1·0 sustained for 12 weeks or at least a 1·5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks. §Based on Cox proportional hazards model, adjusted for baseline EDSS and age (<40 vs ≥40 years). ¶Intention-to-treat population with at least one post-baseline lesion on MRI scan. ||Data after patients switched to alternative multiple sclerosis drugs were deemed missing; all missing data were imputed on the basis of previous visit data assuming a constant rate of lesion development. 18 participants in the placebo group, 23 in the every 4 weeks group, and 18 in the every 2 weeks group had imputed data. **Based on negative binomial regression analysis, adjusted for region and baseline T2 lesion number

4.2.11 ATTAIN extension study

No non-RCTs of relevance were identified. However, data from an extension of the ADVANCE trial (ATTAIN[3]) were included in the CS. Overall, of the 1512 patients randomised in ADVANCE, 1076 (71%) continued treatment in ATTAIN[3] (376 received continuous, and 171 received delayed treatment with pegIFNβ-1a Q2W).

The proportion of the people in year 2 of ADVANCE Q2W group contained 376 subjects who received continuous pegIFNβ-1a Q2W, and 171 who received delayed treatment with pegIFNβ-1a Q2W, which equates to 73.9% (547 subjects out of 740). The slight variation in the percentages (71% overall versus 73.9% in the continuing group) represents the loss in the denominators of the continuing group (the 740) of the 44 patients in the placebo group who withdrew before entering year 2 of ADVANCE, so this is not an ITT population. In the clarification response to question A6, the ATTAIN population is referred to as "*the ITT population for the patients who entered this extension study*". However, the ERG do not consider this to be the ITT population. It is unclear to the ERG as to how reliable the estimates presented in ATTAIN are, for example the ARR by the end of year 5 in ATTAIN is based on only pegIFNβ-1a Q2W, which represents 185 subjects from the original 547 starting ATTAIN (33.8%) (and pegIFNβ-1a Q4W 170 subjects of the original 529 starting ATTAIN [32.1%]) (CS Document C, pg.425).

The primary outcome of ATTAIN reached statistical significance. Over years 0-6, the adjusted ARR was significantly improved in the continuous pegIFNβ-1a every-2-weeks group compared with the continuous every-4-weeks group (0.188 versus 0.263; P=0.0052). Year-over-year adjusted ARRs were generally reduced in the every-2-weeks group, shown in Figure 2 of Newsome et al., 2018, the trial publication.[3]

4.2.12 Safety (adverse events)

The CS provides an overview of safety related to pegIFNβ-1a (Document B, B.2.10.2. pg.91 and Table 19 pg.92), which was assessed in four studies, including the ADVANCE study,[2] the extension study (ATTAIN[3]), a 1-year phase III study to assess patients switching from a non-pegylated IFNβ to pegIFNβ-1a, with focus on flu-like symptoms (ALLOW[48]) and a

pharmacokinetic study to compare the incidence and frequency of AE (injection-site reactions and flu-like symptoms) on 30 healthy patients receiving pegIFNβ-1a or IFNβ-1a 44 mcg (COMPARE[49]) (CS Document B, B.2.10). In ALLOW[48] the majority of patients (89.6%) who switched to pegIFNβ-1a from their previous IFNβ therapy did not experience new/worsening flu-like symptoms over 8 weeks. In COMPARE[49] injection-site reactions were the most common AE reported with both treatment arms, most treatment-emergent AE were mild and overall incidence was similar between treatment groups. The CS reports safety data from the ADVANCE trial and the ATTAIN extension trial.

The CS does not specify the population for which it reports AE data for the ADVANCE trial. However, the ERG note that the CSR (Section 12, pg.255) states that [redacted] The safety data from the ADVANCE year 1 and 2 is summarised in Table 9.

Table 9. Summary of adverse events in ADVANCE trial Year 1 and year 2

	ADVANCE year 1 [a]		ADVANCE year 2[b]		ATTAIN[c]	
Event, %	pegIFNβ-1a Q2W group n=512	Placebo n=500	pegIFNβ-1a Q2W group n=740, including those re-randomised from the placebo group	pegIFNβ-1a Q4W group n=728	pegIFNβ-1a Q2W group n=547	pegIFNβ-1a Q4W group n=529
≥ 1 adverse event	94%	83%	94%	94%	87%	89%
≥ 1 moderate or severe adverse event	66%	57%	70%[d]	71% [d]	NA	NA
≥ 1 severe adverse event	18%	11%	21%	20%	73%	74%
≥ 1 serious adverse event	11%	15%	16%	22%	16%	21%
≥ 1 treatment-related adverse event	90%	53%	90%	88%	73%	76%
Discontinuation due to adverse events	5%[a]	1%	6% [c]	6% [c]	5%	3%
Withdrawal due to adverse events	5%	1%	6%	6%	4%	3%
Death	<1%	<1%	<1%	<1%	NA	NA
Common adverse events						

Injection-site erythema	62%	7%	64%	59%	41%	42%
Influenza-like illness	47%	13%	51%	50%	43%	44%
Pyrexia	45%	15%	43%	41%	24%	28%
Headache	44%	33%	42%	41%	29%	29%
Myalgia	19%	6%	19%	19%	12%	12%
Chills	17%	5%	17%	17%	11%	13%
Injection-site pain	15%	3%	17%	14%	6%	7%
Injection-site pruritus	13%	1%	15%	11%	6%	5%
Back pain	12%	11%	12%	12%	10%	10%
Arthralgia	11%	7%	11%	13%	10%[g]	9%[g]
Fatigue	10%	10%	12%	10%	10%	7%
Pain in extremity	9%	10%	10%	10%	10%[g]	10%[g]
Nausea	[redacted]	6%[d]	10%	9%	NA	NA
Overall infections	33%	39%	[redacted]	[redacted]	NA	NA

[a]Data from Table 3, Calabresi et al 2014,[2] p6
[b]Data from Table 2, Kieseier et al 2015, p1033,[41] except where noted
[c]Data from CS Table 22, p96
[d]Data from CS Document B, Table 19 p92
[redacted]
[g]Data from Table Table 2, Newsome 2018,[3] p5

The CS reports that overall and treatment-related AE in year 1 (ADVANCE) were higher in the Q2W group than the placebo group (CS Document B, pg.93), and that rates in the Q2W groups were similar in year 2 to those in year 1 (CS Document B, pg.94). In the ADVANCE trial, any AE were experienced in 94% of patients in the pegIFNβ-1a Q2W arm and 83% in the placebo arm.

Adverse events in year 2 of ADVANCE were reported for 740 people on the Q2W regimen (the original 512 plus the 228 transferring from placebo) (CS Document B, Table 16 pg.94). Any SAE (including MS relapse) were experienced by 11% in the Q2W group and 15% in the placebo arm in year 1, and by 16% of those in the Q2W group in year 2. Treatment discontinuations due to AE in the treatment arms were the same in years 1 and 2, 5% in the pegIFNβ-1a Q2W group and 1% in the placebo arm in year 1, and 6% in the Q2W group in year 2 (see Table 9).

The company included the following AE in their economic analysis (see Section 5.3.11.5): arthralgia, back pain, fatigue, gastroenteritis, headache, immune thrombocytopenic purpura,

influenza-like illness, injection-site reaction, erythema, injection-site reaction-pain, injection site reaction, pruritus, meningitis listeria, nasopharyngitis, progressive multifocal leukoencephalopathy, pneumonia/urinary tract infection, and pyrexia. The ERG clinical experts consider other clinically important AE to be liver disturbance (clinical or biochemical, such as liver alanine aminotransferase (ALT) or other liver function change), and depression.

The ERG note that the company did not report AE related to liver disturbance or depression in the CS. The CSR states that, in year 1 (ADVANCE), [redacted] of subjects in the QW2 and placebo arms experienced a [redacted] and less than [redacted] (CSR Table 64, pg.327). In year 2, [redacted]-related AE were experienced by [redacted] of participants, both those who switched from placebo to receiving treatment in year 2, and those who received continuous treatment; there were no subjects reported as experiencing [redacted] (CSR, Table 317, pg.2750).

The company reports the most common AE (those with an incidence >=10% in the intervention arm) as flu-like symptoms and injection-site reactions, and that they were mild or moderate in severity (CS Document B, pg.91). It states that these AE led to discontinuation of treatment in less than 1% of study participants, and that they decreased after the first 2 years of treatment based on results of the non-placebo-controlled extension trial (ATTAIN).[3] Discontinuation due to any AE occurred in around 3% of participants (see Table 9).

The company reports that less than 1% of patients (4 in treatment arm, 1 in placebo arm) tested positive for IFN-neutralising antibodies in year 1 of the trial (CS Table 20, p92). The number of deaths among study participants was not reported in the CS. However, the ERG note that the CSR (pg.274) reported [redacted] among all participants, including those in the 4-week treatment group, none of which the investigator considered related to the treatment.

The rates of AE were generally similar between treatment and placebo, with the exception of treatment-related AE: 90% of the pegIFNβ-1a (2-week) group had at least 1 compared to only 53% of the placebo group. The ERG confirmed with the clinical experts that this type of AE is expected in this type of trial, and that injection related AE are "*very common but mild*".

The trial publication for ATTAIN provided the incidence of AE and SAE in patients who received pegIFNβ-1a at any time during ADVANCE and ATTAIN.[3] For clarity, the ERG have combined the reported incidence with that in ADVANCE in Table 10.

Table 10. Comparison of incidence of AEs and SAEs in ADVANCE and ATTAIN adapted from adapted from CS Document B, Table 19 (pg. 92)

Event	AE and SAE n(%)			
	Advance Year 1		ADVANCE Year 2	Attain Years 3-6
	Placebo group (N=500)	pegIFNβ-1a every 2 weeks group (n=512)	pegIFNβ-1a every 2 weeks group (n=740)	ATTAIN pegIFNβ-1a every 2 weeks group (n=547)
Any AE	417 (83%)	481 (94%)	699 (94%)	478 (87%)
All SAEs	76 (15%)	55 (11%)	120 (16%)	90 (16%)
Severe AEs	53 (11%)	90 (18%)	152 (21%)	73 (13%)
Treatment-related AE	266 (53%)	459 (90%)	668 (90%)	399 (73%)
Discontinuation of treatment due to AE	7 (1%)	25 (5%)	41 (6%)	26 (5%)

The ERG note the numerically higher proportion of events in the ADVANCE trial compared to ATTAIN and compared to placebo in year 1. Adverse events in year 2 of the ADVANCE study were reported for 740 people on the Q2W regimen (the original 512 plus the 228 transferring from placebo) (CS Document B, Table 16 pg.94).

4.2.12.1 Ongoing observational study

In the CS Document B, B.2.11 page 99-100, the company refer to an ongoing study "*The Plegridy Observational Programme*".[50] The CS Document B, Figure 31, presents the proportion of patients switching from pegIFNβ-1a to another DMT due to "*adverse events or lack of efficacy*". During clarification, the ERG requested further details on "*the reasons for patients switching treatment because of AE or lack of efficacy. For example, discontinuation by type of AE/SAE or because of problems with adherence or patient choice etc*". The ERG considered this information important for determining potential reasons for discontinuation due to AE and all cause discontinuation in a real world setting. In response to clarification question (A15b) the company stated that "*these broad categories (adverse events/lack of efficacy) were selected by study investigators from a pre-specified list of reasons for discontinuing pegIFNβ-1a in the CRF; therefore, no additional data are available regarding additional details on the reasons for discontinuing pegIFNβ-1a and switching to another DMT*". Therefore, no further information is available to the ERG to assess potential reasons for discontinuation from pegIFNβ-1a.

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

The CS SLR identified 27 studies that were eligible for inclusion in indirect and mixed treatment comparisons of at least one outcome. The search strategy is shown in CS Document C, Appendix D, page 4; the inclusion criteria in CS Document C, Table 22 page 30. The ERG consider the methods of searching, inclusion/exclusion and data extraction largely appear appropriate (see Section 4.1.2). The ERG noted discrepancies in reasons for exclusion compared to those presented in the CS. In Table 1A of Appendix A the ERG provides a comparison of included studies with the included studies listed in CS Document B, Table 16 "*for the primary and secondary outcomes*" and CS Document C, any discrepancies are discussed.

4.3.1.1 Trials included for comparisons of at least one outcome

The CS included 32 studies reported in 561 publications which are presented in CS (Document C Table 26, pg.39-74). Five studies reported no relevant outcomes (CS Document B Table 15, pg.68), leaving 27 with relevant outcomes. Quality assessments of the trials included in the MTCs were not provided in CS Documents B or C, only in the Biogen Data Extraction excel spreadsheet dated August 2018 (CS Reference pack C). The ERG conducted quality assessment of all trials included in the MTC (see Table 2B in Appendix B). The assessments were mostly similar although with some exceptions. Of note, more information is now available for some studies, for example, a full paper has now been published for the APEX trial[51] allowing a more thorough examination of study quality than was possible using only the previously published abstracts. The identified trials listed in the CS were: ADVANCE,[2] APEX,[51-53] BEYOND,[54] Boiko 2017,[55] Bornstein 1987,[56] BRAVO,[57] Calabrese 2012,[58] CAMMS223,[59] CARE MS-I,[60] CARE MS-II,[61, 62] CombiRx,[63] CONFIRM,[64] Copolymer I study,[65] Crentsil 2012,[66] DEFINE,[67, 68] Etemadifar 2006,[69] EVIDENCE,[70] GALA,[71] GLOW,[72] IFNB Multiple Sclerosis Study,[73] INCOMIN,[74] Mokhber 2014,[75] Mokhber 2015,[76] MSCRG,[77] O'Connor 2006,[78] OPERA I,[79, 80] OPERA II,[79, 81] PRISMS,[82] REGARD,[83, 84] TEMSO,[85, 86] TENERE,[87] and TOWER.[88] Six further ongoing studies were identified and presented in CS Document C Table 27 page 74 (109MS305/NCT01838668,[89] ABOVE,[90] DELIVER-MS,[91] Khan 2008,[92] Khan 2009,[93] and PLENO.[94])

4.3.1.2 Direct evidence

The ERG consider that only one source of direct evidence was available. This is the ADVANCE trial described in the CS, which compared 1 year of pegIFNβ-1a 125 mcg Q2W versus placebo.[2]

4.3.1.3 Mixed Treatment Comparisons

Mixed-treatment comparison was performed using a Bayesian approach (CS Document B, pg.66 [see Section 4.4.1.3 for a review of the methods of statistical analysis in the MTC]). A more in-depth description of the MTC methods, analysis and results (compared to the CS Document A, B, C) was provided in The Biogen Full Report and The Biogen Full Report Appendices. These two documents have not previously been published, data from The Biogen Full Report and The Biogen Full Report Appendices have been provided to the ERG for this appraisal.

Only DMTs with a positive reimbursement decision for patients with RRMS that was not highly active or rapidly evolving severe by NICE were included in the MTC (CS Document B pg.65). This appears acceptable and in line with the CS decision problem described in Section 3.

After excluding five studies for no relevant outcomes (CS Document B Table 15, pg.68), there appear to be 23 studies for ARR and 11 or 12 studies for CDP3M and CDP6M (CS Document Table 16 pg.69). The ERG note that 12 studies were included in the network for CDP3M (ADVANCE,[2] BEYOND,[54] BRAVO,[57] CAMMS223,[59] CONFIRM,[64] DEFINE,[67] EVIDENCE,[70] OPERA I,[79] OPERA II,[79] PRISMS,[82] TEMSO,[85] TOWER[88]) (CS Document B on p80) and 13 studies were included in the network for CDP6M (ADVANCE,[2] BRAVO,[57] CAMMS223,[59] CARE MS-I,[60] CARE MS-II,[61, 62] CONFIRM,[64] DEFINE,[67] EVIDENCE,[70] OPERA I,[79] OPERA II,[79] PRISMS,[82] TEMSO,[85] TOWER[88]) (CS Document B, on p82).

The ERG consider this to be an error in CS Table 16 (CS Document B) where TEMSO[85] is stated to have no data for CDP6M. However, this trial is included in the MTC displayed on CS Document B page 82, and it looks as though the "✓c" for TOWER[88] for CDP3M and CDP6M should both be "✓" in CS Table 16. The ERG noted additional discrepancies regarding the inclusion of excluded studies in CS Table 16, which were confirmed in clarification response A10.

4.3.1.4 Outcome selection reported in the MTC

The NICE final scope[1] listed the outcomes which should be considered (see Section 3): the ERG notes that ARR (n=23 studies CS Document B, pg.67; network on pg.78), CDP3M (n=12 studies; CS Document B, network on pg.80) and CDP6M outcomes (n=13 studies; CS Document B, network on pg.82) were combined in meta-analysis, but not relapse severity, NEDA, mortality or safety.

In CS Document B, Table 1 page 15, the company states that the CS addresses the outcomes as per the NICE final scope, but some outcomes (severity of relapse, symptoms, and freedom from disease activity) could not be assessed in an MTC due to lack of comparative data or heterogeneous definitions or scales.

The ERG consider most of the outcomes to be clearly defined, however "*freedom from disease activity*" (CS Document B, Table 1 pg.15) may be measured in many ways, for example changes in the number or volume of brain/CNS T1, T2, Gd+ lesions or black holes on MRI (CS Document B, pg.22). The CS also suggest the composite outcome "*NEDA",* defined as: "*disease stability that compromises no new relapses, no disability progression, and no new or enlarging MRI lesions. Clinical NEDA is defined as no evidence of relapses and onset of CDP, while MRI NEDA is defined as no evidence of Gd+ lesions and no new/newly enlarging T2 lesions*" (CS Document B, pg.22).

The ERG notes that clinical NEDA and MRI NEDA are not necessarily correlated, see CS Document B, Figure 24 page 86 for example. Clinical NEDA over 2 years in matched patients treated with pegIFNβ-1a was 56.0% versus GA versus 55.1% (P=0.762) but the MRI NEDA in the two groups was 27.5% versus 16.4% (P=0.014).

4.3.1.5 MTC results for the primary outcome: Annualised Relapse Rate

ARR was analysed based on MTC of treatment differences using the RR as the effect estimate. The RR is an annualised measure; therefore, the company "*considered it reasonable to combine data across multiple time points for this outcome*" (CS Document B, pg.66).

For ARR (CS Document B, pg.79), the company states the following:

- "*The RR for pegIFNβ-1a was numerically decreased compared with IM IFNβ-1a 30 mcg once weekly (QW) or teriflunomide; however, these differences were not statistically significant."*
- *"PegIFNβ-1a demonstrated a statistically significant increase in RR relative to alemtuzumab or ocrelizumab. The RR for pegIFNβ-1a was also numerically increased compared with DMF; however, these differences were not statistically significant."*
- *"There was no difference in the RR (RR, ≥ 0.9 and ≤ 1.1) for patients receiving pegIFNβ-1a compared with IFNβ-1a 44 mcg, IFNβ-1b, GA 20 mg, or GA 40 mg."*

The ERG note that as the credible intervals (CrL) for the majority of comparisons overlap, it would be more accurate to state the ARR was statistically significantly higher for pegIFNβ-1a than alemtuzumab or ocrelizumab, and statistically significantly lower than placebo. And that there were no significant differences between the ARR for pegIFNβ-1a and any of the other treatments (see [redacted]).

The Biogen Plegridy Full Report Appendices document (Appendix 7, Figure 1, pg.220) shows the ARR for each intervention versus placebo, which is helpful for comparison and therefore is reproduced in [redacted]

The Biogen Plegridy Full Report Appendices document (pg.266) reports the sensitivity analysis to assess the impact of using a random effects model versus a fixed effects model on the MTC for ARR (which showed similar effects). The ERG note that in The Biogen Plegridy Full Report a high heterogeneity in the comparison of GA 20 mg qd versus placebo was observed (I^2 = 86%). This was also noted in Melendez-Torres et al., 2017[6]. This related to one study, Bornstein 1987[56] which appears to be the outlier in this analysis, as the RR from this study does not overlap with the confidence intervals of the other two included studies (pg.260). The Biogen Full Report Appendices conducted a sensitivity analysis excluding the Bornstein 1987 study (Table 33, pg.274-275). The sensitivity analysis in the MTC for the ARR combined network excluding Bornstein 1987, the between-trial standard deviation in the sensitivity analysis. The Biogen Full Report Appendix 11 (pg.260) stated that

A surface under the cumulative ranking curve (SUCRA) diagram was not presented in the CS to summarise the results of the ARR MTC. This was requested at clarification. Clarification response A10c (Table 10) provided a table of ranking for ARR, as reproduced below in . ARR results for pegIFNβ-1a are in bold.

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9	Rank10	Rank11
Alemtuzumab 12 mg qd	[redacted]										
Ocrelizumab 600 mg q24w	[redacted]										
DMF 240 mg bid	[redacted]										
PEG IFN beta-1a 125 mcg q2w	[redacted]										
GA 40 mg tiw	[redacted]										
IFN beta-1b 250 mcg qad	[redacted]										
GA 20 mg qd	[redacted]										
IFN beta-1a 44 mcg tiw	[redacted]										
IFN beta-1a 30 mcg qw	[redacted]										
Teriflunomide 14 mg qd	[redacted]										
Placebo	[redacted]										

[redacted]

Presenting the results of a MTC in a way that can be understood requires the prestation of the sets of relative effects between all pairs of interventions. Ranking tables (such as [redacted]) are based on the ranking probabilities, which describe the probabilities for each treatment to be placed at a specific ranking position (rank 1, rank 2, rank 3 etc) in comparison with all other interventions.[95] The ERG consider the presentation of ranking tables alone to summarise intervention efficacy generated from MTC misleading, as ranking probabilities have a degree of uncertainty. Rankings based on SUCRAs account better for the uncertainty in estimated treatment effects.[95] SUCRAs are conditional on the set of treatments being compared which means SUCRAs and rankings will change if a subset of the treatment are compared. Ranking tables are not a substitute for relative treatment effects and they cannot be interpreted clinically.

Considering the above, the ERG note that the Biogen Plegridy Full Report Appendices document (Table 25, pg.267) presents the results for ARR for all pairwise comparisons (random effects). Table 25 displays the results of a sensitivity analysis which was carried out in the Biogen Plegridy Full Report Appendices to assess the impact of using a random effects model versus a fixed effects model in the MTC. However, the ERG have reproduced it in [redacted] to allow for visual comparison of pegIFNβ-1a ARR to other interventions included in the MTC, ARR results for pegIFNβ-1a are in bold.

[redacted]

	IFN beta-1a 30 mcg qw	IFN beta-1a 44 mcg tiw	**PEG IFN beta-1a 125 mcg q2w**	IFN beta-1b 250 mcg qad	GA 20 mg qd	GA 40 mg tiw	Teriflunomide 14 mg qd	DMF 240 mg bid	Alemtuzumab 12 mg qd	Ocrelizumab 600 mg q24w
IFN beta-1a 30 mcg qw		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a 44 mcg tiw	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEG IFN beta-1a 125 mcg q2w	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1b 250 mcg qad	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA 20 mg qd	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA 40 mg tiw	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg qd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
DMF 240 mg bid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Alemtuzumab 12 mg qd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Ocrelizumab 600 mg q24w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.3.1.6 MTC results for the secondary outcomes: CDP3M and CDP6M

In CS Document B (pg.66) the company states that "*CDP3M and CDP6M were typically reported as an HR for the risk of experiencing disability progression. The analysis for this outcome was based on MTC of treatment differences using the HR as the effect estimate at 24 months follow-up. To achieve a comparison with pegIFNβ-1a … 11 month data from ADVANCE and 18- and 24-month data for comparator treatments were pooled for CDP3M and CDP6M outcomes. This limited the accuracy of the comparison but without combining data from different time points, comparative effectiveness would not be possible*." The ERG note a similar comment in Document A, page 26, which adds: "*Thus, the results should be interpreted with caution*." The ERG consider this pooling acceptable for the purposes of the analysis (see Section 4.4.1.3 for a critique of the MTC statistical methods).

Results of the MTC are reported for CDP3M in CS Document B, B.2.9.3.2. The CS reports results of pegIFNβ-1a compared with all other treatments in the network, and concludes that there

were no statistically significant differences. Results of the MTC are reported for CDP6M in CS Document B, B.2.9.3.3.

For CDP3M (CS Document B, pg.81), that company states the following:

- "*The risk of CDP3M was numerically decreased in patients receiving pegIFNβ-1a compared with those receiving IM IFNβ-1a 30 mcg, IFNβ-1b, GA 20 mg, or placebo; however, these differences were not statistically significant."*
- *"The risk of CDP3M was numerically increased for pegIFNβ-1a compared with either alemtuzumab or ocrelizumab; however, these differences were not statistically significant."*
- *"There was no difference in the risk of CDP3M (HR ≥ 0.9 and ≤ 1.1) in patients receiving pegIFNβ-1a compared with IFNβ-1a 44 mcg, IFNβ-1a 22 mcg, teriflunomide, or DMF. Indirect (Bucher) and direct meta-analyses are presented in Appendix L."*

As the 95% credible intervals for all comparisons overlap, the ERG consider it would be more accurate to present the initial conclusion as MTC analysis demonstrated that there were no statistically significant differences in the risk of disability progression confirmed after 3 months for patients treated with pegIFNβ-1a compared with all other treatments in the network.

For CDP6M (CS Document B, pg.81), that company states the following:

- "*The risk of CDP6M was numerically decreased in patients receiving pegIFNβ-1a compared with those receiving IM IFNβ-1a 30 mcg, IFNβ-1a 44 mcg, GA 20 mg, DMF, teriflunomide, or placebo; however, this difference was only statistically significant against placebo."*
- *"The risk of disability progression was numerically increased for pegIFNβ-1a compared with alemtuzumab and ocrelizumab; however, these differences were not statistically significant. Indirect (Bucher) and direct meta-analyses are presented in Appendix L*."

As the 95% credible intervals for all comparisons overlap, the ERG consider it would be more accurate to present the initial conclusion as there were no statistically significant differences in the risk of CDP6M for patients treated with pegIFNβ-1a compared with all other treatments in the network.

The ERG note that the Biogen Plegridy Full Report Appendices document (Appendix 7, Figure 2, pg.221) shows the CDP3M for each intervention versus placebo, and Figure 3, pg.222 for CDP6M, which are helpful for comparison and therefore reproduced by the ERG below in [redacted] and [redacted].

bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly

bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly

The Biogen Plegridy Full Report Appendices document (pg.284) reports the sensitivity analysis to assess the impact of using a random effects model versus a fixed effects model, and the choice of prior distribution, on the MTC for CDP3M, with similar results between the analyses. The ERG note that for CDP6M, the relative effects for all treatment comparisons were similar in the random effects and fixed effects models (The Biogen Plegridy Full Report, pg.304), and for alternative prior distributions (The Biogen Plegridy Full Report, pg.304).

The CS Document B, page 126 states that "*For the base case, CDP6M was implemented as this is considered a more robust outcome (indicative of permanent disability progression) than CDP3M (which can be influenced by relapse activity)"* (for further discussion of the company's economic analyses see Section 5.1.1.1). The results presented for CDP3M and CDP6M are numerically similar (as can be seen in [redacted] and [redacted]). Noticeable differences in HR estimates between CDP 3 and 6 months were in:

[redacted]

4.3.1.7 CS MTC comparison to MTCs in ID527

To enable external comparison, the ERG compared the MTCs presented in this CS with the MTC conducted by the assessment group for ID527[4], which was undertaken as part of a Multiple Technology Appraisal (MTA), found in Melendez-Torres et al 2017[6] (CS Document B, pg.81). The ERG thought this comparison to be useful since ID527,[4] (which targeted all available beta-interferon, including pegIFN, and GA) was conducted recently.

The interventions included in the CS MTC for ARR (CS Document B, B.2.9.3.2 pg.80), CDP3M and CDP6M are displayed in Table 11. Differences in the trials included for the three outcomes were investigated by the ERG. Based on visual inspection of network plots for ARR, CDP3M, and CDP6M, the ERG have noted a number of differences within the IFN beta and GA comparisons. Noticeably, trials reporting IFN beta-1a 22ug SC tiw were not included in the CS MTC for ARR, or The Biogen Plegridy Full Report. However, they were included in the MTC in ID527.[4]

Table 11. Comparison of MTC in ID527[4] reported in Melendez-Torres et al 2017[6] and MTCs in the CS

Intervention	MTC in ID527[4]			MTC in CS		
	ARR	CDP3M	CDP6M	ARR	CDP3M	CDP6M
Placebo	Y	Y	Y	Y	Y	Y
GA 20mg qd	Y	Y	Y	Y	Y	Y
pegIFNβ-1a 125 mcg	Y	Y	Y	Y	Y	Y
GA 40mg tiw	Y	N	N	Y	N	N
IFN beta-1a 44mcg tiw	Y^	Y	Y	Y	Y	Y
IFN beta-1b 250 mcg qad	Y	Y	Y	Y	Y	N
IFN beta-1a 22ug SC tiw	Y	Y	N	N	Y	N
IFN beta-1a 30mcg qw	Y	Y	Y	Y	Y	Y+
Alemtuzumab	*	*	*	Y	Y	Y
Dimethyl fumarate	*	*	*	Y	Y	Y
Teriflunomide	*	*	*	Y	Y	Y
Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	*	*	*	Y	Y	Y

Grey shading = difference between outcomes included in the two reports of MTCs
*intervention not included in ID527 appraisal[4], not appropriate for comparison.

+One trial MSCGR 1996,[77] for IFNβ-1a 30 mcg QW was not included in CDP6M in the CS, but was included in ID527[4] MTC for this outcome, through the estimation of HR from the reported RR
^One trial PRISMS,[82]published a post-hoc analysis in 2018 providing the HR for CDP6M in IFN beta-1a 44mcg tiw. This was not included in the MTC in the ID527[4] which was performed in 2016.

The ERG note that PRISMS 1998[82] reporting IFN beta-1a, reported mean relapses per patient over 2 years, and percentage relapse-free over 1 year and over 2 years. The MTC in ID527[4] reported the proportions of patients who were free of relapse (pg.57) and calculated ARR from this (Melendez-Torres et al 2017[6] Figure 5).

The IFN beta-1a 22mcg SC tiw data from PRISMS were included in the CDP3M network CS Document B page 80. The company included PRISMS[82] for the IFN44 versus placebo comparison for CDP6 while the Melendez-Torres et al 2017[6] did not. The ERG have checked that the source of evidence for CDP6M in PRISMS, and noted that a paper was published in 2018 reporting this outcome from a post-hoc analysis. Since ID527 accounted for evidence up to year 2016, PRISMS was not included for the CDP6M MTC which informed ID527[4].

A second difference was the exclusion of IFN beta-1b 250 mcg qad from CDP6M presented in the CS Document B, C or the MTC presented in The Biogen Plegridy Full Report Appendices document, Appendix 7, Figure 3, p222. The ERG considered this difference potentially important due to CDP6M informing the base case in the cost-effectiveness model (see Section 5.1.1.1).

The ERG found that IFN beta-1b 250mcg qad was reported in Etemadifar 2006[69] (but this study did not report CDP6M), the IFNB MS study[73] (but this study did not report CDP6M) and INCOMIN 2002[74]. Durelli et al., 2002 (INCOMIN)[74] included "*Progression in EDSS score of 1 point sustained for 6 months and confirmed at end of study*", which is a slightly different definition of outcome and not technically the same as only being confirmed at 6 months. However, during clarification, the ERG noted that "*INCOMIN 2002[74] reports the rate ratio for this outcome (CDP6M) for interferon beta-1b 250 mcg alternate days (information can be found in Melendez-Torres et al 2017[6]) and asked for clarification for the rationale for not calculating the hazard ratio from the reported rate ratio*". The company response to this clarification question (A9a) stated that "*there is no suggestion of assuming rate and hazard ratios are equivalent and can be included in the same analysis. Therefore, we did not include INCOMIN[74] in the CDP6M network*". The ERG agree that RR and HR cannot be assumed to be equivalent. However, the Melendez-Torres et al 2017[6] publication derived the HR from the RR using a

method which is reported in the monograph. Since the MTA and the present STA have been undertaken by the same TAR team, the ERG was able to verify that the HR for CDP6M was not reported in INCOMIN 2002,[74] however, as part of the MTA, the ERG was able to calculate the HR based on the number of patients with progression and the total number of patients.

Nevertheless, in clarification response A9b, the company did provide an updated MTC which includes INCOMIN 2002.[74] However, the sensitivity analyses provided did not derive HR from RR as requested in clarification, and instead used the reported RR. Clarification response A9b, Figure 4 presented the results of a sensitivity analyses which allowed for inclusion of IFN beta-1a 250 mcg qad for the CDP6M outcome, via the inclusion of INCOMIN 2002[74] trial, reporting RR. This is reproduced in [redacted] for completeness. The inclusion of IFN beta-1a 250 mcg qad in the CDP6M network numerically changed the HR estimates and credible intervals of other interventions compared to pegIFNβ-1a 125 mcg by a small amount, but did not generate any statistically significant changes. The ERG do not consider this informative due to the inclusion of RR not derived HR.

bid = twice daily; DMF = dimethyl fumarate; pegIFNβ-1a = pegylated interferon β-1a; q24w = once every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly

A similar consideration can be made regarding publications reporting the MSCGR 1996 trial,[77] for IFNβ-1a 30 mcg QW. The publication reports rates of people with CDP6M, not HR. The ERG consider it possible to include this study for CDP6M, and to derive an estimated HR from the RR (as with INCOMIN 2002). The ERG note that IFNβ-1a 30 mcg QW could be compared to placebo using BRAVO (as reported in the CS Document B, Figure 18 pg.82) but also using MSCGR 1996, which was excluded for CDP6M, as stated in CS Document B, Table 16, page 69.

In the Biogen Plegridy Full Report section 6.3, page 124, the authors have compared its MTC with other recently published MTCs, which includes that undertaken as part of the MTA (ID527[4]). The analysis made by the company to explain the potential discrepancies across MTC is reasonable, this includes a comment on the analysis methods to derive HR based on the number of patients with progression and the total number of patients.

For completeness and to allow for external comparison with results that were used for decision making by NICE recently, the ERG have reported the main results from the MTC undertaken as part of the MTA (reported in Melendez-Torres et al 2017[6]) for ARR, CDP3, and CDP6 within beta-interferons and GA (see Table 12) (see Section 6.2.3)

Table 12. Primary and secondary outcome results comparison from CS MTC and MTC in Melendez-Torres et al 2017[6]

Drug vs. placebo	ARR		CDP3M		CDP6M	
	CS Doc B, Table 36 pg. 127 (CrL)	**MTA[6] Table 8 pg.72 (95% CI)**	**CS Doc B, Table 34 pg. 126 (CrL)**	**MTA[6] Table 12 pg.81 (95% CI)**	**CS Doc B, Table 34 pg. 126 (CrL)**	**MTA[6] Table 13. pg.83 (95% CI)**
IFNbeta 1a 30	[redacted]	0.80 (0.72, 0.88)	[redacted]	0.73 (0.53, 1.00)	[redacted]	0.68 (0.49, 0.94)
IFNbeta 1a 44	[redacted]	0.68 (0.60, 0.76)	[redacted]	0.63 (0.46, 0.86)	[redacted]	0.47 (0.24, 0.93)
IFN beta 1b 250	[redacted]	0.69 (0.62, 0.76)	[redacted]	0.78 (0.59, 1.02)	[redacted]	0.34 (0.18, 0.63)
GA 20mg	[redacted]	0.65 (0.59, 0.72)	[redacted]	0.76 (0.60, 0.97)	[redacted]	0.82 (0.53, 1.26)
pegIFNβ-1a	[redacted]	0.64 (0.50, 0.83)	[redacted]	0.62 (0.40, 0.97)	[redacted]	0.46 (0.26, 0.81)

N/A = not applicable, CrL= credible interval, 95% CI = confidence interval

4.3.1.8 MTC and indirect comparison results for additional outcomes

The CS Document B (Table 18, pg.91) provides key efficacy and safety outcomes of pegIFNβ-1a relative to all other treatments, including mortality, any AE, any SAE and treatment discontinuation due to any cause. The Biogen Plegridy full report appendices reports meta-analyses for NEDA (pg.230), mortality (pg.231), any AE (pg.233), any SAE (pg.234), treatment discontinuation due to any cause (pg.237) and treatment discontinuation due to AE (pg.238). These are discussed below:

4.3.1.9 No Evidence of Disease Activity

NEDA had only two studies, one comparing placebo to pegIFNβ-1a 125 mcg Q2W[2] and one comparing placebo to GA 40 mg tiw.[71] No MTC was conducted, instead the company conducted an indirect comparison using Bucher's method (with placebo in common). The CS Document C (pg.451) states that "*pegIFN beta-1a increased NEDA compared to GA 40 mg tiw, and this difference was statistically significant*." Later, in Table 113 (CS Document C) a HR for pegIFN beta-1a 125 mcg q2w of [redacted] versus GA 40 mg tiw is reported. This suggests that treatment [redacted] pegIFN beta-1a. However, the Biogen Plegridy Full Report document (pg.121) states that "[redacted] It is therefore unclear the direction of benefit between the two drugs.

The GALA[71] study does not refer to NEDA, nor does the Biogen Report indicate what is being referred to as NEDA so the ERG is not able to identify whether the report or the appendices are correct. Results of a direct comparison of pegIFNβ-1a 125 mcg Q2W versus placebo for the ADVANCE study[2] are presented (CS Document C, Table 112 pg.451), with an OR of 2.89 (95% CI 1.11,2.15). The ERG notes that clinical NEDA and MRI NEDA are not necessarily correlated (see Section 4.3.1.4). The ERG therefore questions how useful this composite outcome is.

4.3.1.10 Mortality

The MTC for mortality (n=3 studies) was described narratively (CS Document C, pg.452). There were 12 studies that could not be included in the network because they did not report mortality data. The ERG confirm that there were no usable 12-month mortality data in the 12 studies. The ERG note the MTC confidence intervals were very wide (see CS Document C, Figure 13), presumably due to few events (e.g., 0.2% [1/512] with pegIFNβ-1a 125 mcg Q2W died after 11 months of follow-up versus 0.4% [2/500] with placebo in ADVANCE). The CS Document C page 452 reports numerically changed differences between intervention and placebo which were not statistically significant. The Biogen Plegridy Full Report document (pg.122) states that "[redacted]"

4.3.1.11 Adverse Events

The MTC for AE (n=4 studies) was described narratively (CS Document C, pg.455). The company state that "*heterogeneity in study design and AE reporting was too great to allow pooling of data in an MTC*" (CS Document B, pg.66). In CS Document C page 455 the company report "*no statistically significant differences in the odds of an AE for patients treated with pegIFNβ-1a 125 mcg Q2W compared with all other treatments in the network*".

The Biogen Plegridy Full Report document (pg.122) states that "[redacted]" The Biogen Plegridy Full Report Appendices document (pg.317) states that in sensitivity analyses, the relative effects of all treatments compared to placebo were similar in the random effects and fixed effects models. Odds ratios were similar using alternative prior distributions (pg.317).

Data are available from several other studies for AE (see Table 1A Appendix A), so it is unclear to the ERG why these were not included in the CS.

4.3.1.12 Serious Adverse Events

The MTC for SAE (n=3 studies) was described narratively (CS Document C, pg.457). Any SAE was analysed as a dichotomous outcome based on the proportion of patients who experienced at least one event after 24 months follow-up using odds ratios as the effect measure (CS Document B, pg.66). The company stated that they "*analysed SAE excluding MS relapses where data were available and performed sensitivity analyses of SAE, including MS relapses*"; (CS Document B, pg.66). However, the ERG found no further data on sensitivity analyses for clinical effectiveness were in Documents A, B or C. The CS Document C page 457 states that "*There were no statistically significant differences in the odds of an SAE for patients treated with pegIFNβ-1a 125 mcg Q2W compared with all other treatments in the network*".

The Biogen Plegridy Full Report Appendices document (Table 12, pg.236) provides the data for SAE with and without relapses included, but an OR graph was only presented for the data excluding relapses (Figure 21, pg.234). The Biogen Plegridy Full Report Appendices document (pg.322) states that in sensitivity analyses, the relative effects of all treatments compared to placebo were similar in the random effects and fixed effects models. Odds ratios were similar using alternative prior distributions (pg.322).

Data are available from several other studies for serious AE (see Table 1A Appendix A), so it is unclear to the ERG why these were not included.

4.3.1.13 Treatment discontinuation due to any cause

Treatment discontinuation due to any cause was analysed as a dichotomous outcome based on the proportion of patients who discontinued after 24 months follow-up using ORs as the effect measure (CS Document B, pg.66). The MTC for treatment discontinuation for any cause (n=3 studies) was described narratively (CS Document C, pg.460). In CS Document C, Table 118, the rates of discontinuation of GA (20 or 40mg) are [redacted] different from placebo, whereas those for pegIFNβ-1a 125 mcg Q2W were significantly greater than placebo in CS Document C, Figure 23 page 461. Also, there are data for discontinuation for any cause from several other studies (e.g., all those included in the ARR MTC network) reported in Document C Table 122, pg.464-465, so it is unclear to the ERG why there are not more data available for the MTC for discontinuation for any cause (see Table 1A Appendix A) .

The Biogen Plegridy Full Report document (pg.122) states that "[redacted]" The Biogen Plegridy Full Report Appendices document (pg.327) shows sensitivity analysis results for the fixed and random effect models.

4.3.1.14 Treatment discontinuation due to adverse events

The MTC for treatment discontinuation due to AE (n=2 studies, ADVANCE, GALA) is reported narratively (CS Document C, pg.461). The company states that "*There was heterogeneity in the reporting of discontinuation between studies. One study reported study discontinuation due to AE (ADVANCE) while one study did not specify which definition was used (GALA). Given the heterogeneity between studies and the lack of appropriate data to assess the impact of heterogeneity, we did not consider it valid to perform a quantitative meta-analysis for discontinuation due to AEs*."

Heterogeneity between the studies is discussed (in Section 4.4.1). The ERG reviewed the Khan et al., 2017[96] paper reporting GALA, the authors report discontinuations due to AE at the end of the 1-year placebo-controlled period in Figure 2: 29/943 for GA 40 versus 6/461 for placebo.[96] The ERG assessed these figures using RevMan, and the results suggests that these proportions are not significantly different, whereas in CS Document C, Figure 25, page 462, discontinuations due to AE are significantly higher for pegIFNβ-1a 125 mcg Q2W than placebo, suggesting that, potentially, discontinuation due to AE might be higher for pegIFNβ-1a 125 mcg Q2W than GA 40, if they had been compared. However, comparing the data from The Biogen Plegridy Full Report document page 118, Table 43 in RevMan found no significant difference between the rates of discontinuations due to AE between pegIFNβ-1a 125 mcg Q2W and GA 40. The Biogen Plegridy Full Report document (pg.122) states that "[redacted]"

Similarly to the observation above for discontinuation for any cause, there are data for discontinuation for AE from several other studies (all those included in the ARR MTC network)

reported in CS Document C Table 123, pages 465-466, so it is unclear why there are not more data available for the MTC for discontinuation due to AE (see Table 1A Appendix A).

In addition, Melendez-Torres et al., (2017)[6] conducted pairwise and network meta-analyses of discontinuation because of AE at 24 months in RRMS (pg.87) and included 21 trials (BECOME 2009,[97] BEYOND 2009,[54] Bornstein 1987,[56] BRAVO 2014,[57] CONFIRM 2012,[64] Cop1 MSSG 1995,[65] IFNB MSSG 1995,[73] INCOMIN 2002,[74] MSCRG 1996,[77] PRISMS 1998[82] and REGARD 2008[83]). In the pairwise analysis, almost all individual study estimates and pooled estimates did not suggest that discontinuation was more likely in trial arms corresponding to one drug over another to a statistically significant level. The one exception was 125 μg of SC pegIFNβ-1a every 2 weeks compared with placebo, in which patients receiving the study drug were more likely to discontinue the study because of AE (risk ratio 3.49, 95% CI 1.52,7.99). The network meta-analyses did not offer statistical evidence that any one drug was more likely to result in discontinuation because of AE than any other drug. However, based on SUCRAs, 125 μg of SC pegIFNβ-1a every 2 weeks was ranked highest for risk of discontinuation because of AE (i.e. greatest risk of discontinuation), followed by 44 μg of SC IFN-β-1a three times weekly. Placebo was ranked last.[6]

4.3.1.15 Sensitivity analyses

The company state that "*Sensitivity analyses were conducted using alternative prior distributions for the between-trials SD in networks with fewer than 10 studies*" (CS Document C, pg.34). The CS states that further details of the MTC analysis are presented in Section B.2.10.2 of Document B, however the ERG note that this may be a typographical error as this section describes the safety profile of ADVANCE. The ERG could not find the sensitivity analyses reported in Documents A, B or C, for networks with <10 studies (NEDA, mortality, AE, SAE, discontinuations [all cause or for AE]). However, they are reported in the Biogen Plegridy Full Report Appendices document.

4.3.1.16 Summary of MTC results

The data presented in the CS documents, Biogen Plegridy Full Report and Biogen Plegridy Full Report Appendices document show few differences between pegIFNβ-1a 125 mcg Q2W and

comparators for the primary (ARR) and secondary (CDP3M and CDP6M) outcomes. Key issues for additional outcomes are:

- The lack of clarity about the direction of benefit for NEDA, and the interpretation of this outcome as it is a composite of clinical and MRI assessments which may not correlate with each other
- The lack of inclusion of many studies with data for AE, SAE, treatment discontinuation for any cause and treatment discontinuation for AE (studies with available data are shown in Table 9**Error! Reference source not found.**). This is potentially important considering the findings of Melendez-Torres et al., (2017)[6] pairwise and network meta-analyses of discontinuation because of AE at 24 months in RRMS.

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

4.4.1 Appropriateness of the MTC

The ERG notes that there are two underlying assumptions to MTC: transitivity and consistency. Transitivity refers to there being no systematic differences between the comparisons being made other than the treatments that are being compared. Consistency is the statistical agreement between direct and indirect comparisons. The ERG conducted an appraisal of the methodological reporting of the MTC which is included in Table 3C of Appendix C.

4.4.1.1 Transitivity

The CS states that "*trials should be similar for moderators of relative treatment effec*t" (CS Document B, pg.67), further defined as "*Clinical similarity refers to similarity in patients' characteristics, interventions, settings, length of follow-up, and outcomes measured*." (CS Document C, pg.33). The ERG note that CS Document C page 34 states that clinical similarity was addressed based on an assessment of the study design and patient characteristics including:

- Diagnostic criteria – McDonald (any revision) versus Other (Poser, Schumacher)
- Mean/Median age of included patients
- Proportion of Male versus Female participants

- Mean/Median EDSS score
- Mean/Median duration of disease
- Mean/Median number of relapses prior to enrolment
- Proportion of previously treated patients

However, the ERG consider that there were differences between studies in the disease duration of the patient populations (CS Document B, p67. The ERG provide a full description of baseline characteristics (see Table 4D in Appendix D). The disease duration is reported in CS Document B, page 17; mean/medians ranged from 1-8.8 years between studies. The CS states "*There is no clear basis on which to set a threshold for the inclusion/exclusion of studies in the analysis based on disease duration. Any choice of threshold would be arbitrary, and alternative choices may substantially affect the results; therefore, we did not exclude any studies based on clinical heterogeneity*" (CS Document B, p67). It is unclear to the ERG what effect this heterogeneity would have, for example people who have had the disease for only one year might be very different from those who have had it for 8+ years, it is unclear whether differences could have been explored more in subgroup analyses.

Additional differences between studies highlighted in the Biogen Plegridy Full Report document but not stated in the submission Documents A, B and C include:

- study publication dates ranging from 1987 to post-2010 (pg.36);
- variation across the trials in terms of age inclusion criteria (pg.36);
- MS diagnostic criteria varied across the trials (pg.36);
- variation in EDSS cut-off for inclusion (pg.36);
- variation in the follow-up time between studies (pg.80);
- there was a lack of detail in many studies regarding previous relapses/treatments (pg.37).

The Biogen Plegridy Full Report document (pg.122) states that "[redacted] To investigate this further, during the clarification stage the ERG requested a summary of the key study characteristics (e.g. study design, population size, year, inclusion criteria, baseline population characteristics) of all studies in the MTC for any outcome. (CS Document B Table 17 (section B.2.9.3) provides only the baseline patient characteristics of included).

The company provided the following data in response to clarification question A8. The study details, population sizes and interventions assessed, distribution of MS subtypes, previous treatments prior to enrolment and methodological quality of the trials. Upon review of this data, the ERG note the following:

In clarification response Table 5 (A8):

- While most trials included patients aged 18 to 50, 55 or 60 years, some only included patients in a narrower age band (20-35 years in Bornstein 1987) or did not report the age range (APEX,[51-53] Boiko 2017,[55] CAMMS223,[59] Crentsil 2012,[66] EVIDENCE,[70] Mokhber 2014,[75] Mokhber 2015,[76] PRISMS[82]).
- EDSS was variable, mostly 0-5.0, 5.5 or 6.0, but in some studies it was 0-3.0 (CAMMS223,[59] CARE MS I),[60] 1-3.5 (INCOMIN,[74] MSCRG[77]) or not reported (Crentsil 2012,[66] Mokhber 2014,[75] Mokhber 2015[76]).
- Most studies specified 1 or 2 prior relapses in varying previous time intervals, but in some studies this was not reported (APEX,[51-53] Calabrese 2012,[58] Crentsil 2012,[66] Mokhber 2014,[75] Mokhber 2015,[76] TENERE[87]).
- Some studies included only treatment-naïve patients (APEX,[51-53] BEYOND,[54] BRAVO,[57] CAMMS223,[59] CARE MS-I,[60] Mokhber 2014,[75] Mokhber 2015[76]), most included a mixed population (ADVANCE,[2] CARE MS II,[61, 62] CONFIRM,[64] DEFINE,[67] GALA,[71] OPERA I,[79] OPERA II,[79] TEMSO,[85] TENERE,[87] TOWER[88]) or prior treatment was not reported (Boiko 2017,[55] Bornstein 1987,[56] Calabrese 2012,[58] CombiRx,[63]Copolymer I study,[65] Crentsil 2012,[66] Etemadifar 2006,[69] EVIDENCE,[70] GLOW,[72] IFNB MS study,[73] INCOMIN,[74] MSCRG,[77] O'Connor 2006,[78] PRISMS,[82] REGARD[83]).

In clarification response Table 8 (A8):

- where the previous treatments were reported, they differed between previous treatment with disease modifying treatment (ADVANCE,[2] BRAVO,[57] GALA,[71] TEMSO,[85] TENERE,[87] TOWER[88]); hormone therapy (Boiko 2017[55]); approved and non-approved therapies (CONFIRM,[64] DEFINE[67]); and steroids (REGARD[83]).

The ERG note that with so many characteristics not reported, and the differences between the studies even when they were reported, it is difficult to assess heterogeneity of patient characteristics. The ERG agrees that the clinical similarity of study populations was often unclear.

The Biogen Plegridy Full Report Appendices document (pg.277) stated that the authors planned to conduct subgroup analysis on treatment naïve and previously treated patients. These were reported for ARR on page 277 and page 281, respectively.

For CDP3M, the authors of the Biogen Plegridy Full Report Appendices document (pg.299) stated: "[redacted]" For CDP6M, the authors of the Biogen Plegridy Full Report Appendices document stated that there were insufficient data for any of the subgroups to permit any analysis (pg.316). The ERG note that in the MTC of CDP3M and CDP6M the company explicitly states that "*These data are not directly comparable to studies that reported after 24 months of follow-up for patients who had remained on the same treatment for the full period. However, in order to link pegIFNβ-1a to the rest of the network, ADVANCE (12 months follow-up) was added to a network of studies with 24 months of follow-up. This limited the accuracy of the comparison…"* (CS Document B, pg.80).

Methodological similarity

Methodological similarity was defined in the CS as referring to "*aspects of trials associated with the risk of bias*" (CS Document C, pg.33). The CS state that "*a narrative summary of all of the included studies is presented in Section B.2.10.3 in Document B or in the meta-analysis results section below. This includes a summary of the key study characteristics (e.g. study design, population size, year, inclusion criteria, baseline population characteristics) and methodological quality (according to the Cochrane Collaboration risk of bias tool) of the studies*" (CS Document C, pg.32-33).

The ERG note that patient characteristics were reported in section B.2.9.3 in Document B (Table 17), so it is possible that the above B.2.10.3 is a typographical error for B.2.9.3. However, it is unclear to the ERG where the RoB of included studies was reported. A RoB assessment was located for the studies in the Biogen data extraction spreadsheet. A second RoB of included studies was provided to the ERG in response to clarification question A8.

The ERG repeated the RoB assessment using the same Cochrane Risk of Bias tool as was used in the CS for comparison purposes (see Table 2B in Appendix B). The ERG largely agreed with the CS assessments on most domains for most studies, although there were some differences.

Sensitivity analysis excluding studies at higher RoB was not provided in CS Documents A, B or C. Risk of bias was reported in the Biogen Plegridy Full Report document (pg.75), with only four trials rated as low risk of bias in all domains. Sensitivity analysis excluding studies at higher risk of bias was not found in the Biogen Plegridy Full Report document or The Biogen Plegridy Full Report Appendices document. Therefore, a sensitivity analysis excluding studies at higher risk of bias was requested during clarification (A14). The company response stated that "*16 studies from the networks*" were removed "*for having at least one domain rated as "High" RoB) as presented in response A8,* ***Error! Reference source not found.*** *(Boiko 2017,[55] Bornstein 1987,[56] BRAVO,[57] Calabrese 2012,[58] CAMMS223,[59] CARE MS-I,[60] CARE MS-II,[61, 62] EVIDENCE,[70] INCOMIN,[74] Mokhber 2015,[76] MSCRG,[77] REGARD,[83] TEMSO,[85] and TOWER[88])*". The company provided sensitivity analysis for ARR, CDP3M and CDP6M in clarification response A14 Figures 11-16. The ERG note that the results of the sensitivity analyses were similar to those obtained using all the studies. As expected, the results had wider confidence intervals around the estimates, and there were no data for some of the potential comparators.

In CS Document B (pg.67) the company state that "*Following the assessment of study similarity and clinical heterogeneity, there were 31 studies eligible for inclusion in the analysis of ARR and 30 studies eligible for inclusion in the analysis of other outcomes*." It is unclear to the ERG whether one of the 32 studies had been completely excluded at this stage.

4.4.1.2 Consistency

In the CS, the ERG note that there is little information on which to examine consistency. The CS stated that "*Inconsistency in the MTC networks was investigated using a combination of graphical and statistical methods. Inconsistency can only occur in loops of evidence where direct and indirect evidence come from different studies. Network diagrams for each outcome were assessed for the presence of loops where inconsistency may occur. For those networks with the potential for inconsistency, the node splitting method to check for evidence of inconsistency was used*" (CS Document C, pg.34-35). The ERG found no further information on graphical methods or node splitting was presented in CS Documents A, B or C. Therefore during clarification the ERG requested "*for networks with the potential for inconsistency*" clarification on where this information has been reported (clarification question A13). This information was provided by the company at the clarification stage for 11 comparisons in ARR, 6 comparisons in CDP3M and CDP6M.

Primary outcome ARR

To measure consistency in ARR network, data were only available for 11 out of a possible 55 pairs of comparisons.

The ERG located information regarding consistency in the Biogen Plegridy Full Report Appendices document. The Biogen Plegridy Full Report Appendices document (pg. 276) reported that in the network for ARR: "[redacted]" The ERG consider the relative effects of pegIFNβ-1a 125 mcg Q2W for ARR from the indirect meta-analysis (CS Document C, Table 108, pg.439) were reported to be (and appeared) comparable to the estimates obtained from the MTC (CS Document B, Figure 15, pg.79).

Secondary outcome CPD3M

In the CS Document C (pg.443), the company stated that for CDP3M, no indirect meta-analysis were possible to compare with the MTC. However, the ERG note that in the Biogen Plegridy Full Report Appendices document (pg.299) there is a network for CDP3M, in which there were six treatment comparisons with the potential for inconsistency. The Biogen Plegridy Full Report Appendices stated that they "[redacted]".

To measure consistency in CDP3M network, results were presented in Figure 8, clarification response A13. The ERG note that there was no evidence of statistically significant inconsistency in any of the six comparisons tested.

Secondary outcome CDP6M

To measure consistency in CDP6M network, data were only available for 6 out of a 36 pairs of comparisons (results are presented for 3 of the 67 comparisons, Figure 10, clarification response A13). For CDP6M, indirect meta-analysis results (CS Document C Table 109, pg.448) were reported to be (and appeared) comparable to the MTC (CS Document B, Figure 19, pg.83).

The Biogen Plegridy Full Report Appendices document (pg.316) stated that in the network for CDP6M, there were six treatment comparisons with the potential for inconsistency. The authors "[redacted]".

Other outcomes combined in MTC

The ERG note that in the CS Document C page 34-35 "*Inconsistency in the MTC networks was investigated using a combination of graphical and statistical methods. Inconsistency can only occur in loops of evidence where direct and indirect evidence come from different studies. Network diagrams for each outcome were assessed for the presence of loops where inconsistency may occur. For those networks with the potential for inconsistency, the node splitting method to check for evidence of inconsistency was used*". In The Biogen Plegridy Full Report Appendices document (pg.321) consistency for MTC of AE was assessed. The report states that "[redacted]." A similar statement was made (pg.326 for SAE and pg.329) for discontinuations for any cause.

The ERG agrees that there is no potential inconsistency in a single study. However, to further assess inconsistency in the MTCs presented in the CS, the ERG requested the evidence of graphical and statistically significant inconsistency for those networks with the potential for inconsistency (clarification question A13). In response to question A13, the company provided evidence for ARR, CDP3M and CDP6M networks using the node splitting method. Figures 5-10 in clarification response A13 provided graphical and statistical evidence. The ERG note that tests for inconsistency were not possible for 44 of the 55 comparisons presented in the CS due to the structure of the networks.

4.4.1.3 Methods of statistical analysis in the MTC

Section B.2.9.2 on page 66 of CS explains the statistical methods used. "*Mixed-treatment comparison was performed using a Bayesian approach*" where "*burn-in of 50,000 simulations was used, followed by an additional run of 50,000 simulations to obtain parameter estimates*."

Burn-ins are used to enter the Markov Chain models into what is called a 'high probability region', after initial uncertainty and the ERG considers appropriate for this analysis.

The CS reports that "*Where direct head-to-head meta-analysis was possible statistical heterogeneity was conducted using the I^2 statistic*" (CS Document C, pg.34). The ERG note that as there was only one study in the direct comparison, this was not applicable. Statistical heterogeneity was not stated for the MTC comparisons in Documents A, B and C. In the Biogen Plegridy Full Report document, it was stated that "*heterogeneity in the MTCs was addressed based on an assessment of the study design and patients characteristics of the eligible studies… Only studies which were considered to be sufficiently clinically and methodologically similar were included in the final networks*" (see Section 4.4.1.1 for ERG comment on transitivity).

ARR was analysed using rate ratios as the effect estimate, with MTC of treatment differences combining "*data across multiple time points*". As the ARR is an annualised measure, data was pooled for follow-up periods greater than 48 weeks. During clarification, the ERG requested further justification for including and combining time points other than 12 or 24 months. Response to clarification question A12 the company stated that "*in order to achieve a comparison with pegIFN beta-1a and inform the economic model, the treatment under appraisal, 11, 18, and 24 month follow-ups were pooled for the key outcomes of ARR, CDP3M and CDP6M outcomes*". The company provided a list of study endpoints time for each of the included trials. The ERG deems appropriate considering the data available for this appraisal.

Disability progression, CDP3M and CDP6M, were reported as HR where "*11-month data from ADVANCE and 18- and 24-month data for comparator treatments were pooled for CDP3M and CDP6M outcomes*" (CS Document B, pg.66). The CS acknowledges the fact that pooling the outcomes as such, "*this limited the accuracy of the comparison but without combining data from different time points, comparative effectiveness would not be possible*", the ERG considers this approach appropriate. All other outcomes were based on 12-month data alone.

The CS Document B page 66 reports "*Several studies reported 1-year outcomes after 48 weeks (11 months) of follow-up. Therefore, any study where 1-year outcomes were reported at ≥ 11 months and ≤ 13 months was considered for potential inclusion in the analysis of 12-month outcomes. The actual follow-up period for 2-year outcomes ranged from 96 weeks (22.2 months) to 108 weeks (24.9 months). Therefore, any study where 2-year outcomes were reported at*

≥ 22 months and ≤ 25 months was considered for potential inclusion in the analysis of 24-month outcomes." As there were variations in follow-up times between studies, the ERG find creating a window of acceptable follow-up periods acceptable.

Serious adverse events were "*analysed as dichotomous outcome based on the proportion of patients who experienced at least one event after 24 months follow-up using odds ratios (ORs) as the effect measure*", excluding MS relapses (CS Document B, pg.66). Sensitivity analysis was performed including the MS relapses. Adverse events were was not pooled due to high heterogeneity between studies, and reported as a narrative synthesis only.

Treatment discontinuation "*was analysed as a dichotomous outcome based on the proportion of patients who discontinued after 24 months follow-up using ORs as the effect measure. However, only studies of 12 months follow-up were included in the network analysing treatment discontinuation*." This was also reported as a narrative synthesis only. The ERG finds these approaches to SAE, AE and treatment discontinuation appropriate. The OR (for dichotomous outcomes), HR (for time-to-event outcomes), rate ratios (for rate outcomes) are reported with either 95% credible intervals (CrI, Bayesian methods) or 95% CI (frequentist methods) which the ERG deems appropriate.

4.5 Summary of critique of the MTC

The ERG note that there is little information on which to examine consistency of the MTCs presented in the CS. The results of the tests of potential inconsistency which were presented in the Biogen Plegridy Full Report Appendices and in clarification response A16 are appropriate tests of the statistical agreement between direct and indirect comparisons.

Transitivity of the MTCs included in the CS is unclear. The ERG note systematic differences between the comparisons being made other than the treatments that are being compared. For example, there were differences between studies in the disease duration of the patient populations, study publication dates, age inclusion criteria, MS diagnostic criteria, EDSS cut-off criteria, follow-up time between studies and lack of detail regarding previous relapses/treatments. It was difficult to assess heterogeneity of patient characteristics, and the clinical similarity of study populations was often unclear.

The ERG consider the methods of statistical analysis for the MTCs presented in the CS appropriate.

There are several other concerns relating to the appropriateness of the MTCs:

- Multi-arm studies were sometimes included in the MTC (e.g. Calabrese 2012[58] in the ARR MTC) with a brief explanation of how correlations between the outcomes were accounted for in the models provided in CS Document C section D2.8
- There were few eligible studies. Some of the assessment of whether an MTC is appropriate is reliant upon multiple trials for each comparison. First, prior to conducting an MTC, pairwise meta-analyses of all interventions that have been directly compared should be carried to examine statistical heterogeneity. Confidence in the MTC will be low in the presence of high heterogeneity. In the CS, the MTC for ARR included only 2 direct comparisons with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo, 2 studies comparing GA 20mg versus IFN beta 1-a 30 mcg) the MTC for CDP3M included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo), and the MTC for CDP6M included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo). No other comparisons could be assessed for heterogeneity.

Overall, there is little data on which to assess whether the assumptions of MTCs have been met, but some evidence to suggest that the assumption of transitivity has been violated. Therefore, the ERG cannot be confident of the appropriateness of the MTC or the validity of the results.

4.6 Additional work on clinical effectiveness undertaken by the ERG

Other than the comparison of the MTCs presented in this CS with the MTC conducted by the assessment group for ID527[4] (found in Melendez-Torres et al 2017[6]) shown in Table 11 and Section 4.3.1.7, no additional work on clinical effectiveness was undertaken by the ERG.

4.7 Conclusions of the clinical effectiveness section

The ADVANCE trial[2] provides evidence that pegIFNβ-1a is effective in significantly reducing relapse rates in RRMS patients compared with placebo. However the ERG has a number of concerns about the trial which was the sole source of randomised comparative evidence for the value of pegIFNβ-1a

- It is unclear if the populations, or the care they receive, are representative of the care currently provided or likely to be received in the UK. ADVANCE included 14 patients (out of 1512) from the UK
- There was a differential drop-out between the placebo (n=44) and pegIFNβ-1a every 2 week group (n=74) by the end of year 1 of ADVANCE (14.5% from the every 2 week group, and 8.8% from the placebo arm, in year 1
- The rates of AE were generally similar between treatment and placebo, with the exception of treatment-related AE: 90% of the pegIFNβ-1a (2-week) group had at least 1 compared to only 53% of the placebo group
- The proportion of patients who discontinued study treatment or withdrew in the first 48 weeks due to AE was also lower in the placebo group compared with the intervention group. In the Q2W arm, n=25 discontinued due to an AE and n=25 withdrew due to an AE; in the placebo arm the figures were n=7 and n=6, respectively.

The ERG had the following additional issues with the CS of clinical effectiveness evidence:

- There are differences between the CS decision problem and NICE final scope, however the ERG consider them to be appropriate to the narrower patient definition of RRMS included in the CS decision problem
- The ERG identified discrepancies in the ratings of studies included in the SLR which are high RoB. However, there were no differences in the final number of studies included in the MTCs
- During clarification, the company provided an additional MTC for the secondary outcome CDP6M (included in the economic analysis base case). The updated MTC included additional trial/studies which the ERG consider should have been included in the MTC for this outcome. However, the inclusion of an additional study did not significantly change the overall results
- The ERG note that inconsistency could not be tested in the majority of the MTCs included in the CS as they did not contain closed loops

- There is some evidence to suggest that the assumption of transitivity has been violated in the CS MTCs. The ERG note systematic differences between the comparisons being made for example differences between studies in the disease duration of the patient populations, study publication dates and age inclusion criteria.

5 COST-EFFECTIVENESS

This section focuses on the economic analysis submitted by Biogen Idec, and additional information received from the company in response to the ERG's clarification questions. The ERG critically appraised the evidence submitted and examined the company's electronic model. The chapter starts with a summary of the company's economic analysis, then in detail the systematic review, methods, and results (base-case, sensitivity and scenario analyses) as reported in the CS. The ERG then compare the economic analysis to the NICE reference case, then provide a critique using frameworks on best practices for reporting economic evaluation and economic modelling to assess the overall reporting quality and validity of these analyses. In the subsequent chapter, where possible, the ERG have addressed their concerns in the form of additional analyses undertaken by the ERG.

The submission received by the ERG included:

- A systematic review of the economic evidence for the management of people living with RRMS
- Methods used to undertake the economic analysis, and the company's base-case and sensitivity analysis results
- Electronic version of the *de novo* Markov model built in Microsoft Excel
- Budget impact analysis, which the ERG does not provide a critique

5.1.1.1 Summary of the company's economic analysis

Biogen Idec undertook an economic analysis to assess the cost-effectiveness of pegINFβ-1a 125µg compared to other DMTs for treating people with RRMS. A Markov model was used to depict/simulate the natural history of people with RRMS. Information required on the natural history was based on a British Columbia dataset.[98] RRMS disease progression was simulated by means of 10 EDSS levels ranging from EDSS 0 to 9.5. The hypothetical population that entered

the model was distributed across EDSS levels 0 to 4.5, which reflected the EDSS distribution of the participants in the ADVANCE trial.[2] The mean age of the population was 36 years, with 71% females.

Based on the transition probabilities, in each yearly cycle people could remain in the same RRMS EDSS health state, progress to a more severe EDSS state, regress to a less severe state, progress to SPMS or die. On progression to SPMS, people discontinued DMTs; thus followed a natural history progression, which was based on transition probabilities derived from the London, Ontario dataset.[99] Additionally in each cycle, people may have experienced relapses, treatment-related AE or discontinued treatment, all of which are captured in separate health states.

Treatment effects were assumed to delay the progression of RRMS and reduce the frequency of relapses. Information about treatment effect compared to no treatment was based on the company's MTC. Information on utilities for RRMS and SPMS by EDSS level were based on information from Orme et al., (2007),[9] which were derived from utility values from the UK MS survey. Caregivers utility decrements were based on information obtained from Gani et al., (2008).[10] Utility values for AE associated with each DMT were included in the economic analysis and these were obtained from various sources. It was assumed that there is an increased risk of mortality for people with MS compared to the general population. Age- and gender-specific all-cause mortality rates for a UK general population were derived from the UK ONS data, and adjusted using the mortality rates obtained from Pokorski et al., (1997).[11] Due to the paucity of information, it was assumed that there was no difference between mortality for people with RRMS or SPMS.

Information about resource use and unit their costs were obtained from various sources (literature, British National Formulary, Personal Social Service Research Unit [PSSRU],[100] NHS reference costs).

The analysis was undertaken from the NHS and PSS perspective. The health outcome reported were EDSS changes, relapses, SPMS, reasons for discontinuation, LR and QALYs gained over a 50-year time horizon. Cost outcomes included disease management costs, drug acquisition, administration and monitoring, costs for treating relapses and costs associated with treating AE. The results were presented as an ICER and expressed as cost per QALYs gained. Both costs and effects were discounted at 3.5% per annum. The company undertook a number of sensitivity and

scenario analyses, and PSA to determine the robustness of the base-case results to making changes to model inputs/assumptions.

Base-case results showed that treatment with pegINFβ-1a 125µg dominated all comparators except treatment with alemtuzumab 12mg. Alemtuzumab 12mg when compared to SC pegINFβ-1a 125µg had a mean incremental cost of £1250 with corresponding 1.082 incremental QALYs, which resulted in an ICER of approximately £1200 per QALY gained. Base-case results were robust across all scenario analyses undertaken. Results from the one-way sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except the HR for the confirmed disability progression, which had the greatest impact. The probabilistic sensitivity analysis suggested that at a £20,000 willingness-to-pay threshold for a QALY, pegINFβ-1a 125µg had a 0.17 probability of being cost-effective when compared to alemtuzumab. In comparison to all other comparators pegINFβ-1a 125µg had probabilities >0.85 of being cost-effective.

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

The company undertook a systematic review to identify cost-effectiveness studies, with the purpose of developing an economic model that could be used to assess the cost-effectiveness of DMTs for the treatment of people with RRMS. Also the systematic review was undertaken to:

- Identify resource use and costs and utility information
- Identify economic models
- Critically appraise economic analyses and costing studies
- Summarise economic evidence reported in studies identified in the systematic review
- Extract relevant information about resource use and costs and utility that could be used in the economic analysis.

5.2.1 Search strategy

Searches were undertaken on 29 November 2018 in a range of relevant databases (MEDLINE (PubMed), Embase, The HTA Database, Database of abstracts of reviews of effectiveness, NHS's economic evaluation database (NHSEED) via the Cochrane Library, EconLIT. The methods used were similar to those used in a previous submission for the same condition. Searches were limited

to records published after 1 February 2016, in English. Additional searches of conference websites, international websites and reference lists of included economic analyses, systematic reviews and HTA reports were undertaken. The company justified the time period to search from, as previous searches were considered appropriate; thus only required updating.

The original systematic review was part of the NICE TA320 submission (2003-2014).[101] This was updated from 2014-2016 for TA441.[102] The current systematic review updated this previous search from February 2016-November 2018, with the aim of retrieving all economic evidence relevant to developing an economic model to evaluate MS treatments, including RRMS, SPMS and PRMS. A further Embase search was run in May 2019 but no additional papers were found. The searches were run by RTI-HS.

A single search was conducted to identify economic evaluation, HRQoL, and healthcare resource use and cost studies. Search terms for all treatments are included, including the treatments excluded from the MTC. A comprehensive range of databases were searched (Medline, Embase, Cochrane, EconLit) plus conferences and HTA websites. Individual search strategies were only provided for the database searches. These searches were limited to human only and specific publications types were excluded: comments, editorials, case reports, letters, case study, and phase 1 clinical trials. Section G.1.1.4. of the CS Document C states that the searches were limited to the English language but this is not evidenced in the reported search strategies. Appropriate economic filters were used. The search retrieved 1,132 references. The list of included and excluded studies was provided upon request.

The CS Econlit search strategy used the SU (index) search field throughout for key economic search terms and often found no results, for example, for cost-of-illness and socioeconomic factors. The reported search found one paper when combining the disease and intervention terms (Hawton et al, 2016).[103] The ERG re-ran the disease and intervention section of the search using Econlit with Full Text. This found eight records including the study by Hawton and Green.[103] The other seven records were excluded by the ERG.

5.2.2 Inclusion criteria

A summary of the inclusion and exclusion criteria used to identify potentially relevant studies is presented in Table 13.

Table 13. Eligibility criteria for cost-effectiveness searches (obtained from CS Document C Appendix G, pg.160-161)

Criterion	Included	Excluded
Population: MS	▪ Participants ≥18 years with a diagnosis of MS (classified using an accepted diagnostic technique e.g., Poser or McDonald criteria) regardless of age, sex, degree of disability, and duration of the disease. Restricted to the following clinical phenotypes: ▪ Relapsing-remitting MS/secondary progressive MS ▪ Progressive-relapsing multiple sclerosis (PRMS)	▪ Children (aged < 18 years) ▪ Non-MS patients
Interventions (applied to economic evaluations only)	▪ Following interventions (irrespective of dose [provided within the therapeutic range] or mode of administration): ▪ Interferon β-1b (IFNβ -1b) ▪ IFNβ -1a (Rebif, Avonex) ▪ Glatiramer acetate ▪ Natalizumab ▪ Fingolimod ▪ Teriflunomide ▪ Alemtuzumab ▪ Dimethyl fumarate ▪ Ocrelizumab ▪ Cladribine ▪ Plegridy	▪ Studies that do not have an intervention of interest in at least 1 arm
Comparator	▪ Placebo or any active treatment	-
Outcomes	▪ Direct costs ▪ Direct healthcare costs per patient per year (interventions, concomitant medications, treatment of adverse events/co-morbidities) ▪ Method of valuation (e.g., per capita expenditures, national tariffs, market prices, and published studies) ▪ Indirect costs ▪ Productivity loss costs ▪ Presenteeism: at work productivity level (also from patients' viewpoint) ▪ Short-and long-term sick leave (absenteeism): prevalence, days/patient/year versus national average ▪ Withdrawal from labour force ▪ Method of valuation (Human capital or friction cost approach or contingent valuation) ▪ Patient and family/caregiver costs ▪ Travel, co-payments ▪ Annual loss of income ▪ Formal and informal care	▪ Studies lacking relevant cost data ▪ Studies lacking relevant utility data

Criterion	Included	Excluded
	▪ Caregiver burden ▪ Range of ICERs as per sensitivity analyses ▪ Assumptions underpinning model structures ▪ Key costs drivers ▪ Sources of clinical, cost and quality of life inputs ▪ Discounting of costs and health outcomes ▪ Model summary and structure ▪ Utility values directly elicited using the following techniques: Time trade-off and standard gamble ▪ Utility values based on generic preference-based instruments for relevant health states (baseline utility, dis-utilities associated with AE) ▪ Mapping studies that would allow disease specific measures to be mapped onto preference-based utilities	
Study type	▪ Cost-effectiveness, cost-utility, cost-benefit, and cost-minimisation analyses ▪ Clinical trials or real-world studies (original research articles) ▪ Systematic reviews of economic analyses, resource use, or cost studies	▪ Narrative reviews, guidelines, commentary, letters to the editor ▪ Animal or in vitro studies ▪ Pharmacokinetic or pharmacodynamic studies
Language of publication	▪ English	▪ Non-English
Date of publication	▪ No restriction	-

5.2.3 Included studies

The company identified 66 economic evaluation studies, of which 12 were undertaken in a UK setting. The company further stated that two of the 12 studies were undertaken in the England. Relevant information from these studies were extracted and summarised in Tables 38 and 39 in Appendix G of the CS Document C, and quality appraised.

5.2.4 Systematic review of studies reporting resource use and costs

The search for resource use and costs was incorporated in the broader cost-effectiveness search; hence a separate search was not undertaken.

From the broader search that identified economic evaluation studies, the company also identified studies that reported resource use and costs. The search identified three studies (Kobelt et al., 2017;[7] Thompson et al., 2017[8] and Hawton et al., 2016[104]) that reported resource use and costs by EDSS health state based on UK participants. Additionally, the company included three studies (Karampampa et al., 2012;[105] Kobelt et al., 2006[106] and Tyas et al., 2007[107] that have been used in previous technology appraisals. In Document C, Appendix I, the company reported the studies' characteristics and their results, but little critique of these studies. The company further stated that EDSS health costs used in the base-case were obtained from TA320, as these values were preferred by the assessment group of ID527 following a critique. These we further inflated to current prices.

5.2.5 Systematic review of HRQoL studies

The search for utility values was incorporated in the wider cost-effectiveness search; hence a separate search was not undertaken for HRQoL studies.

5.2.6 Results

Based on the updated search, sixty-six full economic evaluation studies were identified, of which 12 were undertaken in a UK setting. One-hundred and fourteen studies were identified that reported resource use and cost information, of which five were undertaken in the UK. A total of 30 studies reported health–state utility values in people with MS.

5.2.7 Conclusions

The company's systematic review of the cost-effectiveness evidence that compared pegIFNβ-1a versus other DMTs for treating people with RRMS identified those studies undertaken in a UK setting. The ERG is satisfied with the company's search and that all relevant studies have been identified. Additionally, the ERG are satisfied with the company's search to identify studies reporting HRQoL and resource use and cost. However, the ERG would have welcomed further critique/appraisal of the identified studies.

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

In this section, the ERG report an assessment of the company's economic analysis against the NICE reference case for technology assessment.[108] The ERG provide a summary of the company's illustrative model structure, as well as the clinical (treatment effect on confirmed disability progression, ARR, treatment discontinuation and mortality) and economic evidence (DMT acquisition costs, health state costs for RRMS and SPMS, and treatment of AE) used to parameterised the economic model. Along with the summary, the ERG provide a critique of methods and inputs used in the economic analysis in the following sections.

5.3.1 NICE reference case checklist

The ERG have undertaken an evaluation of the CS in relation to the NICE reference case. Findings are summarised in Table 14.

Table 14. NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Defining the decision problem	The scope developed by NICE	Decision problem clearly stated and is in line with the scope developed by NICE
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice for this population	Interferon β-1b (IFNβ -1b) IFNβ -1a (Rebif, Avonex) Glatiramer acetate Teriflunomide Alemtuzumab Dimethyl fumarate Ocrelizumab
Patient group	As per NICE final scope, the population refers to: People living with RRMS	As per NICE final scope
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes between the technologies being compared	50-year time horizon
Synthesis of evidence on outcomes	Systematic review	Systematic review was undertaken by the company

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Outcome measure	Quality adjusted life-years	Results reported in terms of quality adjusted life-years
Health states for QALY	Described using a standardised and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	The standard UK EuroQol five dimensions [EQ-5D] tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	The company undertook PSA and reported these results
Sensitivity analysis		The company undertook a range of sensitivity and scenario analyses.

EQ-5D, EuroQol five dimensions; HRQoL; health-related quality of life; IFN, interferon; NHS; National Health Service; NICE; National Institute for Health and Care Excellence; PSA; probabilistic sensitivity analysis; QALY, quality-adjusted life years; RRMS, relapsing-remitting multiple sclerosis

5.3.2 Model structure

The company used a cohort-based Markov model to depict the natural history of people with RRMS. The model simulated disability progression and regression between EDSS levels, and progression from RRMS to SPMS and the relapsing nature of the disease. People with RRMS or SPMS were allowed to occupy one health-state at any given time, which ranged from 0 to 9.5 in increments of 0.5 (see Figure 2).

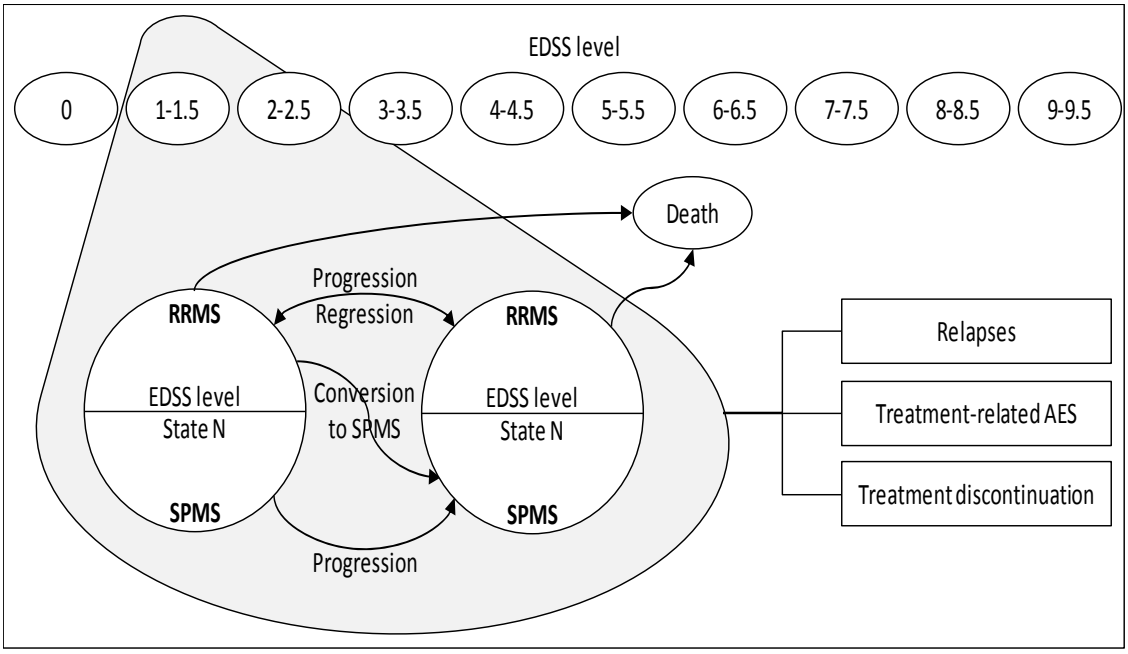

Figure 2. Illustrative survival model (obtained from CS Document B, Figure 33, pg.113)

The model started from a hypothetical cohort of people with RRMS, distributed across EDSS levels <6 (see Table 15) based on the distribution of participants in the ADVANCE trial.[2] The starting age of the population was 36 years, with 29% and 71%, males and females, respectively. Over time, people were at risk of progression to more severe EDSS levels, regress to less severe EDSS levels or death. Transitions between health states were bidirectional and occurred at the end of each one-year cycle, where people remained in the same health state, regressed or progressed. Each cycle, people incurred costs and accrued benefits (QALYs) depending on the EDSS health state occupied. A half-cycle correction was applied in the base-case and the model concluded at a 50-year time horizon.

Table 15. Baseline distribution of people by EDSS

EDSS	**0**	**1-1.5**	**2-2.5**	**3-3.5**	**4-4.5**	**5-5.5**	**6-6.5**	**7-7.5**	**8-8.5**	**9-9.5**
Percentage (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EDSS, expanded disability status scale										

ERG summary

The Markov model appears to capture the key important features (movement between EDSS levels and progressing from RRMS to SPMS) of people living with RRMS. However, it should

be noted that the model does not capture subsequent DMT costs/benefits following discontinuation of pegIFNβ-1a or its comparators. Instead, it is assumed that once treatment is discontinued people follow the British Columbia natural history cohort; thus not having any residual benefit from the DMT.

5.3.3 Population

The population included in the economic analysis is similar to the population included in the ADVANCE trial (71% and 29% females and males, with a mean age of 36 years).[2] The starting distribution of people in each EDSS levels is presented in Table 15.

5.3.4 Intervention and comparators

The cost-effectiveness analysis compared pegIFNβ-1a with other DMTs which are available in the UK for treating people with RRMS. The company excluded DMTs that are recommended for treating people with highly active RRMS (fingolimod and cladribine) and RES-RRMS (natalizumab). Table 16 shows the DMTs and their dosing schedule that were included in the cost-effectiveness analysis.

Table 16. Intervention and comparators included in the cost-effectiveness analysis

Disease-modifying therapy	Dosing schedule
Intervention	
PegIFNβ-1a	125µg every two weeks
Comparators	
IM IFNβ-1a 30	30µg once weekly
IFNβ-1a 22	22µg three times per week
IFNβ-1a 44	44µg three times per week
IFNβ-1b	250µg every other day
GA 20mg	20mg once daily
GA 40mg	40mg once daily
Generic GA 20	20mg once daily
Generic GA 40	40mg once daily
Teriflunomide	14mg once daily
Dimethyl fumarate	240mg twice daily
Alemtuzumab	12mg once daily
Ocrelizumab	600mg every six months
IFN, interferon; IM, intramuscular; peg, PEGylated GA, glatiramer acetate	

The ERG considered that the DMTs included in the economic analysis are in line with the NICE scope.[1] The ERG also agree that it was appropriate to exclude DMTs that are used for treating people with highly active RRMS and RES-RRMS, as pegIFNβ-1a is not used in clinical practice for these populations.

5.3.5 Perspective, time horizon and discounting

The perspective/viewpoint of the analysis is that of the NHS and PSS, which is in line with the NICE Guide to the Methods of Technology Appraisal.[108] The model assumes a 50-year time horizon, which is long enough to capture the long-term costs and benefits of treatment. In the base-case, the costs incurred and benefits accrued are discounted at a rate of 3.5% per annum. A number of sensitivity and scenario analyses were undertaken by the company. The company presented scenario analysis results based on changes made to the time horizon of the economic analysis, annual discount rates for costs and benefits.

5.3.6 Transitions

To show how people moved between the various EDSS levels in the model, information was required for the transitions between RRMS health states, progressing from RRMS to SPMS and transitions between SPMS health states, for the intervention as well as all the comparators. Transition probabilities were derived from the natural history cohort from the British Columbia dataset. Table 17 shows the transitions between the EDSS health states for people ≥ 28 years. In Table 17, it can be seen that people can remain, progress to more severe EDSS states, or regress to less severe health states.

Table 17. Natural history matrix based on information from the British Columbia dataset for people ≥ 28 years

EDSS From/to		EDSS state (to)										
		0	**1-1.5**	**2-2.5**	**3-3.5**	**4-4.5**	**5-5.5**	**6-6.5**	**7-7.5**	**8-8.5**	**9-9.5**	**Total**
EDSS state (from)	**0**	0.695	0.2029	0.0725	0.0217	0.0042	0.0014	0.0018	0.0001	0.0000	0.0000	1.000
	1-1.5	0.058	0.6950	0.1578	0.0609	0.0164	0.0046	0.0064	0.0005	0.0001	0.0000	1.000
	2-2.5	0.015	0.1213	0.6079	0.1680	0.0446	0.0185	0.0216	0.0017	0.0005	0.0000	1.000
	3-3.5	0.005	0.0496	0.1201	0.5442	0.0911	0.0585	0.1165	0.0103	0.0036	0.0003	1.000
	4-4.5	0.001	0.0221	0.0666	0.1152	0.4894	0.1039	0.1681	0.0258	0.0067	0.0006	1.000
	5-5.5	0.000	0.0053	0.0294	0.0587	0.0874	0.4870	0.2731	0.0388	0.0188	0.0010	1.000
	6-6.5	0.000	0.0013	0.0044	0.0250	0.0307	0.0408	0.7407	0.1090	0.0438	0.0042	1.000
	7-7.5	0.000	0.0002	0.0005	0.0025	0.0073	0.0039	0.1168	0.6927	0.1606	0.0156	1.000
	8-8.5	0.000	0.0000	0.0000	0.0003	0.0006	0.0005	0.0188	0.0557	0.9034	0.0207	1.000
	9-9.5	0.000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0018	0.0057	0.1741	0.8183	1.000

EDSS, expanded disability status scale

5.3.6.1 Transition probabilities from RRMS to SPMS

The company used information from the London Ontario natural history cohort to derive the transition probabilities for progressing from RRMS to SPMS in each cycle. On progression from RRMS to SPMS, it was assumed that people who progressed had a one-unit increase in EDSS score. For example, people with RRMS with an EDSS of 5-5.5 would progress to SPMS with an EDSS of 6-6.5. Transition probabilities for RRMS to SPMS were estimated from hazards reported in TA441.[102] Table 18 reports these hazards and the probabilities of transitioning from RRMS to SPMS.

Table 18. Transition probabilities from RRMS to SPMS based on the London, Ontario cohort

EDSS	Hazard	Probability
0	0.004	0.004
1-1.5	0.002	0.002
2-2.5	0.030	0.029
3-3.5	0.103	0.097
4-4.5	0.199	0.181
5-5.5	0.256	0.225
6-6.5	0.184	0.168
7-7.5	0.237	0.211
8-8.5	0.066	0.064
9-9.5	0.167	0.154
EDSS increases by one-unit from transitioning from RRMS to SPMS EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis		

5.3.6.2 Transition probabilities within SPMS

The model required transition probabilities for people who progressed to SPMS. These transition probabilities were derived from information obtained from the London, Ontario dataset. Table 19 shows the transition matrix for people who have SPMS. It can be seen that the transition probabilities are unidirectional; hence, people are not allowed to regress to less severe EDSS levels. In keeping with the assumption that people who progressed from RRMS to SPMS will have a one-unit increase in EDSS score, it can be seen that there is a zero probability of being in EDSS 0 and progressing to more severe EDSS health states.

Table 19. Transition probability matrix for transitioning within SPMS, based in London, Ontario cohort

EDSS From/to		EDSS state (to)										
		0	**1-1.5**	**2-2.5**	**3-3.5**	**4-4.5**	**5-5.5**	**6-6.5**	**7-7.5**	**8-8.5**	**9-9.5**	**Total**
EDSS state (from)	**0**	0.000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	N/A
	1-1.5	0.000	0.7692	0.1538	0.0769	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.000
	2-2.5	0.000	0.0000	0.6357	0.2713	0.0620	0.0233	0.0078	0.0000	0.0000	0.0000	1.000
	3-3.5	0.000	0.0000	0.0000	0.6291	0.2527	0.0769	0.0330	0.0027	0.0055	0.0000	1.000
	4-4.5	0.000	0.0000	0.0000	0.0000	0.4854	0.3504	0.1387	0.0073	0.0182	0.0000	1.000
	5-5.5	0.000	0.0000	0.0000	0.0000	0.0000	0.6325	0.3173	0.0221	0.0261	0.0020	1.000
	6-6.5	0.000	0.0000	0.0000	0.0000	0.0000	0.0000	0.7631	0.1903	0.0446	0.0020	1.000
	7-7.5	0.000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8046	0.1891	0.0062	1.000
	8-8.5	0.000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9258	0.0742	1.000
	9-9.5	0.000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	1.000

EDSS, expanded disability status scale; N/A, not applicable

The ERG agrees with the company's choice of datasets to reflect the natural history of people with RRMS and SPMS.

5.3.6.3 Annualised relapse rates

The economic model required information about relapses experience by people with RRMS or SPMS. Annualised relapse rates were derived based on information obtained from the UK MS survey and Patzold et al., (1982),[109] which are presented in Table 20. Briefly, the UK MS survey collected information on the total number of people who experienced a relapse by EDSS and the number of years since diagnosis. Patzold and colleagues undertook a regression analysis to investigate the relationship between ARRs and the number of years since diagnosis.[109] The natural history ARRs were applied to people who discontinued DMT, and a rate ratio relative to placebo were applied to these natural history ARRs, then applied to people who are on DMT. Further details of these rate ratios are reported in Section 5.3.9.2.

Table 20. Annualised relapse rates for people with RRMS and SPMS

EDSS	Annualised relapse rates (ARRs)	
	RRMS	SPMS
0	0.709	0.000
1-1.5	0.729	0.000
2-2.5	0.676	0.465
3-3.5	0.720	0.875
4-4.5	0.705	0.545
5-5.5	0.591	0.524
6-6.5	0.490	0.453
7-7.5	0.508	0.340
8-8.5	0.508	0.340
9-9.5	0.508	0.340

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

5.3.6.4 Calculation of patient disposition

Each cycle of the model requires information about the patient disposition to affix costs incurred and benefits (LY and QALY) accrued over time for people occupying a specific EDSS health state. In the model the patient disposition is divided into two sub-cohorts:

- People on treatment
- People off treatment

The patient disposition for people on-treatment follows a series of logical steps:

1. People who have discontinued treatment are moved to the off-treatment sub-cohort
2. People who die move to a dead state
3. Relapses are calculated
4. Transition probability matrix is applied
5. People who discontinued due to progressing to EDSS ≥7 are moved to the off-treatment sub-cohort
6. People who discontinued due to progression to SPMS are moved to the off-treatment sub-cohort

Likewise, for people in the off-treatment sub-cohort the patient disposition is derived as follows:

1. People who have discontinued treatment are added to the off-treatment sub-group
2. People who die move to a dead state
3. Relapses are calculated
4. The natural history transition probability matrix is applied
5. People who discontinued due to progressing to EDSS ≥7 are added to the off-treatment sub-cohort
6. People who discontinued due to progression to SPMS are added to the off-treatment sub-cohort

5.3.6.5 Treatment discontinuation

Table 21 presents the annualised risk of all-cause discontinuation and discontinuation due to AE for each DMT. All-cause discontinuation includes discontinuation due to AE, lost to follow-up, and investigator decision or withdrew consent. The probability of treatment discontinuation was based on the all-cause discontinuation rates reported in the studies included in the network meta-analysis for ARR. A total of 18 out of the 23 trials included in the MTC for ARR reported all-cause discontinuation. The probabilities reported in each study were annualised, then weights based on the sample size of the trials were applied to derive the discontinuation risk.

Table 21. Annualised risk of all-cause discontinuation and discontinuation due to adverse drug reaction

Disease modifying therapy	Annual risk (Excel model) (all-cause discontinuation)	Annual risk (adverse drug reaction risk)
PegIFNβ-1a	15.56%	5.3.6.6 5.28%
IM IFNβ-1a 30	7.88%	5.3.6.7 3.07%
IFNβ-1a 22	6.00%	5.3.6.8 1.60%
IFNβ-1a 44	10.53%	5.3.6.9 3.81%
IFNβ-1b	6.87%	5.3.6.10 1.27%
GA 20mg	11.02%	5.3.6.11 2.48%
GA 40mg	8.91%	5.3.6.12 3.08%
Generic GA 20	11.02%	5.3.6.13 2.48%
Generic GA 40	8.91%	5.3.6.14 3.08%
Teriflunomide	18.57%	5.3.6.15 7.84%
Dimethyl fumerate	18.01%	5.3.6.16 7.95%
Alemtuzumab	2.59%	5.3.6.17 1.19%
Ocrelizumab	6.69%	5.3.6.18 1.92%
IFN, interferon; IM, intramuscular; peg, PEGylated GA, glatiramer acetate		

Additionally, the model allows for the cost-effectiveness to be undertaken by using the discontinuation based on adverse drug reactions only, and assuming that the all-cause discontinuation across all DMTs was 5% per annum. The ERG noticed that there were some inconsistencies in the reporting of annual all-cause discontinuation in the CS and that in the economic model. The company further clarified that the correct values reported in the model are correct.

At the clarification stage, the ERG queried the company's rationale for deriving weights for treatment discontinuation based on studies' sample sizes. The company provided updated annual discontinuation rates based on including an element of follow-up time. Table 22 provides the updated annualised risk of all-cause discontinuation.

Table 22. Updated annualised risk of all-cause discontinuation

Treatment	Annual all-cause discontinuation risk			Sources
	Weighted by sample size (base case)	Weighted by person time	Simple average	
PegIFNβ-1a	15.56%	15.56%	15.56%	ADVANCE[2]
IM IFNβ-1a 30	7.88%	8.27%	8.09%	Calabrese (2012),[58] CombiRx,[63] EVIDENCE,[70] BRAVO,[57] INCOMIN[74]
IFNβ-1a 22	6.00%	6.00%	6.00%	PRISMS[82]
IFNβ-1a 44	10.53%	9.74%	10.73%	Calabrese (2012),[58] EVIDENCE,[70] OPERA I[110] & II,[79] CARE MS I,[60] CARE MS II,[61, 62] REGARD[83]
IFNβ-1b	6.87%	7.54%	6.87%	IFNB MS Study,[73] BEYOND,[54] INCOMIN[74]
GA 20	11.02%	8.05%	8.54%	BEYOND,[54] CONFIRM,[64] Copolymer 1 Study,[65] REGARD,[83] Bornstein 1987[56]
GA 40	8.91%	8.91%	8.91%	GALA[71]
genGA 20	11.02%	8.05%	8.54%	Assumed equivalent to GA 20
genGA 40	8.91%	8.91%	8.91%	Assumed equivalent to GA 40
Teriflunomide	18.57%	18.50%	18.12%	TOWER,[88] TEMSO[85]
Dimethyl	18.01%	17.97%	18.01%	CONFIRM,[64]

Treatment	Annual all-cause discontinuation risk			Sources
	Weighted by sample size (base case)	Weighted by person time	Simple average	
Fumerate				DEFINE[67]
Alemtuzumab	2.59%	2.55%	2.59%	CARE MS I,[60] CARE MS II[61, 62]
Ocrelizumab	6.69%	6.69%	6.69%	OPERA I[110] & II[79]
GA, glatiramer acetate; genGA, generic glatiramer acetate; IFN, interferon; IM, intramuscular				

ERG summary

Deriving annual all-cause discontinuation risk weighted by person time may be more appropriate method than using the study sample size. Weighting by person time resulted in slight changes to the discontinuation risk for some DMTs. However, it must be borne in mind that this information was obtained from RCTs, and may not accurately reflect treatment discontinuation that would have been observed in a real-world setting over a longer time horizon.

5.3.7 Mortality

Mortality rates were required in the model to estimate the rate at which people died within in each model cycle over the time horizon. People with MS (both RRMS and SPMS) are at increased risk of death compared to general population mortality. Mortality is accounted for in the model by using age- and gender-specific all-cause mortality risks, and adjusted with different relative risks, independent of RRMS or SPMS. Additionally, it is assumed in the model that people with RRMS and SPMS have the same increased risk of mortality (see Table 36 for ERG discussion of model assumptions). Furthermore, it was assumed that there is no direct effect on mortality associated with treatment. However, there is some indirect treatment effect on mortality because DMTs delay progression; thus avoids the higher mortality multipliers.

Age- and gender-specific mortality from the general population were obtained from the UK ONS (2016),[111] with all–cause mortality risk adjusted by disease-specific risks obtained from Porkorski and colleagues (1997).,[11] as used in the base-case. The company justified their choice of relative risks used in the base-case and considered alternative sources in scenario analyses. Table 23 shows the relative risks applied to general population mortality.

Table 23. Relative risks for RRMS and SPMS mortality

EDSS	Relative risks obtained from Pokorski et al., (1997)[11]
1-3.5	1.60
4-6.5	1.84
7+	4.44
EDSS, Expanded disability status scale	

In scenario analyses the company interpolated the relative mortality risks obtained from Pokorski et al., (1997)[11] (see Table 24). It can be seen that the relative risks increase as EDSS levels increase. In further scenario analysis, the company considered a single relative risk of mortality of 2.88 obtained from Kingwell and colleagues (2012),[112] applied to general population mortality.

Table 24. Relative risks for RRMS and SPMS mortality (interpolated)

EDSS	Relative risks derived from Pokorski et al., (1997)[11]
0	1.000
1-1.5	1.432
2-2.5	1.600
3-3.5	1.637
4-4.5	1.674
5-5.5	1.842
6-6.5	2.273
7-7.5	3.097
8-8.5	4.447
9-9.5	6.454
EDSS, Expanded disability status scale	

ERG summary

Given that EDSS 10 (dead) health state was not included in the natural history cohort transition probability matrix, the ERG considers it appropriate to capture mortality by applying mortality multipliers to general population values.

5.3.8 Stopping rules

People in the model stopped DMT upon progressing to EDSS ≥7 and/or progressing to SPMS. After discontinuing treatment, disability progression in people with RRMS is based on the British Columbia natural history cohort. However, it is assumed that people who progressed to SPMS

their disability progression was based on the London, Ontario natural history cohort. Subsequent DMT was not considered for people with RRMS or SPMS.

5.3.9 Treatment effects

DMTs are considered to have a direct impact on disability progression and relapse frequency. However, there is an indirect treatment effect on mortality, as DMTs delay progression; thus avoids increased mortality multipliers.

5.3.9.1 Disability progression

Treatment specific HRs were derived for each DMT compared with no treatment. These HRs were then applied to the forward transition probabilities for the natural history cohort to determine disease progression for each treatment-specific DMT. DMTs were assumed not to have any direct impact on the backward transition probabilities (i.e., no direct impact to people who regress to less severe EDSS states).

When people in the model discontinue treatment, the treatment benefit is stopped, then people follow disease progression for the natural history cohort. Here, it is assumed that there is no residual benefit from taking DMTs and people would progress at the same rate as people who had not been treated with a DMT. The HRs for each DMT compared to placebo are presented in Table 25.

Table 25. Hazard ratios for confirmed disability progression for all DMTs compared to placebo at 3 and 6 months

Disease modifying therapy	CDP3M (CrI)	CDP6M (CrI)
PegIFNβ-1a	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]
GA 20mg	[redacted]	[redacted]
GA 40mg	[redacted]	[redacted]

Disease modifying therapy	CDP3M (CrI)	CDP6M (CrI)
Generic GA 20mg	[redacted]	[redacted]
Generic GA 40mg	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Dimethyl fumerate	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]

CDP (3 or 6M), confirmed disability progression (3 or 6M); CrI, credible intervals; IFN, interferon; IM, intramuscular; NA, not available, GA glatiramer acetate

5.3.9.2 Relapse

The effect of DMTs on reducing the relapse rates required information about relapse rates in the absence of DMTs (i.e., relapse rates from a placebo or natural history cohort), and the treatment effect of each DMT compared to placebo. Annualised relapse rates (see Table 26) were derived using information from the UK MS Survey and Patzold et al., (1982).[109] The company have provided alternative values obtained from other sources. Little commentary on the methodology was provided in the CS about how these values were derived. It can be seen that using the UK MS survey and Patzold et al.,(1982)[109] the rates range from 0.4900 to 0.7290 across EDSS levels. Treatment specific rate ratios (see Table 27) were applied to the natural history ARR to derive the relapse rates by EDSS for people on DMTs. Rate ratios were derived from the studies included in the company's MTC for ARR.

Table 26. Annualised relapse rates for a natural history cohort, using UK MS Survey and Patzold., 1982[109] and values from alternative sources

EDSS	ARR, using MS Survey and Patzold., (1982)[109] (base-case)		ARR, using ID527[4] Assessment	
	RRMS	SPMS	RRMS	SPMS
0	0.7090	0.0000	0.8895	0.0000
1-1.5	0.7290	0.0000	0.7885	0.0000
2-2.5	0.6760	0.4650	0.6478	0.6049
3-3.5	0.7200	0.8750	0.6155	0.5154
4-4.5	0.7050	0.5450	0.5532	0.4867
5-5.5	0.5910	0.5240	0.5249	0.4226
6-6.5	0.4900	0.4530	0.5146	0.3595
7-7.5	0.5080	0.3400	0.4482	0.3025
8-8.5	0.5080	0.3400	0.3665	0.2510
9-9.5	0.5080	0.3400	0.2964	0.2172

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

Table 27. Rate ratio on annualised relapse rates for each DMT compared to placebo

Disease modifying therapy	ARR (95%CrI)
PegIFNβ-1a	[redacted]
IM IFNβ-1a 30	[redacted]
IFNβ-1a 22	[redacted]
IFNβ-1a 44	[redacted]
IFNβ-1b	[redacted]
GA 20mg	[redacted]
GA 40mg	[redacted]
Generic GA 20	[redacted]
Generic GA 40	[redacted]
Teriflunomide	[redacted]
Dimethyl fumerate	[redacted]
Alemtuzumab	[redacted]
Ocrelizumab	[redacted]

ARR, annualised relapse rates; CrI, credible intervals; IFN, interferon; IM, intramuscular; NA, not available, GA, Glatiramer acetate

5.3.10 Health-related quality of life

The company undertook a systematic review to identify studies reporting HRQoL information for people with RRMS. The CS report 29 studies which were included in the review, of which 11 studies reported utility values by EDSS. The company reported that two studies[7, 8] were undertaken with a UK-specific population. For consistency, as used in previous technology appraisals the company used utility values obtained from Orme et al.,(2007).[9] Table 28 shows the utility values used in the model. Utility values are required for each EDSS level by type of MS and if experiencing a relapse or not. For people experiencing a relapse, the company applied a disutility of 0.071 for each EDSS level. The value placed on a relapse is has the same weight regardless of the EDSS level and type of MS (RRMS and SPMS). Utility values for SPMS were derived based on a utility decrement of 0.045 applied to the mean EDSS for RRMS.

Table 28. Summary of utility values used in company's cost-effectiveness analysis based on information reported by Orme et al., (2007)[9]

EDSS	No relapse		Relapse	
	RRMS	SPMS	RRMS	SPMS
0	0.8700	0.8250	0.7990	0.7540
1-1.5	0.7990	0.7540	0.7280	0.6830
2-2.5	0.7050	0.6600	0.6340	0.5890
3-3.5	0.5740	0.5290	0.5030	0.4580
4-4.5	0.6100	0.5650	0.5390	0.4940
5-5.5	0.5180	0.4730	0.4470	0.4020
6-6.5	0.4600	0.4150	0.3890	0.3440
7-7.5	0.2970	0.2520	0.2260	0.1810
8-8.5	-0.0490	-0.0940	-0.1200	-0.1650
9-9.5	-0.1950	-0.2400	-0.2660	-0.3110

Table 29 shows the utility values obtained from Thompson et al.[8] The company stated that the participants in the Kobelt study are the same as those in the Thompson study, with both having the same mean EDSS health statue values. In general, majority of the RRMS utility values reported in Thompson et al. are similar to those reported in Orme et al.,(2007).[9] Clear differences in the utility values can be seen for EDSS levels 7-7.5 and 8-8.5. For example, Thompson et al., (2017)[8] report a 0.1570 utility value for EDSS 8, while Orme et al., (2002)[9] report a value -0.0490. Using the value from Thompson., (2017)[8], people who occupy this health state would accrue more QALYs compared to Orme et al., (2007).[9]

Table 29. Summary of utility values obtained from Thompson et al., 2017[8]

EDSS	No relapse		Relapse	
	RRMS	SPMS	RRMS	SPMS
0	0.8980	0.8530	0.8270	0.7820
1-1.5	0.7870	0.7420	0.7160	0.6710
2-2.5	0.6950	0.6500	0.6240	0.5790
3-3.5	0.5730	0.5280	0.5020	0.4570
4-4.5	0.6050	0.5600	0.5340	0.4890
5-5.5	0.5690	0.5240	0.4980	0.4530
6-6.5[a]	0.4560	0.4110	0.3850	0.3400
7-7.5	0.3730	0.3280	0.3020	0.2570
8-8.5	0.1570	0.1120	0.0860	0.0410
9-9.5	-0.1100	-0.1550	-0.1810	-0.2260

[a] Derived from taking the mid-point of EDSS 6 (0.480) and 6.5 (0.431)
EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

The model captures the disutility associated with providing care for people with MS. Caregiver's disutilities used in the base-case were obtained from Acaster et al., (2013)[113] and alternative

disutilities obtained from Gani et al., (2008).[10] Table 30 shows the caregivers' disutility by EDSS. It was assumed that the burden associated with caring for people with RRMS and SPMS to be the same.

Table 30. Caregivers' utility decrements by EDSS

EDSS	RRMS/SPMS obtained from Acaster et al., (2013)[113]	RRMS/SPMS obtained from Gani et al., (2008)[10]
0	-0.0020	0.0000
1-1.5	-0.0020	0.0000
2-2.5	-0.0020	-0.0032
3-3.5	-0.0020	-0.0091
4-4.5	-0.0450	-0.0090
5-5.5	-0.1420	-0.0199
6-6.5	-0.1670	-0.0272
7-7.5	-0.0630	-0.0534
8-8.5	-0.0950	-0.1070
9-9.5	-0.0950	-0.1400

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

The company's systematic review to identify the HRQoL information identified two recent studies, with both analysis based on the same participants. Briefly, the Thompson and colleagues conducted a cross-sectional retrospective study of people living with multiple sclerosis. The aim of the study was to collect resource use and cost, and health-related quality of life information. A total of 5928 individuals were contacted via email, of which 779 responded. Participants from the UK had a mean age of 57 (SD = 10.8 years), with 70% being female. Mean EDSS of the sample was 5.5 (SD=2.2). 18% of the participants had a mild form of MS, and 51% and 31%, with moderate and severe MS, respectively. 37% of the participants had RRMS, with 37% and 24% having SPMS and PPMS, respectively. HRQoL information was collected using the EQ-5D, collected at one time point. The authors stated that no methods were used to address missing data. The ERG considers that this study adds to the existing evidence as it is recent and undertaken in a UK-specific population. Additionally, it includes information collected from people receiving treatment with more recent DMTs. Though these utility values may be plausible, it should be noted that the participants were older than those in the Orme study and the sample size was smaller.

Based on the caregivers disutilities obtained from Acaster et al, (2013)[113] it can be seen that there is a higher disutility experienced by caring for people with EDSS 5-5.5 and 6-6.5, as opposed to

higher EDSS levels. Though there may be some explanation for this, the ERG consider it more appropriate to use the disutilities from Gani et al. as these are more in line with our expectation. The model also captures the quality of life impact on people who experienced AE. Disutilities associated with AE are presented in CS Document B, Table 38, pages 136-137 and are reproduced below in Table 31.

Table 31. Disutility and duration associated with serious adverse events and non-serious adverse events

Adverse event	Disutility of non-serious event	Disutility of serious event	Source	Duration of non-serious event (days)	Duration of serious event (days)	Source
Arthralgia	−0.25	−0.25	Retrieved from NICE TA441, Table 91	10.50	24.50	Retrieved from NICE TA441,[102] Table 91
Back pain	−0.25	−0.50	Retrieved from NICE TA441 Table 91	10.50	24.50	Retrieved from NICE TA441 Table 91
Fatigue	0.00	0.00	Assumption	182.50	182.50	Assumption
Gastroenteritis	−0.07	−0.07	Retrieved from Swedish adaptation 2016	10.50	24.50	Retrieved from Swedish adaptation 2016
Headache	−0.14	−0.49	Retrieved from NICE TA533 Table 42	10.50	24.50	Retrieved from NICE TA533[114] Table 42
Immune thrombocytopenic purpura	−0.09	−0.09	Retrieved from NICE TA312 Table B7.4.4	15.00	81.00	Retrieved from NICE TA312[115] Table B7.4.4
Influenza-like illness	−0.08	−0.08	Retrieved from NICE TA441 Table 91	1.00	1.00	Retrieved from NICE TA441 Table 91
Injection-site reaction - erythema	0.00	0.00	Assumption	0.00	0.00	Assumption
Injection-site reaction - pain	0.00	0.00	Assumption	0.00	0.00	Assumption
Injection-site reaction - pruritus	0.00	0.00	Assumption	0.00	0.00	Assumption
Meningitis listeria	−0.02	−0.61	Bennett et al., (2000)[116]	365.00	365.00	Assumption
Nasopharyngitis	0.00	0.00	Retrieved from Swedish	7.00	14.00	Retrieved from Swedish

Adverse event	Disutility of non-serious event	Disutility of serious event	Source	Duration of non-serious event (days)	Duration of serious event (days)	Source
			adaptation from 2016			adaptation from 2016
Progressive multifocal leukoencephalopathy	−0.30	−0.30	Retrieved from NICE TA533 Table 42	365.00	365.00	Retrieved from NICE TA533 Table 42
Pneumonia / upper respiratory tract infection	−0.20	−0.20	Retrieved from NICE TA533 Table 42	7.00	14.00	Retrieved from NICE TA533 Table 42
Pyrexia	−0.11	−0.11	Retrieved from NICE TA441 Table 91	7.00	14.00	Retrieved from NICE TA441 Table 91
NICE, National Institute for Health and Care Excellence; TA, technology assessment;						

The quality of life impact per AE was derived by multiplying the disutility per event by the event duration. It can be seen that disutilities were obtained/derived from different literature sources. The underlying assumption is that these disutilities can be applied to a UK RRMS population. The ERG considers it appropriate to use these disutilities.

5.3.11 Resource use and costs

Cost assessment was based on assigning resource use and costs for pegIFNβ-1a and the comparators, health state management costs, monitoring costs and treatment of AE costs, all from the perspective of the NHS and PSS.

5.3.11.1 Intervention and comparators

Table 32 presents the annual treatment costs for each DMT. Annual costs presented are based on the list price for each DMT. Annual costs were derived from the annual dosage (per week and per year) of each DMT and the price per packet. These unit costs were cross-referenced against the eMC dm+d database and in general, the annual costs were thought to be derived appropriately.[117]

Table 32. Posology, unit costs for peginterferon beta-1a and the comparators (obtained from the company's response to the ERG's clarification questions)

Drug	Dosage	Frequency per week	Strength	Pack size	Price per Pack	Unit cost	Annual cost	Reference
PegIFNβ-1a 125 mcg	Week 0: 63mcg Week 2: 94 mcg Week 4+: 125mcg	0.5	125mcg	6	£1,962.00	£327.00	£8,502.00	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
PegIFNβ-1a 63 mcg & 94 mcg (Initiation pack)			1 x 63mcg 1 x 94mcg	2	£654.00	£327.00		
IM IFNβ-1a 30 mcg	30mcg weekly	1	30mcg	4	£654.00	£163.50	£8,502.00	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
SC IFNβ-1a initiation pack	Week 0-2: 8.8 mcg tiw	3	6x8.8mcg 6x22mcg	12	£552.19	£46.02	n/a	MIMS - June 2017
SC IFNβ-1a 22 mcg	Week 3-4: 22mcg tiw		22mcg	12	£613.52	£51.13	£7,975.76	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
SC IFNβ-1a 44 mcg	week 5+: 44mcg tiw		44mcg	12	£813.21	£67.77	£10,571.73	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018

Drug	Dosage	Frequency per week	Strength	Pack size	Price per Pack	Unit cost	Annual cost	Reference
SC IFNβ-1b 250 mcg	Day 1,3,5: 62.5mcg Days 7,9,11: 125mcg Days 13,15,17: 187.5mcg Days 19+: 250mcg	3.5	250mcg	15	£596.63	£39.78	£7,239.11	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
GA 20mg	20mg daily	7	20mg	28	£513.95	£18.36	£6,681.35	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
GA 40mg	40mg tiw	3	40mg	12	£513.95	£42.83	£6,681.35	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
genGA 20mcg	20mcg daily	7	20mcg	28	£462.56	£16.52	£6,013.28	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018
genGA 40mcg	40mcg tiw	3	40mcg	12	£462.56	£38.80	£6,013.28	British National Formulary. www.mediinescomplete.com , accessed September 10, 2018

Drug	Dosage	Frequency per week	Strength	Pack size	Price per Pack	Unit cost	Annual cost	Reference
Teriflunomide	14mg Daily	7	14mg	28	£1,037.84	£37.07	£13,528.99	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
Dimethyl fumerate	Week 1: 120mg Week 2+: 240mg	14	120mg	14	£343.00	£24.50	£17,848.75	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
			240mg	56	£1,373.00	£24.52		
Alemtuzumab	Year 1: 12mg for 5 days Year 2: 12mg for 3 days Year 3+: 12mg for 3 days	Yearly	12mg	1	£7,045.00	£7,045.00	Year 1: 35,225 Year 2: 21,135	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018
Ocrelizumab	Week 0: 300mg Week 2: 300mg Week 2+: 600mg every 6 months	every 6 months	300mg	1	£4,790.00	£4,790.00	£19,160.00	British National Formulary. www.mediinescomplete.com, accessed September 10, 2018

GA, glatiramer acetate; genGA, generic glatiramer acetate; n/a, not applicable; SC, subcutaneous; tiw, three times per week

5.3.11.2 Health state costs

Two types of disease management costs were considered in the economic model: costs of disease management by EDSS health states, and by disease phase (RRMS and SPMS) and costs of treating MS relapses. Disease management costs in the base-case were obtained from TA320 and inflated to current values using the hospital and community health service (HCHS) pay and price from PSSRU 2018. Values used in TA320 were obtained from TA127, where the resource use was based on a regression analysis of the information collected from the UK MS Survey 2005, which included 2,048 participants representing a 16% response rate from the people in the MS database. The regression analysis estimated/explored the impact of a range of covariates on the likelihood of resource use compare to a reference patient (patient of 0 years, female, RRMS, EDSS 0, no relapse and no DMT). Updated costs were applied to derive EDSS health state costs. Table 33 presents the disease management costs by EDSS health state and disease phase.

Table 33. Disease management costs by EDSS level (2017/18 values)

EDSS	RRMS health state costs (£)	SPMS health state costs (£)
0	965	1,301
1-1.5	1,004	1,340
2-2.5	735	1,071
3-3.5	4,025	4,360
4-4.5	1,950	2,285
5-5.5	3,307	3,644
6-6.5	4,415	4,750
7-7.5	11,621	11,956
8-8.5	28,304	28,640
9-9.5	22,648	22,985

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

5.3.11.3 Relapse costs

The cost of £2,168 for treating MS relapses is based on the relapse costs obtained from TA320 and subsequently inflated using the HCHS pay and price index from PSSRU 2018. Relapse treatment costs are the same for people with RRMS or SPMS on/off treatment. In the model these costs are calculated from the number of relapses in each cycle multiplied by the relapse treatment costs and summed across EDSS health states. Similar methods are used for people who are on/off treatment.

5.3.11.4 Monitoring

Resource use and costs associated with monitoring were clearly reported in CS Document C, Appendix M. Annual monitoring costs were reported for first year of DMT, and subsequent years are derived from the *"expected resource use per patient per year on treatment*" (CS Document C, Appendix M, pg.468). Resource use included visits to health care professionals (Neurology and nurse visits) and undergoing tests (e.g., full blood count, liver function test, renal function test and thyroid function test).

Table 34 reports the annual monitoring costs for the first year and subsequent years by DMT.

Table 34. Annual monitoring costs by disease modifying therapy (2017/18 values)

Disease modifying therapy	Monitoring costs	
	First year (£)	Subsequent years (£)
PegIFNβ-1a	238.07	207.45
IM IFNβ-1a 30	238.07	207.45
IFNβ-1a 22	271.94	207.45
IFNβ-1a 44	271.94	207.45
IFNβ-1b	238.07	207.45
GA 20mg	171.00	171.00
GA 40mg	171.00	171.00
Generic GA 20	171.00	171.00
Generic GA 40	171.00	171.00
Teriflunomide	618.08	345.78
Dimethyl fumerate	441.42	266.47
Alemtuzumab	653.08	580.80
Ocrelizumab	229.98	203.02
GA, glatiramer acetate; genGA, generic glatiramer acetate; n/a, not applicable; SC, subcutaneous; tiw, three times per week		

The ERG notes the higher costs associated with monitoring people on teriflunomide and alemtuzumab. Though not explicitly stated by the company these may reflect the mandatory monitoring for people taking these DMTs.[118] The ERG considers these resource use and costs to be appropriate.

5.3.11.5 Cost of treating adverse events

Resource use and costs associated with the treatment of AE were included in the analysis. Cost of treating AE were based on the annualised incidence of each AE, proportion of AE (non-serious and serious), and unit cost for treating each AE (non-serious and serious). Disutilities and duration of each AE are discussed in Section 5.3.10. The unit costs associated with treating people who experienced each AE are presented in Table 35. These costs were derived by taking the resource use combined with their unit costs. The most costly complications or adverse effects to treat were immune thrombocytopenic purpura, meningitis listeria and progressive multifocal leukoencephalopathy (PML), with treatment costs of £495.70, £15,067.80 and 10,857.00, respectively for both serious and non-serious forms, with the exception of immune thrombocytopenic purpura costing £6,782.80 for a SAE.

Table 35. Cost of managing adverse events (2018 values)

Adverse events	Cost per event (£)	
	Non-serious	Serious
Arthralgia	£0.62	£358.00
Back pain	£0.62	£872.00
Fatigue	£0.00	£66.20
Gastroenteritis	£38.00	£38.00
Headache	£0.52	£212.00
Immune thrombocytopenic purpura	£495.70	£6,782.80
Influenza-like illness	£0.52	£54.54
Injection-site reaction - erythema	£0.00	£536.74
Injection-site reaction - pain	£0.00	£536.74
Injection-site reaction - pruritus	£0.00	£536.74
Meningitis listeria	£15,067.80	£15,067.80
Nasopharyngitis	£0.00	£38.00
Progressive multifocal leukoencephalopathy (PML)	£10,857.00	£10,857.00
Pneumonia / urinary tract infection	£38.00	£38.00
Pyrexia	£0.52	£38.00

Adverse event annual unit costs were derived by weighting the cost for non-serious and serious AE by the proportion of serious events; then applying the incidence. The ERG accepts the methodology and the assumptions used to derive AE annual unit costs.

ERG summary

The ERG considers that the methods used to identify and inflate costs taken from the literature to be appropriate, and in keeping with the viewpoint of the analysis. However, the CS could further benefit with a critique of the resource use and cost studies, which could enhance the justification for selecting inputs for the base-case.

5.3.12 Overview of model assumptions and ERG critique

In Table 36, we present the company's modelling assumptions with comments from the ERG.

Table 36. Model assumptions with ERG's comments

Parameter	Base-case assumption	Justification	ERG's comment
Disability progression	*Disability progression and relapses were modelled independently, with independent treatment effects applied to each.*	*In line with previous NICE TAs (CS Document B, Table 26 pg.115). EDSS progression is a key driver of cost-effectiveness.* *A number of studies have shown a strong correlation between EDSS, resource consumption, and HRQOL. EDSS is the preferred tool for measuring disability in people with MS as recommended by the EMA.* *This approach avoids any potential double counting. In addition, it is a pragmatic approach, as modelling relapses as independent health states would significantly increase size and complexity of the model.* *However, this approach could have overestimated the effect of treatment on the ARRs, as they depended on the EDSS level. However, as the natural history ARRs were lower at higher*	The ERG considers this approach to modelling disability progression and relapses to be appropriate.

Parameter	Base-case assumption	Justification	ERG's comment
		levels of EDSS during the RRMS phase and during SPMS, the possible overestimated effect of treatment in the ARRs for pegIFNβ-1a could have been offset.	
	Treatments had an indirect effect on the risk of progression to SPMS and mortality.	*Delaying progression to higher EDSS levels avoids higher mortality multipliers associated with risk of mortality from MS and avoids higher probabilities of progression to SPMS.*	The ERG agrees with this assumption.
	Transition probabilities within RRMS: "The resulting natural history matrix has non-zero elements below its diagonal, reflecting the assumption that patients can improve to a lower EDSS level within the RRMS phase of the disease". *Transition probabilities within SPMS: This matrix is upper-triangular (i.e., with zero elements below the diagonal), reflecting the assumption that patients cannot improve to a lower EDSS level while in the SPMS phase.*	*As per the definition of RRMS, patients can regress (demonstrated in the BCMS data set), as per the definition of SPMS patients cannot regress – aligned with the London, Ontario, data set.*	The ERG considers using the BCMS dataset to derive natural history transition probabilities for RRMS and using the London, Ontario dataset for transitions in SPMS to be appropriate.
	After treatment discontinuation, patients are assumed to follow the natural disease progression course.	*In line with previous NICE TAs (CS Document B, Table 26 pg.115). An escalation of treatment (such as to fingolimod/ ocrelizumab, and alemtuzumab) would be likely in clinical practice. This approach would make treatments with the highest discontinuation rates most cost-effective ones, as they transition to higher efficacy drugs.*	As suggested by the company, it is likely that people who discontinue initial DMT are likely to receive a subsequent DMT.
Mortality	*The same RRs were assumed for the RRMS and SPMS phases.*	*Due to lack of data (conservative assumption)*	The ERG considers this to be a plausible assumption.
Treatment waning	*The treatment effect assumed to wane over time, with the same decline applying to all DMTs.*	*In line with previous NICE TAs CS Document B, Table 26 pg.115.*	For consistency the company provided this functionality in the economic model.

Parameter	Base-case assumption	Justification	ERG's comment
	▪ ***Year 1-2: 100% of the treatment benefit*** ▪ ***Years 3-5: 75% of the full treatment effect*** ▪ ***Year 6 onwards: 50% of the full treatment effect*** *This assumption was applied equally to all comparators.*		
Time horizon	*50 years*	*Lifetime equivalent consistent with NICE reference case.*	ERG considers the 50-year time horizon to be appropriate to capture the costs and benefits of the treatments.
HRQoL	*Fatigue, injection-site reaction – erythema, injection-site reaction – pain, and injection-site reaction – pruritus assumed not be associated with a disutility.*	*Due to lack of data.*	These assumptions are all plausible.
	It was assumed that a patient who received treatment would incur the risk of disutility and costs associated with AEs for each year in the model. This may have overestimated the impact of AEs, as patients with severe/frequent AEs may have withdrawn from treatment during the first few years.	*Due to lack of data.*	
	Caregiver disutility values by EDSS and disease phase (i.e., RRMS vs. SPMS) were assumed to be the same for both disease phases.	*Due to lack of data (conservative assumption)*	
Costs	*Non-serious type of fatigue, injection-site reaction – erythema, injection-site reaction – pain, injection-site reaction – pruritus, and nasopharyngitis are assumed to have no costs associated with them.*	*Injection-site reactions often do not lead to any resource use, particularly not ones relevant as part of a payer perspective.*	This assumption is in-line with other technology appraisals.

AE, adverse event; BCMS, British Columbia multiple sclerosis; DMT, disease modifying theray; EDSS, expanded disability status scale; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology assessment

5.4 Cost-effectiveness results

The following section presents the company's cost-effectiveness results reported in the CS (Document B). In the CS, results have been reported on the basis of:

- List prices for pegIFNβ-1a and comparators (IM IFNβ-1a 30µg, IFNβ-1a 22µg, IFNβ-1a 44µg, GA 20mg, GA 40mg, generic GA 20mcg, generic GA 40mcg, teriflunomide, dimethyl fumerate, alemtuzumab, and ocrelizumab).

The results of each these analyses are appraised and critiqued in Section 5.4.1.

5.4.1 Cost-effectiveness results: pegIFNβ-1a versus comparators at list prices

The company reports deterministic and probabilistic results, as well as sensitivity and scenario analyses results for the comparison between pegIFNβ-1a versus IM IFNβ-1a 30µg, IFNβ-1a 44µg, GA 20 mg, GA 40 mg, generic GA 20 mcg, generic GA 40 mcg, teriflunomide, dimethyl fumerate, alemtuzumab, and ocrelizumab only. Main outcomes are reported in terms of LY gained and QALY gained; results are reported in the form of an ICER expressed as cost per QALY gained.

5.4.1.1 Company's base-case results

The results in Table 37 show that alemtuzumab dominated all comparators except pegIFNβ-1a. Compared with pegIFNβ-1a, alemtuzumab was £1,250 more costly and expected to yield 1.082 more QALYs, which equates to an ICER of approximately £1,200 per QALY gained.

Table 37. Company's deterministic base-case results

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
PegIFNβ-1a	£273,641	19.275	4.393	-	-	-	-
Alemtuzumab	£274,892	19.281	5.475	£1,250	0.006	1.082	£1,155
Generic GA 20mcg	£282,343	19.194	3.646	£7,451	-0.087	-1.829	Dominated
Generic GA 40mcg	£284,674	19.195	3.658	£9,783	-0.086	-1.818	Dominated
GA 20mg	£285,064	19.194	3.646	£10,173	-0.087	-1.829	Dominated

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
GA 40mg	£287,676	19.195	3.658	£12,784	-0.086	-1.818	Dominated
SC IFNβ-1a 44	£292,969	19.258	4.224	£18,077	-0.024	-1.251	Dominated
IM IFNβ-1a 30	£294,199	19.228	3.929	£19,307	-0.053	-1.547	Dominated
Teriflunomide	£297,437	19.211	3.796	£22,545	-0.070	-1.679	Dominated
Dimethylfumarate	£308,506	19.224	3.949	£33,614	-0.057	-1.526	Dominated
Ocrelizumab	£339,668	19.201	4.894	£64,776	-0.080	-0.581	Dominated

5.4.1.2 Company's probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PAS) was undertaken for the outcome cost per QALY only. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to key model input parameters, and these were considered appropriate. However, were there was missing information about the standard error or confidence interval, the company assumed it to be ±25% of the mean, which the ERG considered appropriate to represent the uncertainty about the input value. As presented in Table 38, the ERG notes that the results for the PSA show that alemtuzumab dominates all treatment options including pegIFNβ-1a, which suggests that alemtuzumab is the least costly and the most effective treatment option. Compared with the deterministic results, the PSA results for the expected costs are underestimated and the expected benefits are overestimated.

Table 38. Company's probabilistic sensitivity analysis results

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	£255,439	19.298	6.378	-	-	-	
pegIFNβ-1a	£256,067	19.350	5.259	£628	0.052	-1.119	Dominated
Generic GA 20mcg	£263,692	19.267	4.575	£8,253	-0.031	-1.802	Dominated
Generic GA 40mcg	£266,683	19.264	4.571	£11,244	-0.034	-1.807	Dominated
GA 20mg	£266,761	19.253	4.560	£11,322	-0.045	-1.818	Dominated
GA 40mg	£269,683	19.267	4.581	£14,244	-0.031	-1.797	Dominated
IFNβ-1a 44	£276,057	19.335	5.125	£20,618	0.037	-1.252	Dominated

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
IM IFNβ-1a 30µg	£277,288	19.305	4.851	£21,849	0.007	-1.527	Dominated
teriflunomide	£279,016	19.264	4.721	£23,576	-0.034	-1.657	Dominated
Dimethylfumarate	£290,828	19.298	4.863	£35,389	0.000	-1.515	Dominated
Ocrelizumab	£329,231	19.292	5.780	£73,792	-0.006	-0.598	Dominated
IFN, interferon; IM, intra-muscular; LY, life-years; QALY, quality adjusted life-years;							

Each simulation of the incremental costs and incremental QALYs for pegIFNβ-1a versus each comparator were graphed/plotted on separate cost-effectiveness planes, along with their respective cost-effectiveness acceptability curves (CEAC). For 5,000 simulations, the scatterplot (see Figure 3. Scatterplot of pegIFNβ-1a versus alemtuzumab on the cost-effectiveness plane, company base-case using list prices) shows that there is some correlation between incremental costs and benefits. Figure 4 shows the results of the PSA in the form of a CEAC for the comparison between pegIFNβ-1a and alemtuzumab. The curves show the proportion of simulations in which treatments are cost-effective at different WTP thresholds for a QALY. Results show that at a WTP threshold of £20,000 per QALY pegIFNβ-1a compared to alemtuzumab has a probability of 0.17 of being cost-effective. The PSA results for pegIFNβ-1a versus other comparisons are reported in Table 39.

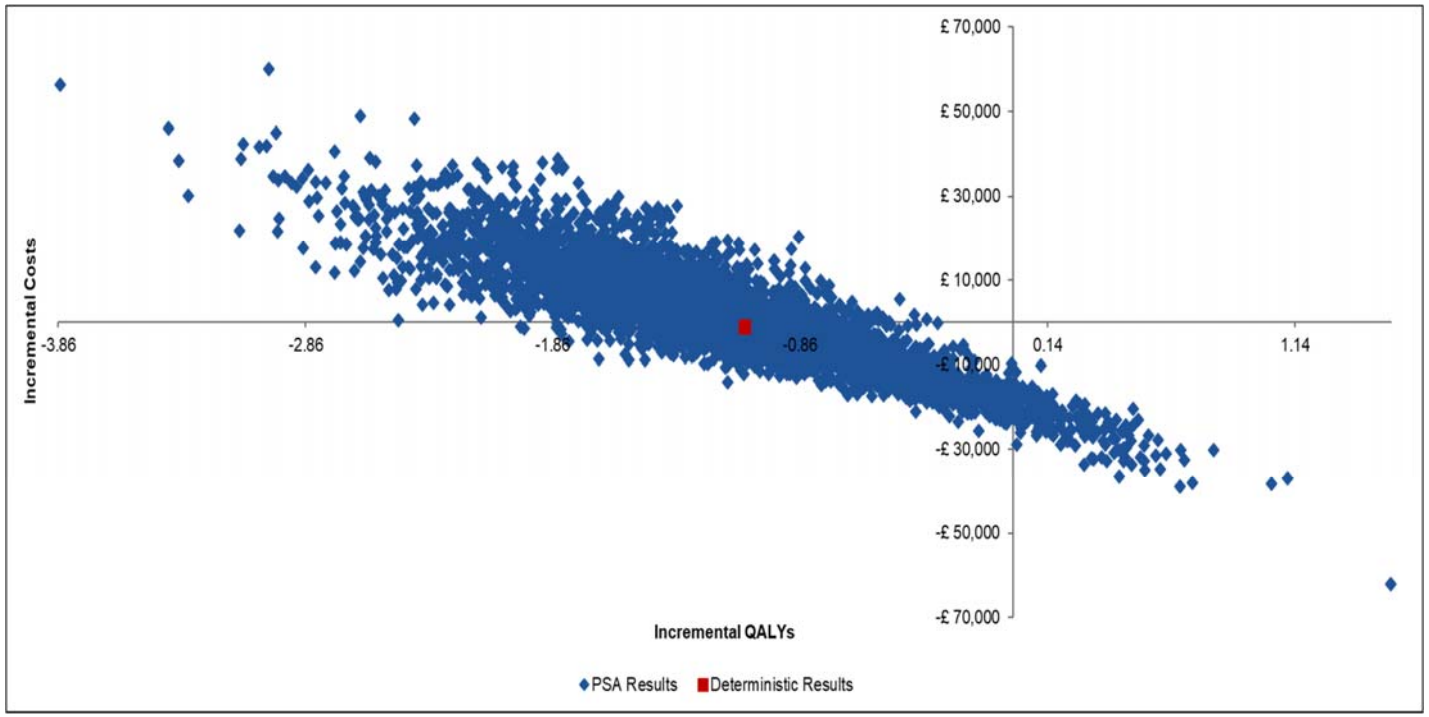

Figure 3. Scatterplot of pegIFNβ-1a versus alemtuzumab on the cost-effectiveness plane, company base-case using list prices

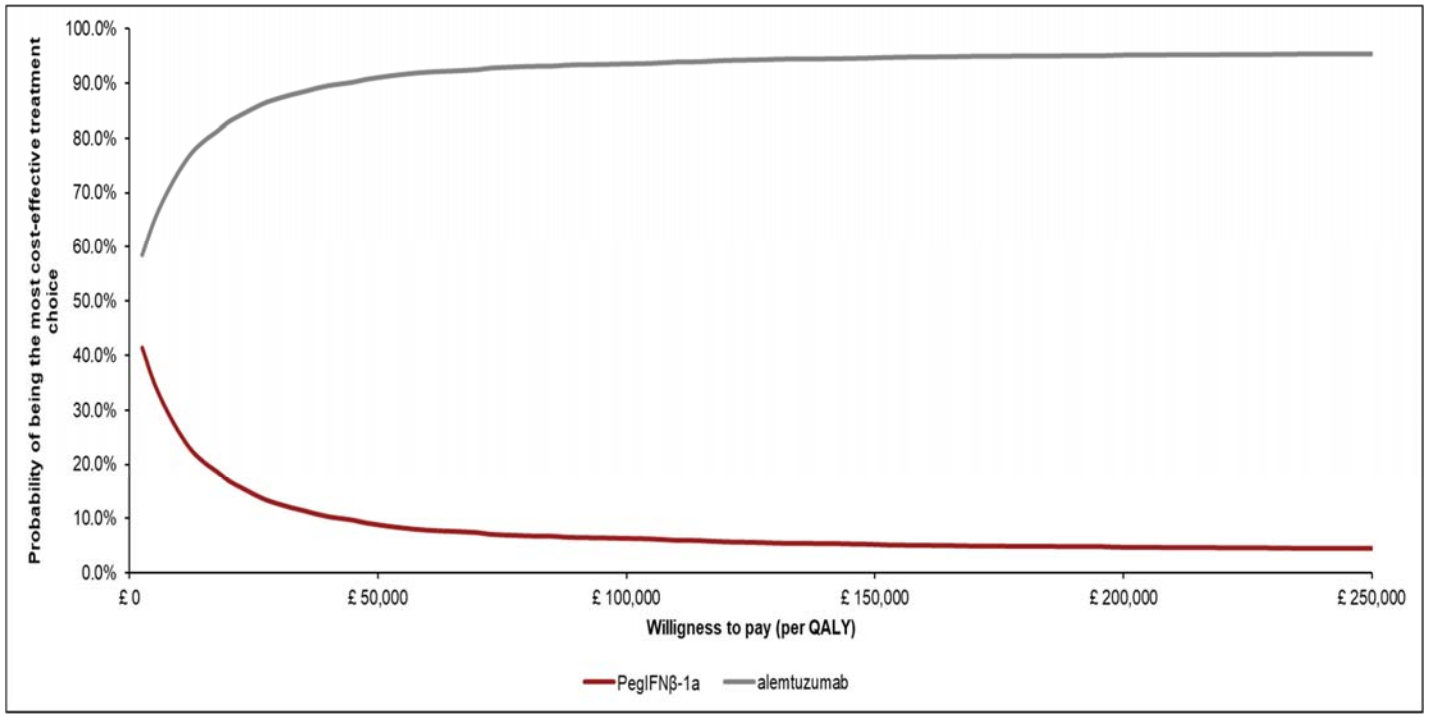

Figure 4. Cost-effectiveness acceptability curve, company base-case using list prices

Table 39. PSA results for pegIFNβ-1a compared to other comparators (WTP threshold of £20,000 per QALY)

Treatment	Probability of being cost-effective
Generic GA 20mcg	0.85
Generic GA 40mcg	0.87
GA 20mg	0.89
GA 40mg	0.90
IFNβ-1a 44µg	0.92
IM IFNβ-1a 30µg	0.95
Teriflunomide	0.98
Dimethyl fumarate	0.99
Ocrelizumab	1.00

IFN, interferon; IM, intramuscular; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years; WTP, willingness-to-pay threshold, GA, Glatiramer acetate

In general, the ERG considers the distributions used around key input parameters, and applying a ±25% variation to the mean values where standard errors of confidence intervals are missing to be appropriate.

5.4.1.3 Company's deterministic sensitivity analysis results

A number of deterministic one-way sensitivity analyses were undertaken to explore the impact on the ICER to making changes to key model input parameters. Parameters were varied according to the lower and upper bound of their respective 95% CI or by assuming uncertainty of ±20% of the point estimate where the standard errors or confidence intervals were missing. The results are presented in the form of tornado diagrams. Figure 10 reports the results for the comparison between pegIFNβ-1a and alemtuzumab and shows that the HR for disability progression had the greatest impact to the ICER.

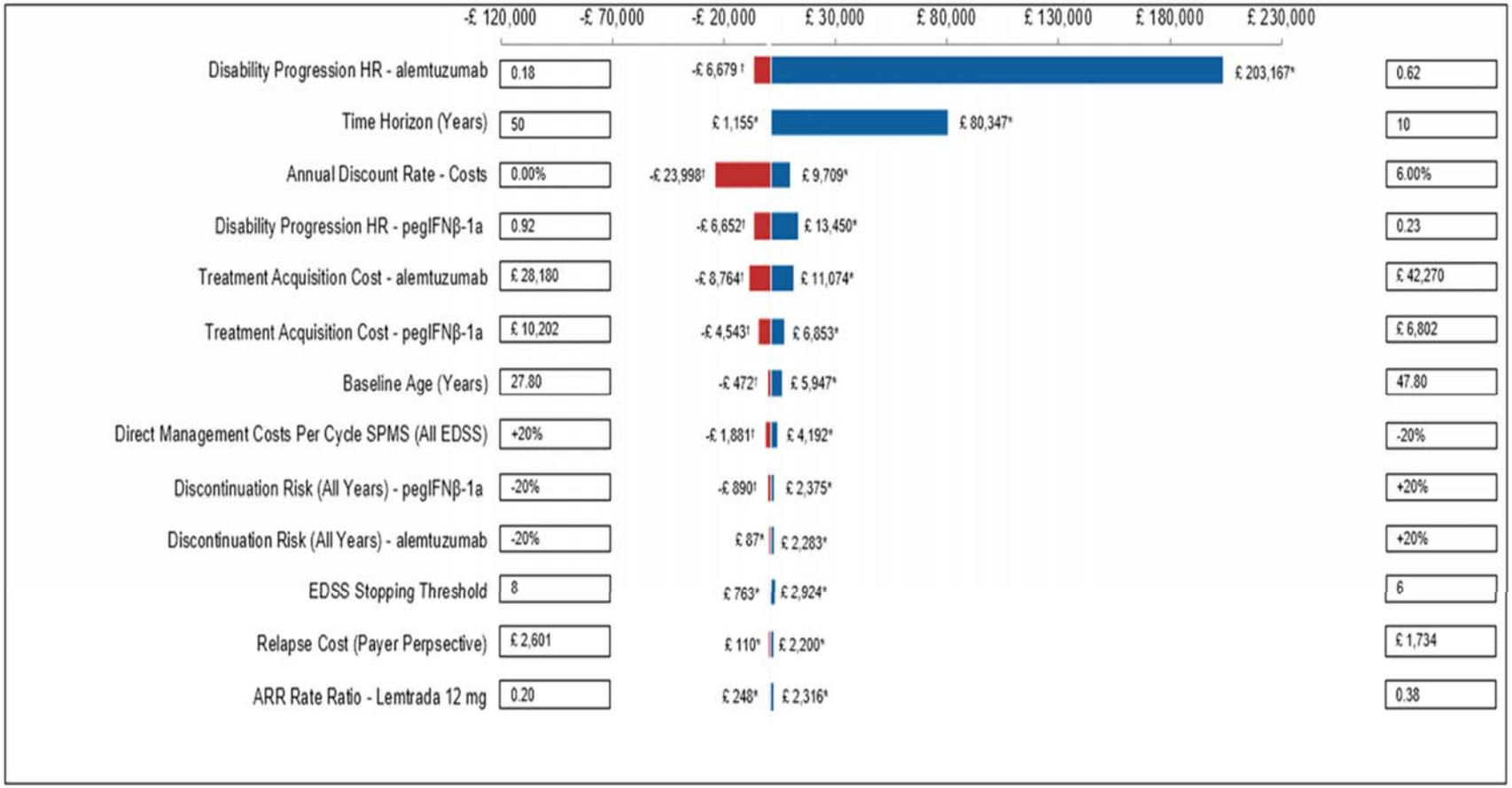

Figure 5. Tornado diagram for the comparison between pegIFNβ-1a and alemtuzumab, using the assumed PAS for comparators

5.4.1.4 Company's scenario analysis results

The company undertook a range of scenario analyses to assess the impact of each change to the base-case results. The following scenario analyses were undertaken (see Table 40):

Table 40. Description of the company's scenario analyses in comparison to the base-case

Scenario	Base-case analysis	Scenario analysis
1	Time horizon: 50 years	Time horizon: 20 years
2	Discounting costs and effects 3.5%	Discounting costs 0%; effects 1.5%
3	Discounting costs and effects 3.5%	Discounting costs 1.5%; effects 0%
4	Patient characteristics from ADVANCE trial	Patient characteristics from TA527[4] report; RSS
5		Natural history relapse rate from TA527[4] report
6	Based on information obtained from the London, Ontario dataset	Natural History transition from RRMS to SPMS = 0
7	Relative efficacy using CDP6M	Relative efficacy using CDP3M
8	Discontinuations; Weighted randomised controlled trial all-cause discontinuation	Discontinuations; parity assumptions 5% for all DMTs; ID527[4] report
9	Discontinuations; Weighted randomised controlled trial all-cause discontinuation	Discontinuations; Weighted randomised controlled trial ADRs only
10	Year 0-2: 100%; Year 2-5: 75%; Year 5+: 50%	Waning effect - none
11	AE- included in analysis	AE - exclude from analysis
12	Health state utility values obtained from Orme et al., (2008)[9]	Health state utility - from TA527[4] report
13	Caregiver disutility - from Acaster et al., (2013)[113]	Caregiver disutility - from Gani et al., (2008)[10]
14	Health state costs obtained from TA320 and inflated to current values using the HCHS pay and price index from PSSRU 2018 (Curtis and Burns., 2018[100])	Health state costs – Tyas et al., (2007)[107] - 25% non-medical costs
15		Health state costs - Tyas et al., (2007)[107]- 100% non-medical costs
16		Health states costs BOI - 100% community & adaptations
17	Mortality obtained from Pokorski et al., (1997)[11]	Mortality SMR 2.8 – Kingwell et al., (2012)[112]

ADR, adverse drug reaction; BOI, burden of illness; CDP, confirmed disability progression; PSSRU, personal and social services research unit; SMR, standardised mortality ratio; TA, technology appraisal

5.4.2 Model validation and face validity check

Face validity checks consisted of exploring the plausibility of the clinical outcome results from the economic model. Table 41 and Table 42 shows the disaggregated results of the base-case clinical model outcomes and the disaggregated results of the incremental cost-effectiveness analysis, respectively.

Table 41. Disaggregated clinical model outcome results of the base-case for Peg-IFNβ-1a versus the comparators

DMTs	PegIFNβ-1a	GA20	GA40	genGA20	genGA40	IFNβ-1b 22	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	Teriflunomide	DMF	Ocrelizumab	Alemtuzumab
Health outcomes													
Life years (undiscounted)	34.64	34.42	34.42	34.41	34.42	NA	34.60	NA	34.51	34.46	34.50	34.41	34.67
EDSS													
Mean baseline	2.232	2.232	2.232	2.232	2.232	NA	2.232	NA	2.232	2.232	2.232	2.232	2.232
Mean change	5.945	6.072	6.067	6.072	6.067	NA	5.956	NA	6.001	6.050	6.030	5.592	5.046
Mean years spent EDSS <7 (undiscounted)	15.203	13.814	13.837	13.814	13.837	NA	14.894	NA	14.387	14.112	14.342	15.997	17.184
Relapse													
Total number	15.850	15.062	15.035	15.062	15.035	NA	15.416	NA	15.649	15.807	15.316	14.004	12.836
Mean annualised rate	0.458	0.438	0.437	0.438	0.437	NA	0.446	NA	0.453	0.459	0.444	0.407	0.357
SPMS													
Years spent SPMS free (undiscounted)	12.69	11.68	11.70	11.68	11.70	NA	12.45	NA	12.08	11.89	12.05	13.16	14.07
Progressions to SPMS (%)	91.87%	92.76%	92.74%	92.76%	92.74%	NA	92.05%	NA	92.37%	92.59%	92.45%	90.61%	88.93%

DMTs	PegIFN β-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 22	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	Teriflu nomide	DMF	Ocreliz umab	Alemtu zumab
Annual rate of discontinuation (mean)	0.027	0.027	0.027	0.027	0.027	NA	0.027	NA	0.027	0.027	0.027	0.026	0.026
Reasons for discontinuation													
Progressing to EDSS ≥7 (%)	6.61%	16.10%	18.94%	16.10%	18.94%	NA	12.61%	NA	18.50%	8.29%	7.83%	13.33%	21.49%
Progression to SPMS (%)	19.36%	24.86%	28.00%	24.86%	28.00%	NA	25.60%	NA	30.02%	17.18%	17.55%	32.85%	47.79%
Dropout (%)	74.03%	59.04%	53.06%	59.04%	53.06%	NA	61.79%	NA	51.48%	74.53%	74.62%	53.81%	30.73%

DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate (Copaxone); genGA, generic glatiramer acetate (Brabio); IFN, interferon; intramuscular; NA, not applicable; SC, subcutaneous; SPMS, secondary-progressive multiple sclerosis

Table 42. Disaggregated economic model outcome results of the base-case for Peg-IFNβ-1a versus the comparators

DMTs	PegIFN β-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 22	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflun omide	DMF	Ocreliz umab	Alemtu zumab
Health outcomes (undiscounted)													
Total QALYs	4.20	2.95	2.97	2.95	2.97	NA	3.93	NA	3.45	3.20	3.44	5.20	6.37
Patient	6.77	5.62	5.64	5.62	5.64	NA	6.53	NA	6.08	5.84	6.07	7.67	8.79
Caregiver	-2.570	-2.668	-2.667	-2.668	-2.667	NA	-2.593	NA	-2.630	-2.648	-2.631	-2.473	-2.387

DMTs	PegIFN β-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 22	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	Ocrelizumab	Alemtuzumab
Cost outcomes													
Direct costs (undiscounted)													
Disease management	£490,544	£516,403	£515,978	£516,403	£515,978	NA	£496,414	NA	£505,845	£510,813	£506,526	£466,761	£446,154
Drug	£35,915	£32,134	£36,009	£28,921	£ 32,408	NA	£56,086	NA	£50,569	£47,232	£64,609	£131,775	£56,824
Administration and monitoring	£1,046	£968	£1,068	£968	£ 1,068	NA	£1,305	NA	£1,410	£1,446	£1,119	£9,383	£5,784
Relapses	£34,359	£32,652	£32,594	£32,652	£32,594	NA	£33,420	NA	£33,925	£34,266	£33,202	£30,359	£26,850
AE management	£5	£0	£0	£0	£0	NA	£3	NA	£2	£0	£10	£0	£284
Total	£561,870	£582,157	£585,649	£578,944	£582,049	NA	£587,228	NA	£591,751	£593,758	£605,465	£638,278	£535,897
Cost-effectiveness													
Incremental QALYs		1.26	1.23	1.26	1.23	NA	0.27	NA	0.76	1.01	0.77	-1.00	-2.17
Incremental Cost (£)		-£20,288	-£23,780	-£17,075	-£20,179	NA	-£25,358	NA	-£29,882	-£31,888	-£43,596	-£76,408	£25,973
ICER (£)		PegIFN β-1a dominates	PegIFN β-1a dominates	PegIFN β-1a dominates	PegIFN β-1a dominates	NA	PegIFN β-1a dominates	NA	PegIFN β-1a dominates	PegIFN β-1a dominates	PegIFN β-1a dominates	PegIFN β-1a less costly, less effective	PegIFN β-1a dominated

AE, adverse event; DMF, dimethyl fumarate; DMT, disease-modifying therapy; GA, glatiramer acetate; genGA, generic glatiramer acetate; ICER , incremental cost-effectiveness ratio; NA, not applicable, PegIFN, PEGylated interferon; SC, subcutaneous

5.5 Exploratory and sensitivity analyses undertaken by the ERG

5.5.1 The ERG's suggested amendments

Based on our critique of the company's economic model, the ERG made changes to the company's model to explore the impact of each change to the company's base-case results. The suggested changes, along with the justification are presented:

- Interpolated disease-specific relative risk obtained from Pokorski et al., (1997)[11](see Table 43)

Table 43. Increased risk of mortality using the interpolated values from Pokorski et al.(1991)[11]

EDSS	Values used in the company's base-case	ERG's preferred values	Justification
0	1.600	1.000	The ERG agrees that there is an increased risk of mortality compared to the general population. Mortality multipliers applied to some EDSS levels might have been over- or underestimated. For example, people with EDSS 0, it is assumed that there is a 1.6 increased risk of mortality compared to the general population. Conversely, the interpolated value for EDSS 0 assumes that there is no increased risk of mortality compared to the general population. The ERG considers the interpolated values to better reflect the increased risk of mortality compared to the general population
1-1.5	1.600	1.432	
2-2.5	1.600	1.600	
3-3.5	1.600	1.637	
4-4.5	1.840	1.674	
5-5.5	1.840	1.842	
6-6.5	1.840	2.273	
7-7.5	4.440	3.097	
8-8.5	4.440	4.447	
9-9.5	4.440	6.454	
EDSS, expanded disability status scale; ERG, evidence review group			

- Caregivers utility decrements obtained from Gani et al., (2008)[10](see Table 44)

Table 44. Caregivers utility decrements obtained from Ganie et al., (2008)[10]

EDSS	Values used in the company's base-case from Acaster et al., (2013)[113]	ERG's preferred values from Gani et al., (2008)[10]	Justification
0	-0.0020	0.0000	In consultation with our clinical advisor, the caregivers utility decrements obtained from Gani et al., (2008)[10] appear to be more appropriate, we would expect the caregivers utility decrements to increase as EDSS levels rise. Caregivers utility decrements for EDSS 5-5.5 and 6-6.5 appear to be higher compared to the utility decrements for more severe EDSS levels
1-1.5	-0.0020	0.0000	
2-2.5	-0.0020	-0.0032	
3-3.5	-0.0020	-0.0091	
4-4.5	-0.0405	-0.0090	
5-5.5	-0.1420	-0.0199	
6-6.5	-0.1670	-0.0272	
7-7.5	-0.0630	-0.0534	
8-8.5	-0.0950	-0.1070	
9-9.5	-0.0950	-0.1400	
EDSS, expanded disability status scale; ERG, evidence review group			

- All-cause discontinuation risk of 5% per annum (see Table 45)

Table 45. Annualised risk of all-cause discontinuation

Disease-modifying therapy	Annual all-cause discontinuation risk		Justification
	Weighted by sample size (base case)	Based on evidence from the RSS	
PegIFNβ-1a	15.56%	5% per annum	In consultation with our clinical advisor, using RCTs may not be the best way to capture real-life tolerability/discontinuations. First, RCTs can be considered artificial, with highly selected/motivated participants. Second, there may be various non-clinical reasons for discontinuation (e.g. withdrawal of consent), and third, limited long-term follow-up. Given the limitations, the ERG considers it more appropriate to use estimates from post-marketing surveillance/real life clinical studies (e.g. RSS), as these can provide better rates for discontinuation. A parity of 5% per annum was used in a previous assessment, (Melendez-Torres et al., 2017[6]) which was based on evidence from the RSS. The ERG acknowledges that some of the DMTs (pegIFNβ-1a, teriflunomide, alemtuzumab, dimethyl fumerate, and ocrelizumab) included in the economic analysis were not included in the RSS. The ERGs preference would be to use 5% per annum for the older DMTs and another estimate for newer DMTs. However, given the paucity of real-life studies following up people on newer DMTs, we assumed that the discontinuation rate is the same for the newer DMTs. Our clinical advisor suggested that there is not a good reason why the annual all-cause discontinuation for pegIFNβ-1a is higher compared to other IFNs.
IM IFNβ-1a 30	7.88%		
IFNβ-1a 22	6.00%		
IFNβ-1a 44	10.53%		
IFNβ-1b	6.87%		
GA 20	11.02%		
GA 40	8.91%		
genGA 20	11.02%		
genGA 40	8.91%		
Teriflunomide	18.57%		
Dimethyl fumarate	18.01%		
Alemtuzumab	2.59%		
Ocrelizumab	6.69%		

GA, glatiramer acetate; genGA, generic glatiramer acetate; IFN, interferon; IM, intramuscular; RCTs, randomised-controlled trials; RSS, Risk-Sharing Scheme

- RRMS relapse frequency from the ID527[4] assessment (see Table 46) (Melendez-Torres et al., 2017)[6]

Table 46. RRMS relapse frequency from the ID527[4]

EDSS	Values used in the company's base-case (UK MS Survey and Patzold., 1982)[109]	ERG's preferred values (based on ID527[4] assessment)	Justification
0	0.7090	0.8895	Values shown here are for the annual relapse frequency by EDSS for a natural history cohort (i.e. in the absence of DMTs). The values used by the company show that there is a steady decrease in the annual relapse rates. In consultation with our clinical advisors, they suggested that they would expect there to be a gradual decrease in the annual relapse frequency. Hence, we considered the values reported in ID527[4] assessment, which is based on the British Columbia cohort to be more appropriate. These values show that annual relapse rates decreases as EDSS levels increases
1-1.5	0.7290	0.7885	
2-2.5	0.6760	0.6478	
3-3.5	0.7200	0.6155	
4-4.5	0.7050	0.5532	
5-5.5	0.5910	0.5249	
6-6.5	0.4900	0.5146	
7-7.5	0.5080	0.4482	
8-8.5	0.5080	0.3665	
9-9.5	0.5080	0.2964	

EDSS, expanded disability status scale; ERG, evidence review group

- SPMS relapse frequency from the ID527[4] assessment (see Table 47) (Melendez-Torres et al., 2017)[6]

Table 47. SPMS relapse frequency from the ID527[4]

EDSS	Values used in the company's base-case (UK MS Survey and Patzold., 1982)[109]	ERG's preferred values (based on ID527[4] assessment)	Justification
0	0.000	0.000	Annual relapse rates for people with SPMS were derived from information obtained from the UK MS and Patzold et al., (1982).[109] Given that people with SPMS is characterised by increasing disability commonly without relapses; though some people continue to experience relapses, we considered that some of these values to overestimate the annual relapse rate. For example, the annual relapse rate for people with EDSS 3-3.5 (SPMS) is 0.875, which is higher than EDSS 2-2.5 (SPMS) with a value of 0.4650. This suggests that people in EDSS 3-3.5 health state experience more relapses than people in EDSS 2-2.5. Furthermore, the annual relapse rate for people in EDSS 3-3.5 (SPMS) is more frequent than people in the corresponding health state but with RRMS (0.720). The ERG considered the ID527[4] assessment values to be more appropriate because the
1-1.5	0.000	0.000	
2-2.5	0.465	0.605	
3-3.5	0.875	0.515	
4-4.5	0.545	0.487	
5-5.5	0.524	0.423	
6-6.5	0.453	0.360	
7-7.5	0.340	0.303	
8-8.5	0.340	0.251	
9-9.5	0.340	0.217	

EDSS	Values used in the company's base-case (UK MS Survey and Patzold., 1982)[109]	ERG's preferred values (based on ID527[4] assessment)	Justification
			relapse rates decrease as EDSS levels increase and the annual relapse rates in people with SPMS are less than the relapse rates for people with RRMS.
EDSS, expanded disability status scale; ERG, evidence review group; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis			

5.5.2 Probabilistic sensitivity analysis

The ERG re-run the PSA to obtain results that reflect the values and assumptions forming the ERG suggested base-case. The revised PSA results, which shows the joint distribution of cost and QALY estimates were generated through 5000 iterations and are depicted incrementally in the form of a scatterplot plotted on a cost-effectiveness plane, and cost-effectiveness acceptability curves, presented in Figure 6 and Figure 7, respectively.

5.6 Conclusions of the cost-effectiveness section

The company's submission is based on an economic analysis of pegIFNβ-1a compared to other DMTs for treating people with RRMS. The model captured the key features of the natural history of people RRMS: RRMS disease progression (and regression), progression to SPMS, progression within SPMS, relapses and AE associated with treatment. Using the current model structure and the company's assumptions, the base-case results are unlikely to be unbiased. However, it should be noted that these results are based on the list price for each DMT; hence the analysis does not incorporate any commercial agreements between the companies and the Department of Health.

6 IMPACT OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Impact of ERG changes on the company's base-case results

Here we present the results following the ERG's suggested changes to the company's model inputs and the impact of each change to the company's base-case results. Results are presented using the list prices for all comparators.

6.1.1 Impact of ERG's suggested changes on comparison between peginterferon beta-1a and its comparators

In Table 48, we present the results for each change and its impact to the company's base-case results, using the list prices for each comparator.

- Interpolated disease-specific relative risk obtained from Pokorski et al., (1997)[11]

Table 48. Exploratory results, using interpolated relative risk obtained from Pokorski et al., (1997)[11]

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
PegIFNβ-1a	£266,720	19.00	4.52	-	-	-	-
Alemtuzumab	£268,897	19.05	5.60	£2,177	0.06	-1.08	£2,019
Generic GA 20mcg	£274,659	18.88	3.78	£7,939	0.116	0.739	Dominated
Generic GA 40mcg	£277,005	18.88	3.80	£10,286	0.114	0.727	Dominated
GA 20mg	£277,382	18.88	3.78	£10,662	0.116	0.739	Dominated
GA 40mg	£280,008	18.88	3.80	£13,289	0.114	0.727	Dominated
SC IFNβ-1a 44	£285,882	18.97	4.36	£19,163	0.026	0.167	Dominated
IM IFNβ-1a 30	£286,836	18.93	4.06	£20,116	0.068	0.459	Dominated
Teriflunomide	£289,924	18.90	3.93	£23,204	0.092	0.591	Dominated
Dimethylfumarate	£301,126	18.92	4.08	£34,406	0.073	0.439	Dominated
Ocrelizumab	£333,334	18.95	5.02	£66,614	0.049	-0.499	Dominated

- Caregivers utility decrements obtained from Gani et al., (2008)[10](see Table 49)

Table 49. Exploratory analysis, using the caregivers' utility decrements obtained from Gani et al., (2008)[10]

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
PegIFNβ-1a	£273,641	19.28	4.66	-	-	-	-
Alemtuzumab	£274,892	19.28	5.74	£1,250	0.006	1.088	£1,149
Generic GA 20mcg	£282,343	19.19	3.90	£8,701	0.081	0.754	Dominated
Generic GA 40mcb	£284,674	19.20	3.91	£11,033	0.080	0.742	Dominated
GA 20 mg	£285,064	19.19	3.90	£11,423	0.081	0.754	Dominated
GA 40 mg	£287,676	19.20	3.91	£14,035	0.080	0.742	Dominated
SC IFNβ-1a 44	£292,969	19.26	4.49	£19,328	0.017	0.169	Dominated
IM IFNβ-1a 30	£294,199	19.23	4.19	£20,557	0.047	0.467	Dominated
Teriflunomide	£297,437	19.21	4.05	£23,796	0.064	0.602	Dominated
Dimethyl fumarate	£308,506	19.22	2.21	£34,865	0.051	0.448	Dominated
Ocrelizumab	£339,668	19.20	5.16	£66,027	0.074	-0.505	Dominated

- All-cause discontinuation risk using a parity of 5% per annum (see Table 50)

Table 50. Exploratory analysis, using a parity of 5% per annum for all DMTs

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	£279,131	19.24	5.17	-	-	-	-
PegIFNβ-1a	£285,041	19.94	4.95	£5,910	0.70	-0.22	Dominated
Generic GA 20 mcg	£289,568	19.20	3.70	£10,437	-0.04	-1.47	Dominated
Generic GA 40 mcg	£289,853	19.20	3.69	£10,722	-0.04	-1.48	Dominated
GA 20 mg	£293,246	19.20	3.70	£14,115	-0.04	-1.47	Dominated
GA 40mg	£293,531	19.20	3.69	£14,400	-0.04	-1.48	Dominated
IM IFNβ-1a 30	£300,018	19.24	3.99	£20,887	0.00	-1.18	Dominated
SC IFNβ-1a 44	£304,937	19.29	4.44	£25,806	0.05	-0.73	Dominated
Teriflunomide	£328,915	19.24	4.03	£49,784	0.00	-1.14	Dominated
Dimethyl fumarate	£349,257	19.26	4.29	£70,126	0.02	-0.88	Dominated
Ocrelizumab	£350,209	19.22	5.05	£71,078	-0.02	-0.12	Dominated

- Relapse frequency from the ID527[4] assessment for RRMS (see Table 51)

Table 51. Exploratory analysis, using the relapse frequency from the ID527[4] assessment

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
PegIFNβ-1a	£273,422	19.28	4.40	-	-	-	-
Alemtuzumab	£274,807	19.28	5.48	£1,385	0.006	1.079	£1,284
Generic GA 20 mcg	£282,039	19.19	3.65	£8,617	0.081	0.745	Dominated
Generic GA 40 mcg	£284,371	19.20	3.66	£10,948	0.080	0.734	Dominated
GA 20 mg	£284,761	19.19	3.65	£11,338	0.081	0.745	Dominated
GA 40 mg	£287,372	19.20	3.66	£13,950	0.080	0.734	Dominated
SC IFNβ-1a 44	£292,732	19.26	4.23	£19,309	0.017	0.169	Dominated
IM IFNβ-1a 30	£293,917	19.23	3.94	£20,495	0.047	0.463	Dominated
Teriflunomide	£297,136	19.21	3.80	£23,713	0.064	0.596	Dominated
Dimethylfumarate	£308,238	19.22	4.00	£34,816	0.051	0.443	Dominated
Ocrelizumab	£339,536	19.20	4.90	£66,114	0.074	-0.499	Dominated

- Relapse frequency from the ID527[4] assessment for SPMS (see Table 52)

Table 52. Exploratory analysis, using the relapse frequency from the ID527[4] assessment

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
PegIFNβ-1a	£271,591	19.28	4.44	-	-	-	-
Alemtuzumab	£272,991	19.28	5.52	£1,400	0.006	1.079	£1,297
Generic GA 20 mcg	£280,189	19.19	3.70	£8,598	0.081	0.744	Dominated
Generic GA 40 mcg	£282,522	19.20	3.71	£10,932	0.080	0.733	Dominated
GA 20 mg	£282,911	19.19	3.70	£11,320	0.081	0.744	Dominated
GA 40 mg	£285,524	19.20	3.71	£13,933	0.080	0.733	Dominated
SC IFNβ-1a 44	£290,892	19.26	4.27	£19,301	0.017	0.168	Dominated
IM IFNβ-1a 30	£292,084	19.23	3.98	£20,493	0.047	0.463	Dominated
Teriflunomide	£295,306	19.21	3.85	£23,715	0.064	0.595	Dominated
Dimethylfumarate	£306,392	19.22	4.00	£34,801	0.051	0.442	Dominated
Ocrelizumab	£337,700	9.20	4.92	£66,110	0.074	-0.500	Dominated

In the majority of the exploratory analyses, the base-case model results were robust to each individual change made to the model inputs. Treatment with pegIFNβ-1a continued to dominate all comparators except alemtuzumab. However, the results showed that using a parity of 5% per annum for all-cause discontinuation across all DMTs, treatment with alemtuzumab dominated all other treatments.

6.2 Results of ERG base-case analysis

The ERG's base-case analysis compares pegIFNβ-1a versus comparators (at list prices). In Table 53, we present a summary of the ERG's base-case with justifications to the changes made to the company's base-case.

The ERG's preferred base-case includes making the following changes simultaneously:

- Interpolated disease-specific relative risk obtained from Pokorski et al., (1997)[11]
- Caregivers utility decrements obtained from Gani et al., (2008)[10]
- All-cause discontinuation risk using a parity of 5% per annum
- RRMS relapse frequency from the ID527[4] assessment (Melendez-Torres et al., 2017)[6]
- SPMS relapse frequency from the ID527[4] assessment (Melendez-Torres et al., 2017).[6]

Table 5E in Appendix E presents the details of the changes made in the spreadsheets used to amend the company's economic model.

Table 53. Changes made to the company's base-case with justifications

Model inputs	Options for inputs	Company's base-case	ERG's base-case
Mortality risk	Kingwell et al., (2012)[112]		
	Pokorski et al., (1997)[11]	✓	
	Pokorski., (1997)[11] interpolated		✓
Caregivers utility decrement	Acaster et al., (2013)[113]	✓	
	Gani et al., (2008)[10]		✓
All-cause discontinuation risk	User inputs		
	Weighted RCTs Disc	✓	
	Parity assumption (ID527)[4]		✓
	Weighted RCT ADRs only		
Annual relapse rates by EDSS (RRMS)	User inputs		
	ID527[4] assessment		✓
	UK MS Survey and Patzold et al (1982)[109]	✓	
Annual relapse rates by EDSS (SPMS)	User inputs		
	ID527[4] assessment		✓

Model inputs	Options for inputs	Company's base-case	ERG's base-case
	UK MS Survey and Patzold., (1982)[109]	✓	
EDSS, expanded disability status scale; MS, multiple sclerosis, RCT, randomised-controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis			

6.2.1 ERG's base-case deterministic results

The ERG's base-case results show that treatment with alemtuzumab dominated all other treatment options. Alemtuzumab was the least costly treatment option and yielded the most QALYs (see Table 54).

Table 54. ERG's deterministic base-case results (using list prices)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	£270,928	19.00	5.63	-	-	-	-
PegIFNβ-1a	£276,655	19.10	5.41	£5,727	0.10	-0.22	Dominated
Generic GA 20 mcg	£279,583	18.89	4.17	£8,655	-0.21	-1.46	Dominated
Generic GA 40 mcg	£279,864	18.89	4.17	£8,936	-0.21	-1.46	Dominated
GA 20 mg	£283,265	18.89	4.17	£12,337	-0.21	-1.46	Dominated
GA 40 mg	£283,545	18.89	4.16	£12,617	-0.21	-1.47	Dominated
IM IFNβ-1a 30	£290,440	18.94	4.46	£19,512	-0.16	-1.17	Dominated
SC IFNβ-1a 44	£295,916	19.01	4.91	£24,988	-0.09	-0.72	Dominated
Teriflunomide	£319,397	18.94	4.50	£48,469	-0.16	-1.13	Dominated
Dimethyl fumarate	£340,051	18.98	4.76	£69,123	-0.12	-0.87	Dominated
Ocrelizumab	£342,067	18.98	5.51	£71,139	-0.12	-0.12	Dominated

6.2.2 ERG's probabilistic sensitivity analysis results

The PSA results are presented in Table 55. These results show that alemtuzumab dominates all treatment options including pegIFNβ-1a, which suggests that alemtuzumab is the least costly and the most effective treatment option. In comparison to the ERG's deterministic results, the PSA results show that the expected costs are underestimated and the expected benefits (QALYs) overestimated.

Table 55. ERG's probabilistic sensitivity analysis results (using list prices)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	£254,772	19.19	6.56	-	-	-	-
PegIFNβ-1a	£265,389	19.30	6.31	£10,617	0.11	-0.25	Dominated
Generic GA 20 mcg	£266,026	19.10	5.14	£11,254	-0.20	-1.42	Dominated
Generic GA 40 mcg	£266,426	19.10	5.13	£11,654	-0.21	-1.43	Dominated
GA 20 mg	£269,763	19.08	5.16	£14,992	-0.22	-1.41	Dominated
GA 40 mg	£270,525	19.10	5.12	£15,753	-0.20	-1.44	Dominated
IM IFNβ-1a 30	£278,129	19.15	5.44	£23,357	-0.15	-1.12	Dominated
SC IFNβ-1a 44	£284,937	19.22	5.87	£30,165	-0.08	-0.70	Dominated
Teriflunomide	£309,658	19.10	5.48	£54,886	-0.21	-1.08	Dominated
Dimethyl fumarate	£332,740	19.20	5.73	£77,968	-0.11	-0.83	Dominated
Ocrelizumab	£336,666	19.20	6.44	£81,894	-0.11	-0.12	Dominated

Each simulation was plotted incrementally on a cost-effectiveness plane as shown in Figure 6. These results show that there is some correlation between costs and benefits.

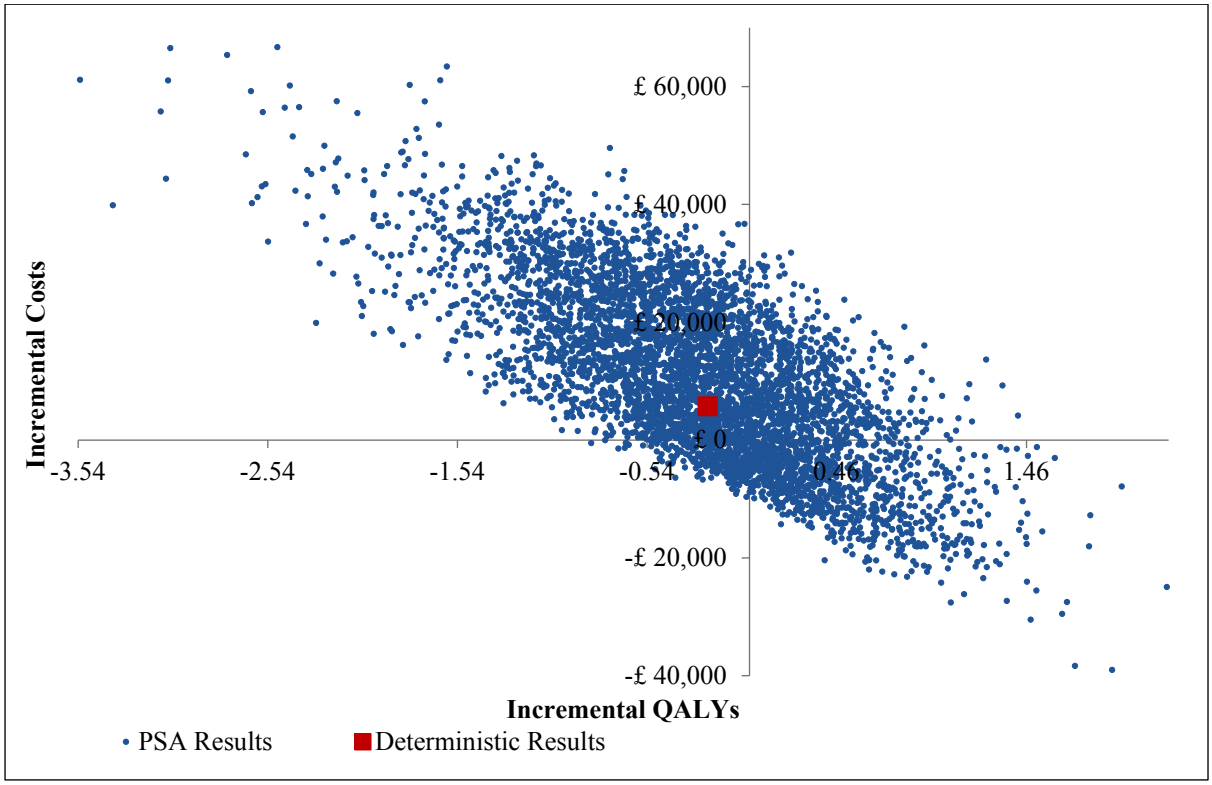

Figure 6. Scatterplot of pegIFNβ-1a versus alemtuzumab on the cost-effectiveness plane, ERG's base-case using list prices

Figure 7 shows the results of the PSA in the form of a CEAC for the comparison between pegIFNβ-1a (Plegridy 125 µg) and alemtuzumab (Lemtrada 12 mg). The curves show the proportion of simulations in which treatments are cost-effective at different WTP thresholds for a QALY. These results show that at a WTP threshold of £20,000 per QALY pegIFNβ-1a when compared to alemtuzumab has a probability of 0.28 of being cost-effective.

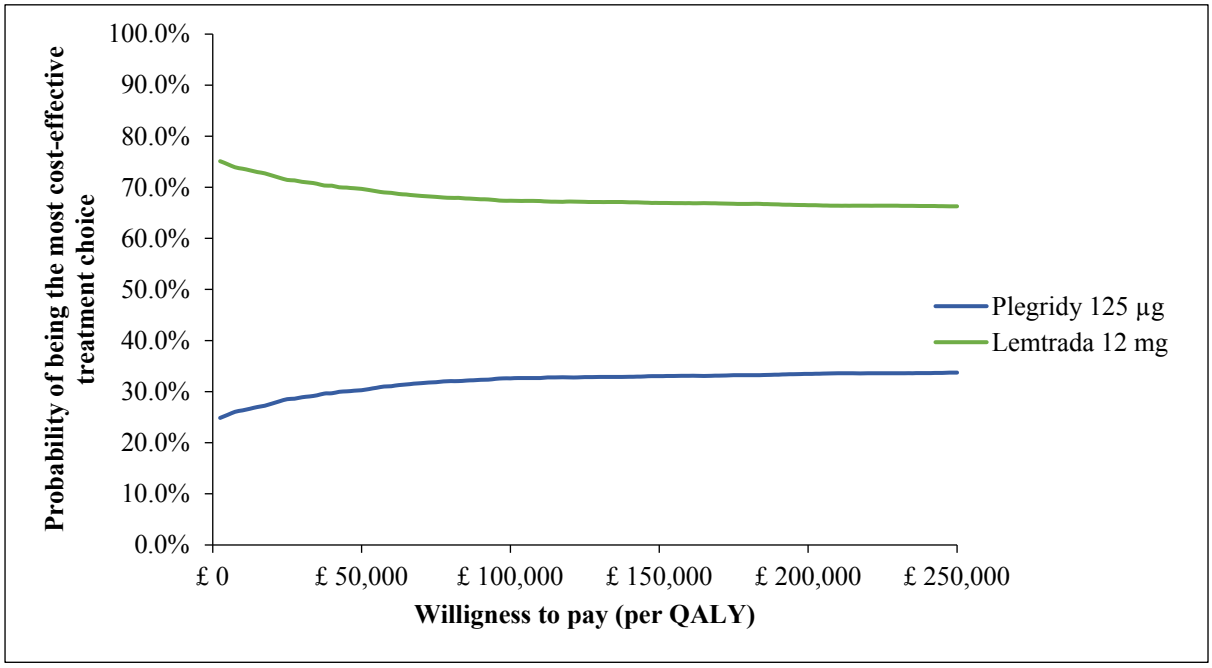

Figure 7. Cost-effectiveness acceptability curve, company base-case using list prices

6.2.3 ERG scenario analysis

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

- All-cause discontinuation weighted by person-time (see Table 56)

Table 56. All-cause discontinuation weighted by person-time

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
PegIFNβ-1a	264,531	19.00	4.85	-	-	-	-
Alemtuzumab	266,902	19.06	5.94	2,371	0.06	1.09	2,192
Generic GA 40 mcg	274,639	18.88	4.13	7,737	-0.18	-1.81	Dominated
Generic GA 20 mcg	275,396	18.88	4.13	8,494	-0.18	-1.81	Dominated
GA 40 mg	277,642	18.88	4.13	10,740	-0.18	-1.81	Dominated
GA 20 mg	278,529	18.88	4.14	11,627	-0.18	-1.80	Dominated
IM IFNβ-1a 30	283,843	18.93	4.39	16,941	-0.13	-1.55	Dominated
SC IFNβ-1a 44	285,008	18.98	4.71	18,106	-0.08	-1.23	Dominated
Teriflunomide	287,677	18.90	4.26	20,775	-0.16	-1.68	Dominated
Dimethyl fumarate	298,904	18.92	4.42	32,002	-0.14	-1.52	Dominated
Ocrelizumab	331,309	18.95	5.35	64,407	-0.11	-0.59	Dominated

- Utility values by EDSS as reported in ID527[4] assessment (Melendez-Torres et al., 2017)[6] (see Table 57)

Table 57. ERG scenario analysis, using utility values reported in ID527[4] assessment

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	270,928	19.00	5.45	-	-	-	-
PegIFNβ-1a	276,655	19.10	5.22	5,727	0.10	-0.23	Dominated
Generic GA 20 mcg	279,583	18.89	4.00	8,655	-0.21	-1.45	Dominated
Generic GA 40 mcg	279,864	18.89	4.00	8,936	-0.21	-1.45	Dominated
GA 20 mg	283,265	18.89	4.00	12,337	-0.21	-1.45	Dominated
GA 40 mg	283,545	18.89	4.00	12,617	-0.21	-1.45	Dominated
IM IFNβ-1a 30	290,440	18.94	4.29	19,512	-0.16	-1.16	Dominated
SC IFNβ-1a 44	295,916	19.01	4.73	24,988	-0.09	-0.73	Dominated
Teriflunomide	319,397	18.94	4.33	48,469	-0.16	-1.12	Dominated
Dimethyl fumarate	340,051	18.98	4.58	69,123	-0.12	-0.87	Dominated
Ocrelizumab	342,067	18.98	5.33	71,139	-0.12	-0.12	Dominated

- No waning of the treatment effect (see Table 58)

Table 58. ERG scenario analysis, assuming no treatment waning on CDP6M

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	254,137	19.20	6.62	-	-	-	-
PegIFNβ-1a	268,315	19.25	6.13	14,178	0.05	-0.49	Dominated
Generic GA 20µg	278,689	18.90	4.23	24,552	-0.35	-2.39	Dominated
Generic GA 40µg	278,972	18.90	4.22	24,835	-0.35	-2.40	Dominated
GA 20µg	282,398	18.90	4.23	28,261	-0.35	-2.39	Dominated
GA 40µg	282,681	18.90	4.22	28,544	-0.38	-2.40	Dominated
IM IFNβ-1a 30	287,970	18.98	4.66	33,833	-0.27	-1.96	Dominated
SC IFNβ-1a 44	291,497	19.09	4.32	37,360	-0.16	-2.30	Dominated
Teriflunomide	317,520	18.98	4.71	63,383	-0.27	-1.91	Dominated
Dimethyl fumarate	338,130	19.04	5.07	83,993	-0.21	-1.55	Dominated
Ocrelizumab	338,738	19.16	6.42	84,646	-0.09	-0.20	Dominated

- Using the utility values reported in Thompson et al., (2017)[8] (see Table 59)

Table 59. ERG scenario analysis, assuming no treatment waning on CDP6M

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Alemtuzumab	270,928	19.00	6.67	-	-	-	-
PegIFNβ-1a	276,655	19.10	6.47	5,727	0.10	-0.20	Dominated
Generic GA 20 mcg	279,583	18.89	5.38	8,655	-0.21	-1.29	Dominated
Generic GA 40 mcg	279,864	18.89	5.38	8,936	-0.21	-1.29	Dominated
GA 20 mg	283,265	18.89	5.38	12,337	-0.21	-1.29	Dominated
GA 40 mg	283,545	18.89	5.38	12,617	-0.21	-1.29	Dominated
IM IFNβ-1a 30	290,440	18.94	5.63	19,512	-0.16	-0.06	Dominated
SC IFNβ-1a 44	295,916	19.01	6.03	24,988	-0.09	-0.64	Dominated
Teriflunomide	319,397	18.94	5.67	48,469	-0.16	-1.00	Dominated
Dimethyl fumarate	340,051	18.98	5.90	69,123	-0.12	-0.77	Dominated
Ocrelizumab	342,067	18.98	6.57	71,139	-0.12	-0.10	Dominated

- Applying estimates for CDP6M and ARR from the ID527[4] assessment (see Table 60)

Table 60. ERG scenario analysis, assuming no treatment waning on CDP6M

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
INFβ-1b	263,918	19.16	5.80	-	-	-	-
PegIFNβ-1a	276,608	19.10	5.41	12,690	-0.06	-0.39	Dominated
GA 20 mg	279,446	18.93	4.43	15,528	-0.23	-1.37	Dominated
IM IFNβ-1a 30	286,374	18.99	4.77	22,456	-0.17	-1.30	Dominated
SC IFNβ-1a 44	290,488	19.09	5.39	26,570	-0.07	-0.41	Dominated

The ERG undertook a number of scenario analyses to assess the impact of these changes to our base-case results. In general, the results were robust to some changes made to the assumptions. Using the all-cause discontinuation weighted by person-time resulted alemtuzumab dominating all other treatment strategies except treatment with pegIFNβ-1a. In comparison to pegIFNβ-1a, alemtuzumab was approximately £2,400 more costly and was expected to yield 1.09 more QALYs, with an ICER of approximately £2,200 per QALY. Additionally, using the network-meta analysis treatment efficacy estimates obtained from ID527 assessment[4], the results showed that IFNβ-1b dominated all other treatment options.

7 END OF LIFE

The company have not discussed any end of life considerations in the submission, which the ERG agrees is appropriate.

8 OVERALL CONCLUSION

Discrepancies between the ERG and CS regarding the clinical effectiveness evidence did not significantly change the overall results of the SLR or MTCs. The ERG do not believe that any discrepancies in the information presented in the clinical effectiveness section will influence the size of the ICER.

The company's economic analysis was based on a Markov cohort model programmed in Microsoft Excel. The ERG considered the choice of the model and its structure to be appropriate to simulate the experience of people with RRMS, and to capture the long-term costs and benefits associated with treating RRMS with DMTs. The comparators included in the base-case analysis were appropriate, and

in line with the NICE scope[1] for treatment of people with RRMS. All comparators were in keeping with their marketing authorisation and licensed dosing schedule.

Appropriate methods were used to identify information to populate the economic model, with the clinical information for pegIFNβ-1a obtained from the ADVANCE trial and MTCs undertaken by the company. The resource use and costs were in keeping with the viewpoint of the economic analysis, with information obtained from published sources and using current prices. To have a workable model the company made some simplifying assumptions, which the ERG considered to be plausible. Under the company's assumptions and the economic model used, the base-case deterministic results showed that pegIFNβ-1a dominated all treatment strategies except treatment with alemtuzumab. Treatment with alemtuzumab was more costly and effective, resulting in an ICER of approximately £1200 per QALY gained. Probabilistic sensitivity analysis results showed that pegIFNβ-1a, when compared to alemtuzumab, had a 0.17 probability of being cost-effective at a WTP threshold of £20,000 per QALY. When compared to the other DMTs pegIFNβ-1a had >0.85 probability of being cost-effective. The company's base-case results were robust to changes made to the model inputs.

The ERG made some amendments to the company's economic model inputs, which formed the basis for the ERG's base-case model. These changes resulted in differences between the company's base-case results and those reported by the ERG. The company's results were presented based on using the list prices for all DMTs, and this was the basis/approach to the ERG's analysis.

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

- Interpolated disease-specific relative risk obtained from Pokorski et al., (1997)[11]
- Caregivers utility decrements obtained from Gani et al., (2008)[10]
- All-cause discontinuation risk using a parity of 5% per annum
- RRMS relapse frequency from the ID527[4] assessment (Melendez-Torres et al., 2017)[6]
- SPMS relapse frequency from the ID527[4] assessment (Melendez-Torres et al., 2017).[6]

Based on the changes made simultaneously, the results now show that alemtuzumab dominates all other treatment strategies, by being least costly and most effective. PSA results demonstrated that at a WTP threshold of £20,000 per QALY pegIFNβ-1a compared with alemtuzumab had a 0.28 probability of being cost-effective. However, it should be noted that these results are based on the list price for each DMT; hence the analysis does not incorporate any commercial agreements between the companies and the Department of Health.

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10 APPENDICES

Appendices Table of Content

A. ERG comparison to CS list of included and excluded studies in the MTC

B. ERG quality assessment of all trials included in the MTC

C. ERG quality appraisal of the CS MTC

D. Baseline characteristics of participants in the randomised controlled trials across randomised groups

E. ERG's individual parameter changes to the Company's base-case analysis

Appendix A: ERG comparison to CS list of included and excluded studies in the MTC

Table 1A. ERG comparison to CS list of included and excluded studies in the MTC

Note: Grey shaded cells represent a mismatch between the CS SLR and the ERG assessment.

	CS Document B Table 16 p69			CS Document C			
Study ID	**ARR**	**CDP3M**	**CDP6M**	**Any AE p453**	**SAE p455**	**Discontinuation (any cause) p458**	**Discontinuation due to AE p460**
ADVANCE	✓ Y (Calabresi 2014)	✓[a] Y (Calabresi 2014)	✓[a] ? Biogen Data extraction spreadsheet and clarification letter reference Biogen Idec. 105MS301 Interim - TLGs. Year 1 trial results. 2013 (not in reference pack)	✓ Y (Calabresi 2014)	✓ Y (Calabresi 2014)	✓ Y (Calabresi 2014)	✓ Y (Calabresi 2014)
APEX	×[b] Y Only abstracts available at time of submission; later publications now available: Saida 2019 states that tertiary endpoints included ARR over 24 weeks	×[b] N	×[b] N	× Y (Saida 2019)	× Y (Saida 2019)	× N	× Y (Saida 2019)
BEYOND	✓ Y (O'Connor 2009)	✓ Y (O'Connor 2009)	×[b] N	× N	× Y (O'Connor 2009)	× N	× N
Boiko 2017	×[b] N	×[b] N	×[b] N	✓ Y	✓ Y	✓ Y	× N
Bornstein 1987	✓ Y (Bornstein 1987)	×[b] N	×[b] N	× N	× N	× N	× N

	CS Document B Table 16 p69			CS Document C			
Study ID	**ARR**	**CDP3M**	**CDP6M**	**Any AE p453**	**SAE p455**	**Discontinuation (any cause) p458**	**Discontinuation due to AE p460**
BRAVO	✓ Y (Vollmer 2014)	✓ Y (Vollmer 2014)	✓ Y (Vollmer 2014)	× Y (Vollmer 2014)	× Y (Vollmer 2014 online Supplementary Table S-2 from https://link.springer.com/article/10.1007%2Fs00415-014-7264-4)	× Y (Vollmer 2014)	× Y (Vollmer 2014)
Calabrese 2012	✓ Y (Calabrese 2012)	×[b] N	×[b] N	× N	× N	× N	× N
CAMMS223	✓ Y (CAMMS23)	✓ Y (CAMMS23)	✓ Y (CAMMS23)	× Y CAMMS23	× Y CAMMS23	× Y CAMMS23	× Y CAMMS23
CARE MS I	✓ Y (Cohen 2012)	×[b] N	✓ Y (Cohen 2012)	× Y (Cohen 2012)	× Y (Cohen 2012)	× Y (Cohen 2012)	× Y (Cohen 2012)
CARE MS II	✓ Y (Coles 2012)	×[b] N	✓ Y (Coles 2012)	× Y (Coles 2012)	× Y (Coles 2012)	× Y (Coles 2012)	× Y (Coles 2012)
CombiRx	✓ Y (Lublin 2013)	×[b] N	×[b] Y (Lublin 2012) Confirmed progression in a participant was defined as a 1.0 increase in the EDSS from baseline, when baseline ≤ 5.0; or an increase of 0.5 from baseline, when baseline ≥ 5.5, sustained for 6 months	× N	× Y (Lublin 2012 supplementary tables from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631288/)	× Y (Lublin 2012)	× Y (Lublin 2012)

	CS Document B Table 16 p69			CS Document C			
Study ID	**ARR**	**CDP3M**	**CDP6M**	**Any AE p453**	**SAE p455**	**Discontinuation (any cause) p458**	**Discontinuation due to AE p460**
CONFIRM	✓ Y (Fox 2012)	✓ Y (Fox 2012)	✓ Y (Fox 2012)	× Y (Fox 2012)	× Y (Fox 2012)	× Y (Fox 2012 supplement from https://www.nejm.org/doi/suppl/10.1056/NEJMoa1206328/suppl_file/nejmoa1206328_appendix.pdf)	× Y (Fox 2012)
Copolymer I	✓ Y (Johnson 1995)	×[b] Y (Johnson 1995): progression to sustained disability defined as an increase of one or more EDSS steps maintained for > 90 days	×[b] N	× N	× N	× Y (Johnson 1995)	× Y (Johnson 1995)
DEFINE	✓ Y (Gold 2012)	✓ Y (Gold 2012)	✓ ? Stated in clarification letter to be from Biogen Idec Inc. Clinical study report. Full final. Study Number: 109MS301. A randomized, multicenter, double-blind, placebo-controlled, dose-comparison study to determine the efficacy and safety of BG00012 in subjects with relapsing-remitting multiple sclerosis. Cambridge, MA: Biogen Idec Inc, 2012 – not in reference pack	× Y (Gold 2012)	× Y (Gold 2012)	× Y (Gold 2012 supplement from https://www.nejm.org/doi/suppl/10.1056/NEJMoa1114287/suppl_file/nejmoa1114287_appendix.pdf)	× Y (Gold 2012)

	CS Document B Table 16 p69			CS Document C			
Study ID	**ARR**	**CDP3M**	**CDP6M**	**Any AE p453**	**SAE p455**	**Discontinuation (any cause) p458**	**Discontinuation due to AE p460**
Etemadifar 2006	×[c] N	×[b] N	×[b] N	× N	× N	× N	× N
EVIDENCE	✓ Y (Panitch 2002)	✓[a] Y (Panitch 2002)	✓[a] Y (Panitch 2002)	× N	× Y (Panitch 2002)	× Y (Panitch 2002)	× Y (Panitch 2002)
GALA	✓ Y (Khan 2013)	×[b] N	×[b Y] Not in Khan 2013 but available in Khan 2017	✓ Y (Khan 2013)	✓ Y (Khan 2013)	✓ Y (Khan 2013)	✓ Y (Khan 2013)
GLOW	× N (https://clinicaltrials.gov/ct2/show/results/NCT01578785)	× N	× N	✓ Y (https://clinicaltrials.gov/ct2/show/results/NCT01578785)	× Y (https://clinicaltrials.gov/ct2/show/results/NCT01578785)	× N (https://clinicaltrials.gov/ct2/show/results/NCT01578785; study terminated)	× N (https://clinicaltrials.gov/ct2/show/results/NCT01578785; study terminated)
IFNB MS	✓ Y (IFNB MS 1993)	×[b] N	×[b] N	× N	× N	× Y (IFNB MS 1993)	× Y (IFNB MS 1993)
INCOMIN	✓ Y (Durelli 2002)	×[b] N	×[b] Y Durelli 2002 had "Progression in EDSS score of 1 point sustained for 6 months and confirmed at end of study"	× N	× N	× Y (Durelli 2002)	× Y (Durelli 2002)
MSCRG	✓ Y (Jacobs 1996)	×[b] N	×[b] Y (Jacobs 1996) "The proportion with progression of disability (CDP6M) by 104 weeks estimated for Kaplan-Meier curves was 34.9% in placebo recipients and 21.9% in interferon beta-1a recipients"	× N	× N	× Y (Jacobs 1996)	× Y (Jacobs 1996)

	CS Document B Table 16 p69			CS Document C			
Study ID	**ARR**	**CDP3M**	**CDP6M**	**Any AE p453**	**SAE p455**	**Discontinuation (any cause) p458**	**Discontinuation due to AE p460**
OPERA I	✓ Y (Hauser 2017)	✓ Y (Hauser 2017)	✓ Y (Hauser 2017)	× Y (Hauser 2017)	× Y (Hauser 2017)	× Y (Hauser 2017 supplementary appendix from https://www.nejm.org/doi/suppl/10.1056/NEJMoa1601277/suppl_file/nejmoa1601277_appendix.pdf)	× Y (Hauser 2017)
OPERA II	✓ Y (Hauser 2017)	✓ Y (Hauser 2017)	✓ Y (Hauser 2017)	× Y (Hauser 2017)	× Y (Hauser 2017)	× Y (Hauser 2017 supplementary appendix from https://www.nejm.org/doi/suppl/10.1056/NEJMoa1601277/suppl_file/nejmoa1601277_appendix.pdf)	× Y (Hauser 2017)
PRISMS	×[b] Y (PRISMS 1998 reported mean relapses per patient over 2 years, and % relapse-free over 1 year and over 2 years)	✓ Y (PRISMS 1998)	✓ Y (Wong 2018)	× N	× N	× Y (PRISMS 1998)	× Y (PRISMS 1998)

	CS Document B Table 16 p69			CS Document C			
Study ID	**ARR**	**CDP3M**	**CDP6M**	**Any AE p453**	**SAE p455**	**Discontinuation (any cause) p458**	**Discontinuation due to AE p460**
REGARD	✓ Y (Mikol 2008)	×[b] N	×[b] Y Mikol 2008 states: The proportion of patients with 6-month confirmed EDSS progression was low and similar between the two groups (interferon beta-1a 11.7% [45 of 386] vs glatiramer acetate 8.7% [33 of 378]; P=0·117).	× N (Mikol 2008 reports numbers of events not numbers of patients with ≥1 event)	× N	× Y (Mikol 2008)	× Y (Mikol 2008)
TEMSO	✓ Y (O'Connor 2011)	✓ Y (O'Connor 2011)	×[b] N	× Y (O'Connor 2011)	× Y (O'Connor 2011)	× Y (O'Connor 2011)	× Y (O'Connor 2011)
TENERE	✓ Y (Vermersch 2014)	×[b] N	×[b] N	× Y (Vermersch 2014)	× Y (Vermersch 2014)	× Y (Vermersch 2014)	× Y (Vermersch 2014)
TOWER	✓ Y (Confavreux 2014)	✓ Y (Confavreux)	✓ Y (https://www.ema.europa.eu/en/documents/assessment-report/aubagio-epar-public-assessment-report_en.pdf Table 21 p63)	× Y (Confavreux 2014)	× Y (Confavreux 2014)	× Y (Confavreux 2014)	× Y (Confavreux 2014)

ARR = annualised relapse rate; CDP3M = confirmed disability progression sustained for 3 months; CDP6M = confirmed disability progression sustained for 6 months.
[a] Included with 11 or 18 months of follow-up. [b] This outcome was not reported by the indicated study.
[c] Data were not reported in the appropriate patient population
Comparison between CS and ERG analysis of data that should be included in the MTC
✓ or × = included or not included from CS
Y or N = should have been included or not included from ERG analysis
? unclear where data came from for inclusion in the CS
Grey shading = data not included in CS but present in the study publication (× Y) or data present in CS but unclear source (✓?)

Appendix B: ERG quality assessment of all trials included in the MTC

Table 2B. ERG quality assessment (RoB) of all trials included in the MTC

		Randomisation		Allocation concealment		Are participants blinded?		Are caregivers blinded?		Blinding of assessors		Incomplete outcome data		Selective reporting		Other biases		Overall
CS or ERG	**Study ID**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**	**Reason**	**RoB**
CS	ADVANCE	Unclear	No information on how randomisation sequence was generated.	Low	Randomisation was done by a centralised interactive voice response and web system, stratified by site	Low	All study management and site personnel, investigators, and patients were masked to treatment assignment. Appropriate matched placebo medication was used.	Low	All study management and site personnel, investigators, and patients were masked to treatment assignment	Low	All study management and site personnel, investigators, and patients were masked to treatment assignment. Central MRI reading centre by an assessor masked to treatment allocation	Low	The ITT population for year 1 included all randomised patients who received at least one dose of study drug, only 4 patients were excluded, Low risk. The analysis population for year 2 included only those patients who completed year 1 of the study, High risk.	Low	All specified outcomes were reported	Low	No other apparent sources of bias	unclear
ERG	**ADVANCE**	Low	Centralised Interactive Voice/Web Response System stratified by site	**Low**	**Centralised Interactive Voice/Web Response System**	**Low**	**Masked; matched placebo used**	**Low**	**Masked; matched placebo used**	**Low**	**Central MRI reading centre by an assessor masked to treatment allocation**	**Low for 1 ye**	**At baseline: 500 placebo patients; 512 pegIFN beta-1a every 2 weeks and 500 pegIFN beta-1a every 4 weeks. 1332/1512 (88%) patients completed Year 1**	**Low**	**All specified outcomes were reported.**	*High*	*Differential drop-out between the placebo and Q2W groups by the end of year 1 (comparing*	High

												a r	**of study and continued with active treatment in Year 2 (patients receiving placebo in Year 1 re-randomized to pegIFN beta-1a every 2 or 4 weeks at Week 48). Completed Year 2: pegIFN beta-1a every 2 weeks, 391/438 (89%), pegIFN beta-1a every 4 weeks, 411/438 (94%), and delayed treatment 396/456 (87%); total completing year 2: 1198 of the original 1512 (79%).**				*456/500 vs. 438/512 in RevMan gives p=0.005). Placebo: 44 discontinued 5 adverse events 3 lost to follow-up 30 withdrew consent 2 died 4 other. Q2W: 74 discontinued 24 adverse events (4 influenza-like illness) 2 lost to follow-up 35 withdrew consent 4 investigator decision 1 died 8 other Q4W: 62 discontinued 24 adverse events (5 influenza-like illness) 4 lost to follow-up*	

																	30 withdrew consent 1 investigator decision 1 died 2 other	
CS	APEX	Unclear	No information on how randomisation was performed	Unclear	No description of allocation concealment.	Low	Double-blind (participant, investigator)	Low	Double-blind (participant, investigator)	Unclear	No information provided on blinding of assessors	Low	All pre-defined data analyses appear to be presented	Low	No evidence of selective reporting	Low	No clear sources of other bias	Low
ERG	**APEX abstract**	**Unclear**	**Abstract only; no information**	**Unclear**	**Abstract only; no information**	**Low**	**Double-blind**	**Low**	**Double-blind**	**Unclear**	**Abstract only; no information**	Unclear	Abstract only; no information	**Low**	**All pre-defined data analyses appear to be presented**	Unclear	Abstract only; no information	Unclear
ERG	**APEX full paper**	Low	A stratified block randomization procedure was used for Part I, with 5 strata, 1 for each country (block size: 4; 50 blocks per country), using a centralized interactive voice/web response system;	Low	Centralized interactive voice/web response system	**Low**	**Double-blind (matching placebo). Patients, their families, and all study staff were blinded to patient treatment assignments.**	**Low**	**Double-blind (matching placebo) Patients, their families, and all study staff were blinded to patient treatment assignments. Patients were instructed not to take a dose of study treatment within 4h before their scheduled appointment to prevent any**	**Low**	**Separate study personnel were designated to treat patients and to conduct efficacy and relapse assessments.**	Low	224 patients were randomized and received ≥1 dose of study treatment, 113 in the placebo group and 111 in the DMF group; 2 patients (both in the placebo group) switched to an alternative MS medication during the study; 213 patients (95% of the ITT population) completed the study. All subjects who received at least one dose of	**Low**	**Efficacy outcome measures stated in clinical trials.gov (https://clinicaltrials.gov/ct2/show/NCT01838668) were reported**	**Low**	**No clear sources of other bias**	**Low**

									drug-induced reactions necessitating unblinding of study personnel.				study treatment were included in the safety analysis.					
CS	BEYOND	Low	Central randomisation with SAS-based block randomisation	Low	Central randomisation with SAS-based block randomisation	Low	To ensure masking between the two doses of interferon beta-1b, medication was identical in appearance, packaging, and labelling. Physicians and patients were double-blind to comparisons between the two doses.	Low	Physicians and patients were double-blind to comparisons between the two doses.	Low	Masked evaluating physicians did all neurological assessments and ascertained functional system and EDSS scores	Low	For the main clinical outcomes the analysis population appears to be the total number randomised although the authors do not clearly state this. Incomplete outcome data for secondary outcome: Only patients with assessable MRI data at the applicable analysis timepoints were included.	Low	All specified outcomes were reported	Low	No other apparent sources of bias	low
ERG	**BEYOND**	**Low**	**Central randomisation using SAS-based block randomisation with regional stratification.**	**Low**	**Central randomisation**	High	To ensure masking between the two doses of interferon beta-1b, medication was identical in appearance, packaging and labelling. Physicians and patients were double-blind to comparisons between the two doses. However, 500µg alternate days dose not eligible, only 250 µg dose vs. GA. Ibuprofen	High	The treating physicians and the patients were therefore aware of treatment assignments (interferon beta-1b vs. GA).	**Low**	**The evaluating physicians were masked to all randomisations.**	Unclear	2244 patients randomised: 500 µg interferon beta-1b (n=899), 250 µg interferon beta-1b (n=897), or glatiramer acetate (n=448). 24 patients did not receive treatment (12 [1.3%], 9 [1.0%] and 3 [0.7%] patients, respectively). Of the 2220 who received treatment, 336 (15%) discontinued treatment prematurely (161 [18%], 104 [12%]	**Low**	**All specified outcomes were reported**	**Low**	**No clear sources of other bias**	High

							or acetaminophen were given at the same time as random assignment to interferon beta-1b, at least during the first 3 months, to reduce flu-like symptoms. The treating physicians and the patients were therefore aware of treatment assignments (interferon beta-1b vs. GA), which is the comparison of interest to the review.						and 71 [16%], respectively). Primary endpoint: hazard ratio; n not stated. Secondary outcome measures: Time to confirmed Expanded Disability Status Score (EDSS) progression; n not stated; and Magnetic Resonance Imaging (MRI): Change from screening in volume of hypointense lesion on enhanced T1 weighted images: All patients had MRI at screening, but owing to technical reasons the MRI scans for 18 patients could not be assessed. The number of patients available for analysis of at least one post-screening MRI measure decreased with time (2053 [91.5%] at year 1, 1930 [86.0%] at year 2, and 316 [14.1%] at year 3). MRI scans from 2096 [93.4%] patients were included in the last available scan analysis for at least one post-screening MRI				

													measure.				
CS	Boiko 2018	Unclear	No information on how randomisation was performed; ratio 2:2:1	Unclear	No description of allocation concealment.	Low	Double-blind	Low	Double-blind	Low	Objective measures of efficacy were obtained by ensuring that the specialists reporting MRI scan data were not familiar with which drug patients received	High	Five patients were excluded from efficacy analysis due to contravention of inclusion/ exclusion criteria (but received treatment in the framework of the study)	Low	No evidence of selective reporting; all pre-defined analyses appear to be reported	Low	No clear sources of other bias	Low
ERG	**Boiko 2018**	**Unclear**	**No information on how randomisation was performed; ratio 2:2:1**	**Unclear**	**No description of allocation concealment.**	**Low**	**Double-blind**	**Low**	**Double-blind**	**Low**	**Objective measures of efficacy were obtained by ensuring that the specialists reporting MRI scan data were not familiar with which drug the patients received**	**High**	**Of the 158 patients, 3 (1.9%) were not included in the main efficacy analysis as they did not receive any doses of study drug. Of the 155 patients who received treatment, 5 (3.2%) were excluded from the efficacy analysis (2 CopaxoneTeva and 3 placebo) due to contravention of inclusion/exclusion criteria. Modified ITT population (mITT): all patients receiving at least one dose of study drug. Final analysis of efficacy included 150 (94.9%) patients (61 BCD-063, 61 CopaxoneTeva, and 28 placebo). The MRI**	**Low**	**No evidence of selective reporting; all pre-defined analyses appear to be reported**	**Low**	**No clear sources of other bias**	**High**

													measures included 121 (76.6%) patients; some were lost to the study before repeat MRI. The primary endpoint was the number of MRI-confirmed exacerbations per patient per year.					
CS	Bornstein1987	Unclear	Method of sequence generation not reported	Unclear	Method of allocation concealment not reported: `treatment assignments were made known to the clinical assistant`	Unclear	Although reported as double-blinded, it is unclear whether the vials were identical	High	The neurologist was unaware of patient`s treatment group, but the clinical assistant was not blinded	Unclear	The neurologist was unaware of patient`s treatment group, but the clinical assistant was not blinded. Unclear what the final adjudication of the outcomes was based on	High	Two patients in the placebo group were excluded from all analyses	Low	All prespecified outcomes are presented in the results	Low	No other apparent sources of bias	High
ERG	**Bornstein1987**	**Unclear**	**Quasi-randomised; patients were matched into pairs (based on sex, number of exacerbations per year and degree of disability); the random assignment of the first patient of the pair (method not stated) determined**	High	Quasi-randomised; patients were matched into pairs (based on sex, number of exacerbations per year and degree of disability); the random assignment of the first patient of the pair (method not stated) determined	**Unclear**	**Sterile single dose vials contained the active ingredient or only saline; not stated that the vials were identical; stated to be double-blind**	Unclear	Treatment assignments were made known to the clinical assistant responsible for the production, labelling and distribution of medication	**Unclear**	**A neurologist unaware of the patient's treatment group completed neurological and status assessment. Patients reported side effects and changes in neurological status to the non-blinded clinical assistant**	Low	7/50 (14%) patients did not complete the 2 years of the trial; 2 (in placebo group; 8%) had unusable data; the other 5 had partial data that was included. So data included: 22 matched pairs (n=44) in the matched analysis, and an unmatched analysis that additionally included 2 who had never been matched plus 2 who had been matched to the 2 with unusable data	**Low**	**All specified outcomes were reported**	**Low**	**No clear sources of other bias**	**High**

			the assignment of both. 2 patients were not matched but randomly allocated 1 to each group,		the assignment of both.													
CS	BRAVO	Low	`Computer-generated randomization scheme`	Unclear	Method of allocation concealment not reported	High	`Patients and treating neurologists were blinded to oral treatment assignment (laquinimod or placebo), but not to IFNb-1a IM assignment. …The study was designed to: (1) assess the safety, efficacy, and tolerability of laquinimod compared with placebo in a double-blinded design; (2) assess the safety, efficacy, and tolerability of IFNb-1a IM compared with placebo in a rater-blinded design`	High	`Patients and treating neurologists were blinded to oral treatment assignment (laquinimod or placebo), but not to IFNb-1a IM assignment.	Low	Examining neurologist blinded to all treatments	Low	Analysis of the main efficacy outcomes included all randomised patients.	Low	All outcomes described in the methods are reported in the results.	Low	No other apparent sources of bias	High
ERG	BRAVO	**Low**	**The computer-generated randomization scheme prepared by the Teva**	**Unclear**	**Method of allocation concealment not reported**	**High**	**Patients and treating neurologists were blinded to oral treatment assignment (laquinimod or**	**High**	**Patients and treating neurologists were blinded to oral treatment assignment (laquinimod or**	**Low**	**The examining neurologist was blinded to all treatments.**	**Low**	**1,331 were randomised to once-daily laquinimod 0.6 mg (n=434) or placebo (n=450), or IFNb-1a 30 µg**	High	Clinicaltrials.gov reported SF-36 and the cumulative number of new hypointense lesions on enhanced T1 scans as outcomes	**Low**	**No other apparent sources of bias**	**High**

			Global Biostatistics Unit employed a 1:1:1 treatment assignment ratio stratified by study center				**placebo), but not to IFNb-1a IM assignment.**		**placebo), but not to IFNb-1a IM assignment.**				**once-weekly (n=447). 1,090 patients (82%) completed the 24-month treatment phase (353 [81.3%], 359 [79.8%] and 378 [84.6%], respectively). The safety-evaluable population comprised 433 (99.8%), 449 (99.8%) and 442 (98.9%), respectively; efficacy results appeared to include all patients.**		(not reported in Vollmer 2014)			
CS	Calabrese2012	Low	Random allocation sequence computer generated	Unclear	Method of allocation concealment not reported	Unclear	Blinding of participants not reported	Unclear	Blinding of caregivers not reported	Low	`All images were assessed by the consensus of two experienced observers who were blinded to the patients' identity and treatment`	High	14.5% of patients were lost to follow-up and excluded from all analyses	Unclear	Primary and secondary outcomes are not clearly listed and AE not reported	Unclear	Unclear if selection biased as no clear flow chart provided, reasons for lost to f-up are not given, number discontinued not provided	High
ERG	Calabrese20	**Low**	**The random allocation sequence was computer generated.**	**Unclear**	**Method of allocation concealment not reported**	High	Interventions were subcutaneous (sc) interferon (IFN) beta-1a (44 mcg three times weekly), intramuscular (im) IFN beta-1a (30 mcg weekly)	High	Interventions were subcutaneous (sc) interferon (IFN) beta-1a (44 mcg three times weekly), intramuscular (im) IFN beta-1a (30 mcg weekly)	**Low**	**All imaging was carried out at a single imaging centre, and all images were assessed by the consensus of two experienced observers who**	Low	165 were randomized (55 per group); 141 (85.5%) completed the 2-year follow-up (46 [83.6%] in the sc IFN beta-1a group, 47 [85.5%] in the im IFN beta-1a group and 48 [87.3%] in the GA	**Unclear**	**Efficacy outcome were reported as listed: ARR, EDSS score, development of cortical lesions, cortical atrophy. Adverse events not reported**	**Unclear**	**No chart of patients flow; no reasons stated for loss to follow up**	**High**

	12							or glatiramer acetate (GA; 20 mg daily). No mention of masking or use of placebos		or glatiramer acetate (GA; 20 mg daily). No mention of masking or use of placebos		**were blinded to the patients' identity and treatment.**		group); 24 (14.5%) randomized patients were lost to follow-up.					
CS	CAMMS223	Low	"Eligible patients were randomly assigned in a 1:1:1 ratio to receive alemtuzumab (…12 mg per day or 24 mg per day) or interferon beta-1a with the use of the Pocock and Simon minimization algorithm to balance the study groups with regard to age (<30 years or ≥30 years), sex, and baseline EDSS score (<2.0 or ≥2.0)."	Unclear	No description of allocation concealment.	High	"Rater-blinded phase II study"	High	"Rater-blinded phase II study"	High	"Rater-blinded phase II study", but only EDSS and efficacy were reported to be judged blindly. Safety was evaluated by treating neurologist, who was aware of study-group assignment	Low	All randomised patients were included in the analysis for efficacy and all those who received study drug were considered for safety	Low	All outcomes described in the methods are reported in the results.	Low	No other biases plausible.	high
ERG	CAMMS223	**Low**	**Use of the Pocock and Simon minimization algorithm – implies computer generated randomisation**	**Unclear**	**No description of allocation concealment.**	**High**	**Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months**	**High**	**Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months**	**High**	**EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. Patients wore clothing that covered injection**	**Low**	**One patient who received alemtuzumab was included in the safety analysis but was excluded from the efficacy analyses because the initial diagnosis of**	**Low**	**NCT record states the outcome as: Sustained Accumulation of Disability (SAD); ARR; Relapse Free at 3 Years After Initial Treatment; Percent Change**	High	More patients discontinued interferon beta-1a than alemtuzumab, principally because of	**High**

							12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per liter). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation. No mention of masking or use of placebos.		**12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×106 cells per liter). Interferon beta-1a (at a dose of 44 µg) was administered subcutaneously three times weekly after dose escalation. No mention of masking or use of placebos.**		**sites. The effectiveness of blinding was assessed at the end-of-study visit. Safety was assessed quarterly by the treating neurologist, who was aware of study-group assignment.**		**multiple sclerosis was incorrect. All other patients (333/334; 99.7%) were included in efficacy analyses. IFNβ-1a 107/111 (96.4%); alemtuzumab 12mg 108/113 (95.6%) and 24mg 108/110 (98.2%) in safety analysis.**		**From Baseline in T1 Cerebral Volume; Percent Change From Baseline in MRI T2 Lesion Volume. All reported; also safety and adverse events.**		a lack of efficacy and adverse events, so that only 59% of the original group of patients receiving interferon beta-1a completed the 36-month study, as compared with 83% of patients receiving alemtuzumab	
CS	CARE-MSI	Unclear	Method of randomization sequence generation not reported	Low	Patients were allocated through an IVRS	High	Participants were not blinded. "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment"	High	Caregivers were not blinded. "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment"	Low	Clinical and MRI rater masking. 5 (3%) of 563 patients had one or more assessments done by an unmasked rater	Low	All randomised patients who received at least one dose of study drug were included in the analysis for efficacy and safety	Low	All outcomes described in the methods are reported in the results.	Low	No other biases plausible.	High
ERG	CARE-MSI	**Unclear**	**Randomisation was stratified by site (no further details)**	**Low**	**Interactive voice response system**	**High**	**Authors stated that "both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment**	**High**	**Authors stated that "both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment**	**Low**	**The authors stated that they "secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six**	**Low**	**All randomised patients who received at least one dose of study drug were included in the analysis for efficacy and safety**	**Low**	**NCT record states the outcome measures as: Sustained Accumulation of Disability; ARR; Relapse Free at Year 2; Change From Baseline in Expanded Disability Status**	High	Fewer patients in the alemtuzumab group than in the interferon beta 1a group discontinued treatment	**High**

							assignment, and … subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo"		**assignment, and … subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo"**		**independent and masked neurologists. Raters completed a questionnaire assessing quality of the masking at each EDSS assessment. In the absence of a masked rater, unmasked raters could submit EDSS assessments… Masking was successful for 5172 (>99%) of 5193 EDSS assessments. Only 15 (3%) of 563 patients had one or more assessments done by an unmasked rater. Sensitivity analyses, including exclusion of unmasked assessments, supported the absence of effect of rater unmasking on study results"**				**Scale (EDSS) Score; Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score and Percent Change From Baseline in Magnetic Resonance Imaging Time Constant 2 (MRI-T2) Hyperintense Lesion Volume at Year 2. All reported**		or study participation because of an adverse event: 5 (1%) vs. 11 (6%)	
CS	CARE-MS II	Unclear	Method of randomization sequence generation not reported	Low	Patients were allocated through an IVRS	High	Participants were not blinded. "Because both study drugs have adverse effects that precluded masking of patients and treating	High	Caregivers were not blinded. "Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to	Low	Clinical and MRI rater masking. Only 12 (2%) of 672 patients had one or more assessments done by an unmasked rater; although included in efficacy analyses,	Low	All randomised patients who received at least one dose of study drug were included in the analysis for efficacy and safety	High	No results presented for smaller 24mg arm	Low	No other biases plausible.	High

							clinicians to treatment assignment"		treatment assignment"		sensitivity studies showed these unmasked data had no effect on outcomes							
ERG	CARE-MSII	**Unclear**	**Randomisation was stratified by site (no further details)**	**Low**	**Interactive voice response system**	**High**	**Both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo**	**High**	**Both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo**	**Low**	**The authors stated that: "clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses. Raters, who were masked to treatment-group assignment, did the EDSS assessments every 3 months and when a relapse was suspected, and the multiple sclerosis functional composite (MSFC) once every 6 months. Raters completed a questionnaire assessing quality of the masking at each EDSS assessment. In the absence of a masked rater, unmasked raters could submit EDSS assessments… Masking was successful for 5850 (>99%) of 5865 EDSS assessments. Only**	Unclear	A protocol amendment in December, 2008, discontinued randomisation in the alemtuzumab 24 mg group to accelerate recruitment to the other two study groups. The decision to close recruitment into the alemtuzumab 24 mg arm was made by the Neurology Steering Committee and Genzyme management without review of safety or efficacy data from this study. However, data are included for safety assessments. Nine patients originally assigned alemtuzumab 24 mg actually received the 12 mg per day dose; the authors included these patients in the 24 mg per day group for efficacy but in the 12 mg per day for safety analyses.	Low	NCT record states outcomes as: Sustained Accumulation of Disability; Annualized Relapse Rate; Relapse Free at Year 2; Change From Baseline in Expanded Disability Status Scale (EDSS) Score; Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score; Percent Change From Baseline in Magnetic Resonance Imaging Time Constant 2 (MRI-T2) Hyperintense Lesion Volume. All reported, plus adverse events.	High	More patients randomly allocated interferon beta 1a than alemtuzumab discontinued the trial before treatment (29 [13%] of 231 patients for interferon beta 1a vs 13 [2%] of 609 patients for alemtuzumab) and after starting treatment (27 [12%] of 202 vs 16 [3%] of 596).	**High**

											12 (2%) of 672 patients had one or more assessments done by an unmasked rater; although included in efficacy analyses, sensitivity studies showed these unmasked data had no effect on outcomes"							
CS	CombiRx	Low	Distributed computerized data entry system	Low	Distributed computerized data entry system that masked treatment arm allocation	Low	Distributed computerized data entry system that masked … drug dispensing to participants ...for the entire duration of the trial period	Low	Distributed computerized data entry system that masked … drug dispensing to ...all site personnel for the entire duration of the trial period	Low	Distributed computerized data entry system that masked … drug dispensing to ...all site personnel for the entire duration of the trial period	Unclear	Imbalance in early terminations; missing data not imputed (discontinued patients censored but unclear whether censoring can be assumed to be unbiased); and unclear that patients were analysed according to the group they were assigned; ITT cannot be assured	Unclear	MSQLI and Rankin assessments were measured (Lindsey) but not yet reported - unsure about impact on bias as there may be a follow-on publication with these results	Low	Not a placebo-controlled trial - borderline results in subjective evaluations may be viewed as successes; however, outcomes in this study appear sufficiently objective	unclear
ERG	CombiRx	**Low**	**Computerized Data Entry System (DES); permuted block design within sites with block sizes of 6 and 12**	**Low**	**DES masked treatment arm allocation and drug dispensing to participants and all site personnel for the entire duration**	**Low**	**DES masked treatment arm allocation and drug dispensing to participants and all site personnel for the entire duration of the trial period. All participants administered the same number of injections.**	**Low**	**DES masked treatment arm allocation and drug dispensing to participants and all site personnel for the entire duration of the trial period. All participants administered the same number of injections.**	**Low**	**Participants returned to clinic every 12 weeks for neurological assessments by a treating clinician and an examining clinician, both blinded to treatment assignment.**	High	ITT (all participants who were randomized) used for the primary analyses. The safety population was all who received ≥1 dose of study drug and had ≥1 post-baseline assessment of the safety parameter. Participants withdrawn for adverse reactions	Low	NCT record states the outcomes as: Annualized relapse rate of protocol-defined exacerbations; Confirmed Progression on the Expanded Disability Status Scale; Change in the Multiple Sclerosis Functional Composite; Change in MRI Composite	**Low**	**No other apparent sources of bias**	High

					of the trial period		**Interferon-β1a (IFN, Avonex, Biogen-Idec) 30 µg was administered intramuscularly weekly and glatiramer acetate (GA, Copaxone, Teva Pharmaceuticals) 20 mg was administered subcutaneously daily, with matched placebo preparations**		**Interferon-β1a (IFN, Avonex, Biogen-Idec) 30 µg was administered intramuscularly weekly and glatiramer acetate (GA, Copaxone, Teva Pharmaceuticals) 20 mg was administered subcutaneously daily, with matched placebo preparations**				and/or drop-out were considered failures in safety assessment. The modified ITT (mITT) population included all randomized participants that had taken ≥1 dose of study medication and had ≥1 valid post-baseline MRI. For the primary outcome and analysis, the Cox Model allows for use of time on study for all participants and thus no imputation was utilized. Those that terminated the study prior to relapse were censored; only their time on study contributed to time relapse free. Differential drop-out: In the IFN+GA group: 499 randomised; 499 (100%) analysed for primary endpoint; 397 (79.6%) analysed for clinical endpoint at month 36; 388 (77.8%) for MRI endpoint at month 36. In the IFN group: 250 randomised; 250 (100%) analysed for primary		Score. All reported; also post hoc Disease Activity Free Status and safety assessments			

													endpoint; 194 (77.6%) analysed for clinical endpoint at month 36; 187 (74.8%) for MRI endpoint at month 36. In the GA group: 259 randomised; 259 (100%) analysed for primary endpoint; 223 (86.1%) analysed for clinical endpoint at month 36; 215 (83.0%) for MRI endpoint at month 36.					
CS	CONFIRM	Low	"...randomization scheme and codes developed by the Sponsor. Randomization … across all … sites using a centralized Interactive Voice Response System (IVRS)."	Low	Centralized Interactive Voice Response System (IVRS)"	Low	Except for GA patients, ...patients were unaware of assignment to the BG-12 and placebo groups	Low	All study management and site personnel, investigators...were unaware of assignment to the BG-12 and placebo groups	Low	Rater blinded	Low	Proportion that did not complete study appears balanced between groups; sensitivity analysis conducted to include patients switched to alternative MS meds; missing data imputed for MRI end points	Low	NR in biogen data extraction	Low	No other biases detected	low
ERG	CONFIRM	Unclear	Not stated in Fox 2012	Unclear	Not stated in Fox 2012	Unclear	Patients receiving glatiramer acetate were aware of their treatment assignment. All study management and site personnel, investigators,	**Low**	**All study management and site personnel, investigators, and patients were unaware of assignment to the BG-12 and placebo groups.**	**Low**	**Examining neurologists, technicians at the magnetic resonance imaging (MRI) reading center, and members of the independent neurologic evaluation committee**	**Low**	**Primary and secondary end points were analysed in the intention-to-treat (ITT) population (all randomly assigned patients who received study treatment) and in the MRI cohort (patients in**	**Low**	**NCT record reported outcomes as: Annualized Relapse Rate; Number of New or Newly Enlarging T2 Hyperintense Lesions; Number of New T1 Hypointense Lesions; Proportion of**	High	The rate of study drug discontinuation was higher in the placebo group than in the other groups (36% vs. 30% in the BG-12 bd	High

							and patients were unaware of assignment to the BG-12 and placebo groups.				**were unaware of all study-group assignments. Each site used separate examining and treating neurologists, thereby maintaining rater blinding for all study groups, including the group that received glatiramer acetate.**		**the ITT population for whom any post-baseline MRI data were available). All patients receiving ≥1 dose included in safety population. 1430 randomised: placebo 363; BG-12 bd 362 (of whom 3 not dosed: 2 withdrew consent and 1 withdrawn by the investigator for an abnormal ECG reading); BG-12 tid 345; GA 360 (10 not dosed: 8 withdrew consent on learning that they had been randomized to open-label GA treatment and 2 withdrew consent for other unstated reasons). One patient randomised to the BG-12 tid group took GA throughout the study. This patient was counted in the thrice-daily BG-12 group of the ITT population and in the GA group of the safety population.**		**Subjects Relapsed; Progression of Disability Assessed Using the Expanded Disability Status Scale (EDSS). All reported in Fox 2012 plus safety outcomes.**		group, 28% in the BG-12 tid group, and 25% in the GA group) as was the proportion of patients who switched to alternative multiple sclerosis medications (11% vs. 7%, 8%, and 6%, respectively).	

CS	Copolymer I Study	Unclear	Method of randomization not discussed	Low	Centralized randomization scheme	Low	Double-blind	Low	Double-blind. The nurse coordinator and both neurologists were blinded to study medication assignment throughout the trial.	Low	The nurse coordinator and both neurologists were blinded to study medication assignment throughout the trial	Low	84.8% and 86.5% completed study treatment respectively and the authors stated that ITT analysis involved all randomized patients; method of handling missing data was not described	Low	All outcomes described in the methods are reported in the results.	Low	No other biases detected	unclear
ERG	Copolymer I Study	**Unclear**	**Method of randomization not discussed**	**Low**	**Centralized randomization scheme**	**Low**	**Double-blind; placebo used assumed identical to active drug**	**Low**	**Double-blind. The nurse coordinator responsible for distributing the medication and both neurologists were blinded to study medication assignment throughout the trial.**	**Low**	**The nurse coordinator and both neurologists were blinded to study medication assignment throughout the trial**	**Low**	**84.8% and 86.5% completed study treatment respectively and the authors stated that ITT analysis involved all randomized patients; method of handling missing data was not described**	**Low**	**Pre-specified outcomes of relapse rates and disease progression were reported, and also adverse events**	**Low**	**No other biases detected**	**unclear**
CS	Crentsil 2012	Unclear	No description of randomisation	Unclear	No description of allocation concealment.	Unclear	Conference abstract only. Insufficient detail on study design	Unclear	Conference abstract only. Insufficient detail on study design	Unclear	Conference abstract only. Insufficient detail on study design	Unclear	Conference abstract only. Insufficient detail on study design	Unclear	Conference abstract only. Insufficient detail on study design	Unclear	Conference abstract only. Insufficient detail on study design	NR in biogen data aex

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ERG	Crentsil2012	**Unclear**	**No description of randomisation**	**Unclear**	**No description of allocation concealment.**	**Unclear**	**Conference abstract only. Insufficient detail on study design**	**Unclear**	**Conference abstract only. Insufficient detail on study design**	**Unclear**	**Conference abstract only. Insufficient detail on study design**	**Unclear**	**Conference abstract only. Insufficient detail on study design**	**Unclear**	**Conference abstract only. Insufficient detail on study design**	**Unclear**	**Conference abstract only. Insufficient detail on study design**	Unclear
CS	DEFINE	Unclear	Method of sequence generation not reported. "Randomization was performed centrally"	Low	Randomisation used a centralized interactive voice response system	Low	The study used a matched placebo capsule designed to mimic DMF capsules	Low	To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial).	Low	"All scans were evaluated in a blinded manner at a central reading facility (NeuroRx Research).""To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial)." "All protocol-defined relapses were evaluated by an independent neurologic evaluation committee, whose	Low	The authors used a modified ITT and included all pts who received at least one dose of study drug	Low	All prespecified outcomes are presented in the results	Low	No other apparent sources of bias	Unclear

												members reviewed a standardized set of blinded clinical records (which did not include MRI data) from the treating and examining neurologists"								
ERG	DEFINE	**Unclear**	**Randomization was performed centrally and was stratified according to site (no further details).**	**Low**	**Randomization was performed centrally**	**Low**	**Double-blind**	**Low**	**Double-blind. The treating neurologists were responsible for all aspects of patient care, including the treatment of relapses and other disease symptoms. To ensure that the study-group assignments would not be revealed, patients were instructed to take the assigned study drug at least 4 hours before study visits, in case patients in the BG-12 groups had a side effect of flushing.**	**Low**	**To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial). The examining neurologists conducted neurologic assessments, including assessment of the EDSS score. All scans were evaluated in a blinded manner at a central reading facility.**	**Low for clinical outcomes; high for MRI**	**1237 randomised; 1234 received at least one dose of the study drug (intention-to-treat population); Placebo (n=408), Twice-Daily BG-12 (n=410), Thrice-Daily BG-12 (n=416). Clinical results are derived from the 1234 patients in the intention-to-treat population; MRI results are derived from the 469 patients in the MRI cohort with post-baseline data (165 [40.4%] in the placebo group, 152 [37.1%] in the twice-daily BG-12 group, and 152 [36.5%] in the thrice-daily BG-12 group).**	**Low**	**NCT record specifies the following outcomes: Proportion of Subjects Relapsed; Number of New or Newly Enlarging T2 Hyperintense Lesions; Number of Gadolinium-enhancing T1-weighted Lesions; Number of Subjects With Gadolinium (Gd)-Enhancing Lesions; Annualized Relapse Rate; Proportion of Subjects Experiencing Progression of Disability Assessed Using the Expanded Disability Status Scale (EDSS). These were reported and also safety outcomes.**	**Low**	**No other apparent sources of bias**	**Unclear**
CS	Etem	Uncl	Method of randomisation was not reported	Uncl	No description of allocation	High	No indication that blinding was attempted. The interventions all	High	The interventions all have different dosing schedules	Low	"The trial was single-blinded in that patients were aware but	Low	Analysis is described as ITT	Low	All outcomes described in the methods are	Low	No other apparent sources of bias	High

	adifar2006	ear		ear	concealment.		have different dosing schedules so it likely that the study was unblinded		and patients were unblinded so it likely that the blinding would be broken		physicians who assessed the outcome were unaware of the treatment type that the patient had received."				reported in the results.			
ERG	Etemadifar2006	**Unclear**	**Method of randomisation was not reported**	Low	"Concealed treatment allocation" mentioned in the Discussion section	**High**	**"Because of the difference in the frequency of injections and side-effect profiles of IFN-β products administered intramuscularly or subcutaneously, it is impossible to keep patients blinded in a study of this nature."**	**High**	**"The treating physicians dealing with clinical and laboratory adverse events can easily become unblinded."**	**Low**	**"The trial was single-blinded in that patients were aware but physicians who assessed the outcome were unaware of the treatment type that the patient had received." "One physician who did not know which patients had received which treatment made clinical evaluation of all patients."**	**Low**	**"Statistical analysis was based on an intention-to-treat principle." 90 patients randomised (30 per group) and all 90 patients who completed treatment were available for follow-up at 6, 12, and 24 months**	**Low**	**Methods reported outcomes of side effects, number of relapses, the proportion of relapse-free patients, the EDSS scores, and other medical events that occurred. All were reported although the side effects were only reported very briefly as: "IFN-β products were well tolerated and most of the adverse events reported were mild in severity"**	Unclear	The lack of safety assessment in the trial is a limitation (given that it was mentioned in the Methods under patient evaluation) but the authors state that "the safety of IFN-β products in the treatment of RRMS had already been established for the three drugs in previous studies."	**High**
CS	EVIDEN	Low	"Treatment assignments were determined using a computer-	Low	"Treatment assignments were determined using a computer-	High	Separate treating and evaluating physicians were designated prior to randomization.	Low	Separate treating and evaluating physicians were designated prior to randomization.	Low	"Assessors blinded to treatment performed neurologic and MRI evaluations"	Low	All randomized patients included in the efficacy analysis	Low	All prespecified outcomes are presented in the results	Low	No other apparent sources of bias	High

	CE		generated randomizatio n list, and were allocated through a centralized telephone randomizatio n system to unblinded site personnel."		generated randomizat ion list, and were allocated through a centralized telephone randomizat ion system to unblinded site personnel."		Patients were instructed not to disclose their treatment assignment or symptoms related to their treatment regimen, to the blinded evaluating physician: "Patients and a treating physician who was not involved in end point assessment were aware of treatment assignments"		Patients were instructed not to disclose their treatment assignment or symptoms related to their treatment regimen, to the blinded evaluating physician								
ERG	EVIDENCE	**Low**	**Computer-generated randomizati on list**	**Low**	**Allocated through a centralized telephone randomiza tion system. Randomiz ation was stratified by center, with an initial block size of six followed by block sizes of four in order to reduce the ability of sites to determine subsequen**	**High**	**Because of the different injection frequency and side-effect profile of IFNβ-1a administered IM or SC, it would have been impossible to keep patients blinded in a study of this nature**	High	The treating physicians dealing with clinical and laboratory adverse events can easily become unblinded.	**Low**	**Separate treating and evaluating physicians were designated prior to randomization. Patients were instructed not to disclose their treatment assignment or symptoms related to their treatment regimen, to the blinded evaluating physician, and to cover injection sites before scheduled and relapse-related neurologic examinations. MRI evaluation was performed centrally (University of**	**Low**	**677 randomised, 339 to 44µg tiw and 338 to 30µg qw. The primary analysis was conducted on the intent-to-treat cohort. For patients who withdrew from the study without follow-up, missing data for the primary outcome were imputed using random number allocation based on the overall proportion of patients not experiencing a relapse during the 24- and 48-week treatment periods for both groups**	**Low**	**Methods section specified the following outcomes: free of relapses, relapse rate, relapse severity, use of steroids for relapses, time to first relapse, disability (progression by one point on the EDSS scale), safety evaluations and the number of combined unique (CU) active lesions per patient per MRI scan. All reported although details of relapse severity were sparse, only stating: "The**	**Low**	**No other apparent sources of bias**	**High**

					t treatment allocation based on prior allocation.						**British Columbia MS/MRI Research Group, Vancouver, Canada) by blinded examiners who had no knowledge of a patient's treatment or outcome. Evaluating physicians guessed treatment allocation correctly in 52% of patients (47% correct in the 30 µg qw group and 57% in the 44 µg tiw group). Protocol violations wherein treating physicians served as evaluators occurred in 1% of patients in both groups.**		**combined. Sensitivity analyses were conducted to evaluate the impact of different missing data assumptions on the results for the primary endpoint.**		**number of relapses was fewer for the 44 µg tiw group than for the 30 µg qw group at each severity level, although the proportions of relapses in each group that were mild, moderate, or severe were not different."**			
CS	GALA	Low	Block randomization scheme provided by Teva Pharmaceutical - therefore assumed sequence generation was appropriate	Low	Randomization scheme produced by the study sponsor (Teva Pharmaceuticals)	Low	Double blind	Low	The investigators, the sponsor, and any personnel involved in patients' assessments, monitoring, analysis, and data management were blinded to treatment assignment. Study drugs were packaged and labeled in a way that	Low	The investigators, the sponsor, and any personnel involved in patients' assessments, monitoring, analysis, and data management were blinded to treatment assignment. Study drugs were packaged and labeled in a way that maintained the masked nature of the study; the	Low	All randomized patients were analysed for the primary outcome	Low	Outcomes reported in methods section were reported in the results	Low	No other biases were apparent	Low

									maintained the masked nature of the study; the appearance, shape, color, and smell were identical.		appearance, shape, color, and smell were identical.							
ERG	GALA	**Low**	**Randomization scheme produced by the study sponsor (Teva Pharmaceuticals). The randomization scheme used constrained blocks stratified by center**	Unclear	Not stated	**Low**	**Double-blind. Study drugs were packaged and labeled in a way that maintained the masked nature of the study; the appearance, shape, color, and smell were identical.**	**Low**	**The investigators, the sponsor, and any personnel involved in patients' assessments, monitoring, analysis, and data management were blinded to treatment assignment. Study drugs were packaged and labeled in a way that maintained the masked nature of the study; the appearance, shape, color, and smell were identical.**	**Low**	**All follow-up neurological examinations were performed by the blinded examining neurologist.**	**Low**	**1,404 were randomized to study treatment (GA 40mg tiw, n=943; placebo, n=461) and received at least 1 dose of treatment. All were included in evaluation of adverse events and immediate post-injection reactions. From Figure 1, in the GA group, 84/943 (8.9%) discontinued; 859 (91.1%) completed 12 months and 816 (86.5%) were evaluable (completed study without major protocol violations). In the placebo group, 31/461 (6.7%) discontinued; 430 (93.3%) completed 12 months and 403 (87.4%) were evaluable. However, the authors state that "The principal analysis for the**	**Low**	**Outcomes reported in methods section were reported in the results**	**Low**	**No other biases were apparent**	**Unclear**

													primary endpoint of total number of confirmed relapses during the 12-month PC phase was performed on the intent-to-treat (ITT) cohort, defined as all randomized patients." They used a baseline-adjusted quasi-likelihood (over-dispersed) negative binomial regression analysis with an offset based on the log of the patient's exposure to treatment, baseline EDSS score, log of the number of relapses in the previous 2 years, volume of T2 lesions at baseline, status of Gd-enhancing T1 activity at baseline, and country or geographical region as covariates. Secondary analyses were similarly adjusted to account for missing scans. Patients who missed both 6- and 12-month				

													scans were excluded from the analysis. Brain atrophy was analyzed using a baseline-adjusted analysis of covariance, with normalized brain volume at baseline, the number of Gd-enhancing lesions on T1-WI at baseline, and country or geographical region as covariates. Patients who missed brain volume measurements at 12 months were excluded from the analysis. From Table 3: Secondary MRI endpoints included GA n=884 (93.7%) and placebo n=441 (95.7%) except brain atrophy: GA 840 (89.1%), placebo 423 (91.8%)					
CS	GLACIER	Low	"...computerized randomization sequence … generated and maintained by …Teva	Low	"...randomization was conducted centrally using the Interactive Response Technology system"	High	"...participants were not blinded or masked to the open-label treatment assignment"	High	" Investigators ...were not blinded or masked to the open-label treatment assignment"	High	Open label	Low	All randomized participants were analysed	High	AEs (other than injection site AEs) were measured but not reported	Low	No other apparent sources of bias	NR inbioge

			Pharmaceuticals"																
ERG	GLACIER	**Low**	**Computerized randomization sequence**	**Low**	**Randomization was conducted centrally using the Interactive Response Technology system**	**High**	**"...participants were not blinded or masked to the open-label treatment assignment"**	**High**	**" Investigators ...were not blinded or masked to the open-label treatment assignment"**	**High**	**" Investigators ...were not blinded or masked to the open-label treatment assignment"**	**Low**	**209 were randomized to the study treatment (GA20, n=101; GA40, n=108). The safety analysis cohort consisted of all 209 patients, and the full analysis cohort consisted of 208 patients (GA20, n=100; GA40, n=108).**	**High**	**NCT record states outcomes measures as: Injection-Related Adverse Event Rate; Adjusted Mean Participant-Reported Impact on Physical and Psychological Wellbeing Using Multiple Sclerosis Impact Scales; Participant-Reported Treatment Satisfaction Questionnaire for Medication Convenience and Satisfaction; Adverse Events Other Than Injection Related Reactions. All reported except AEs (other than injection site AEs) were measured but not reported**	**Low**	**No other apparent sources of bias**	High

CS	GLOW	Unclear	Method of generating random sequence was not reported	Unclear	Method of concealing allocation was not reported	Low	Double blind (Subject, Investigator)	Low	Double-blind (Subject, Investigator)	Unclear	NR in biogen data extraction	High	Study was terminated early by sponsor, efficacy outcomes not investigated as planned.	Unclear	Study was terminated early by sponsor	Unclear	Study was terminated early by sponsor	high
ERG	GLOW	**Unclear**	**Method of generating random sequence was not reported**	**Unclear**	**Method of concealing allocation was not reported**	**Low**	**Double (Participant, Investigator)**	**Low**	**Double (Participant, Investigator)**	**Unclear**	**Not stated**	**High**	**Intent to treat population was planned for efficacy outcomes. However analysis was not performed due to early termination of the study. Adverse events were collected by non-systematic assessment**	High	Analysis was not performed due to early termination of the study.	**Unclear**	**Study was terminated early by sponsor**	**High**
CS	IFNBMS study	Unclear	Method of generating random sequence was not reported	Unclear	Method of concealing allocation was not reported	Low	Double blind	Low	Double blind. All personnel…were blinded to treatment categories	Low	All personnel…were blinded to treatment categories	Unclear	Intent to treat analysis was cited but it was not clear how missing data were dealt with	Low	Outcomes reported in methods section were reported in the results	Low	No other biases were apparent	Unclear
ERG	IFNBMS study	**Unclear**	**Method of generating random sequence was not reported**	**Unclear**	**Method of concealing allocation was not reported**	**Low**	**Double blind**	**Low**	**All personnel at each study site were blinded to treatment categories**	**Low**	**Two physicians at each site were designated: one neurologist who was not aware of drug side effects to do the periodic examinations, and another "treating" neurologist who knew about side effects and injection site reactions, reviewed**	Low	Randomised: Placebo (n=123), IFNB 1.6MIU (n=125), 8MIU (n=124). Three-year exacerbation data for the same number of patients. Disability at 3 years: 122 (99.2%), 125 (100%) and 122 (98.4%), respectively.	Unclear	Outcomes mentioned in the Methods section were: annual exacerbation rate and proportion of exacerbation-free patients; time to first exacerbation; exacerbation duration and severity; change in EDSS and NRS scores; quantitative disease burden as	**Low**	**No other biases were apparent**	**Unclear**

												laboratory findings for toxicity, and was responsible for overall care. All MRIs were interpreted by the Radiology Department of the University of British Columbia in a blinded fashion.				measured by annual MRI; and disease activity as measured by MRI in a frequent-scanning substudy. Duration of exacerbations not reported, nor disease activity in this paper, although further MRI results referenced to a companion paper (Paty DW, Li DKB, MS/MRI Study Group, IFNB MS Study Group. Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662-667) which does show more MRI data.			
CS	INCOMIN	Low	Randomisation was done centrally by the coordinating centre. Randomisation followed computer-generated random sequences of digits.	Low	These codes were randomly assigned to treatments by an independent team of statisticians unaware of the patient's clinical	High	No blinding for participants	High	No blinding for caregivers	High	All clinical outcomes were assessed in an open-label manner: "Scans were analysed centrally by investigators at the University of Torino MRI Analysis Centre, who were unaware of treatment allocation and clinical	Low	97% of patients had completed follow up at 2 years, clinical outcome analysis was modified ITT	Low	All prespecified outcomes are presented in the results	Low	No other apparent sources of bias	High

					characteristics						characteristics of patients"							
ERG	INCOMIN	**Low**	**Randomisation followed computer-generated random sequences of digits that were different for each centre and for each sex, to achieve centre and sex stratification**	**Low**	**Randomisation was done centrally by the coordinating centre.**	**High**	**Patients were randomly assigned to self-administer either interferon beta-1b (250 µg [8 MIU] subcutaneously, every other day) or interferon beta-1a (30 µg [6 MIU] intramuscularly, once a week). Not blinded.**	**High**	**No blinding for caregivers**	**High**	**All clinical outcomes were assessed in an open-label manner. Personnel unaware of treatment allocation and clinical characteristics of patients assessed all MRI outcomes.**	Unclear	Analysis was by intention to treat. All data were included, using complete 2-year data for the patients who completed as well as for those who discontinued treatment. The data of patients lost at follow up were retained in the analysis until the point they were lost; for subsequent analyses, these patients were considered as having a bad outcome. MRI scans were available from 149/188 (79.3%) of patients. Four centres (which included 35 patients) did not participate in the MRI part of the study because their MRI equipment was unable to meet the study requirements, in particular it was unable to produce contiguous slices. Furthermore, four patients (three of the beta-1a, one of the beta-1b group) refused to have MRI scans. 39	**Low**	**Outcomes stated in the Methods section were: proportion of patients free from relapses; annualised relapse rate; annualised treated relapse rate (required corticosteroids); patients free from sustained and confirmed progression in disability (an increase in EDSS of ≥1point sustained for ≥ 6 months and confirmed at end of follow-up); EDSS score; time to sustained and confirmed progression in disability; patients free from new proton density/T2 hyperintense lesions; patients free from gadolinium-enhancing lesions; patients free from MRI activity (the occurrence of new proton density/T2 hyperintense or enhancing lesions throughout the study); burden of disease; and**	**Low**	**No other apparent sources of bias**	**High**

													patients, therefore, participated only in the clinical portion of the study.		**safety. All were reported.**			
CS	Mokhber 2014	Low	The study neurologist enrolled the participants and allocated the subjects using a computer-generated list of random numbers.	Unclear	No description of allocation concealment.	Unclear	It is stated that the study is double blinded, but no details are provided to explain whether and how blinding was achieved	Unclear	It is stated that the study is double blinded, but no details are provided to explain whether and how blinding was achieved	Low	The study psychologist and neuropsychiatrist, both blinded to the treatment groups, evaluated the cognitive function before treatment, and 12 months after treatment	Low	Low % of incomplete outcome data.	Unclear	Trial was done to measure cognition and EDSS, but other usual outcomes in MS trials are missing.	Low	No other apparent sources of bias	Unclear
ERG	Mokhber 2014	**Low**	**Computer-generated list of random numbers**	**Unclear**	**No description of allocation concealment.**	**Unclear**	**The authors stated that "participants and all those assessing outcomes were blinded to the treatment groups." But Avonex was administered 30 mcg once per week via intramuscular injection; Rebif was administered 44 mcg three times per week via subcutaneous injection; and Betaferon was administered 0.25 mg every other day via subcutaneous injection.**	**Unclear**	**The authors stated that "participants and all those assessing outcomes were blinded to the treatment groups." But Avonex was administered 30 mcg once per week via intramuscular injection; Rebif was administered 44 mcg three times per week via subcutaneous injection; and Betaferon was administered 0.25 mg every other day via subcutaneous injection.**	**Low**	**The study psychologist (MMG) and neuropsychiatrist (NM), both blinded to the treatment groups, evaluated the cognitive function before treatment, and 12 months after treatment.**	**Low**	**69 patients were randomly allocated into the 3 treatment groups of 23 patients. Three patients in the Avonex group and 1 in the Betaferon group did not attend the follow-up sessions. Therefore, the authors managed to evaluate and follow up 65 cases by the end of the trial.**	Low	Outcomes were cognitive function (using the Brief Repeatable Battery of Neuropsychological Tests) and EDSS; both reported.	**Low**	**No other apparent sources of bias**	**Unclear**

CS	Mokhber 2015	Low	Patients were randomly assigned using a computer-generated list of random numbers	Unclear	Methods to conceal treatment allocation were not described	High	Method of treatment administration differed between study arms	Unclear	Method of treatment administration differed between study arms	Low	Single blind	Low	Missing data was balanced across groups with similar reasons	Low	All outcomes described in the methods are reported in the results.	Low	No other apparent sources of bias	NR in bio gen data extraction
ERG	Mokhber 2015	**Low**	**Patients were randomly assigned using a computer-generated list of random numbers**	**Unclear**	**Methods to conceal treatment allocation were not described**	**High**	**Avonex was administered 30 µg once per week via intramuscular injection. Rebif was administered 44 µg three times per week via subcutaneous injection. Betaferon was administered 0.25 mg every other day via subcutaneous injection.**	**Unclear**	**Method of treatment administration differed between study arms**	**Low**	**Single blind**	**Low**	**69 patients were randomly allocated into the 3 treatment groups of 23 patients; the study lost 3 patients in the Avonex group (1 refused to continue, 2 loss of contact), 2 in the Rebif group (both due to changing their place of residence), and 4 in the Betaferon group (3 loss of contact, 1 refused to continue), leaving 60 patients**	**Low**	**Outcomes (quality of life, EDSS) specified in the Methods section were reported.**	Unclear	The numbers lost to follow up are not the same as those reported in Mokhber 2014 above	High

													who completed the study					
CS	MSCRG	Low	Efron's biased coin method	Low	Only the DMSC had access to randomization schedules containing treatment arm assignments and listing subject names.	Low	All personnel and patients were blinded to treatment status, labeled vials provided to the centers did not contain any information on treatment arm assignments; vials were identified only by ID and lot number.	Low	All personnel and patients were blinded to treatment status	Low	Examining physicians were prohibited from participating on the Advisory, Quality Control or Statistical Monitoring Committees or communicating with other study personnel in any matter that might compromise blinding.	Low	Study was terminated early by sponsor. Efficacy outcomes are analysed by a combination of per protocol and data available for completers. Safety appears to be ITT.	High	Full data were not reported for all specified outcomes	Low	No other apparent sources of bias	High
ERG	MSCRG	**Low**	**Efron's biased coin method**	Unclear	Not stated in Jacobs 1995	**Low**	**All personnel and patients were blinded to treatment status.**	**Low**	**All personnel and patients were blinded to treatment status.**	**Low**	**Independent examining physicians determined the EDSS score. Patients did not discuss medical issues with rhe examining physician.**	**Low**	**The study was designed on an intent-to-treat basis. 301 patients were randomised to placebo (n=143) or interferon beta-la (n=158). Adverse events data and primary analyses included all patients. Several analyses were repeated on the subset of patients who were accrued early enough to complete 104 weeks of follow-up by the end of the study, i.e. only 87 placebo (60.8%) and 85 interferon beta la (53.8%). MRI results were available for 123 (86.0%) and 134 (84.8%) patients,**	Low	Outcomes specified in the Methods section were: time to onset of sustained worsening in disability; on-study exacerbations; number and volume of discrete gadolinium-enhanced lesions on MRI. These were all reported in Jacobs 1995	unclear	Potential confounding due to differential steroid use between the two treatment arms	Unclear

													respectively at year 1 and 82 (57.3%) and 82 (51.9%) in year 2.					
CS	O'Connor2006	Unclear	Method of sequence generation not reported	Unclear	Method of allocation concealment not reported	Low	Matching Placebo	Low	Relapse and disability assessments were made by the treating (blinded) neurologist	Low	Relapse and disability assessments were made by the treating (blinded) neurologist	Low	All randomised patients were included in the analysis	Low	All outcomes described in the methods are reported in the results.	Low	No other apparent sources of bias	NR in biogen data extraction
ERG	O'Connor2006	**Unclear**	**Method of sequence generation not reported**	**Unclear**	**Method of allocation concealment not reported**	**Low**	**Matching Placebo**	**Low**	**Both relapse and disability assessments were made by the treating (blinded) neurologist.**	**Low**	**Both relapse and disability assessments were made by the treating (blinded) neurologist.**	**Low**	**179 were randomized, and treated with placebo (n=61), teriflunomide 7 mg/day (n=61), or teriflunomide 14 mg/day (n=57); all these patients included in MRI evaluations and adverse events reporting. The primary analysis populations were the intent-to-treat (ITT) population**	Unclear	Methods stated outcomes were: number of CU active (new and persisting) lesions per MRI scan; number of T1 enhancing lesions, number of T2 active lesions, number of patients with CU active, T1 enhancing, and T2 active lesions, and percentage change from baseline to endpoint in the	Unclear	Study only 36 weeks; may not be long enough to capture relevant changes in disability	Unclear

													(all randomized patients) and the safety-evaluable population (all randomized patients who received ≥1 doses of study medication). The secondary analysis population was the efficacy evaluable (all randomized patients for whom there was at least one on-treatment MRI assessment and including all data collected during the period from baseline to the last day of study medication + 14 days inclusively).		burden of disease (T2 lesion volume); number of patients experiencing an MS relapse, annualized relapse rate, and number of relapsing patients requiring a course of steroids; changes in EDSS score; number of patients in whom disability increased; safety. The number of patients experiencing an MS relapse and change in EDSS scores were not reported, although the other specified outcomes were (including ARR and EDSS increase in disability).			
CS	OPERAI	Low	Randomization was performed centrally with the use of an independent interactive Web-response system.	Unclear	Method of allocation concealment not reported	Low	Double blind (including patients), according to NCT page. Matching placebo	Low	Double blind (including investigator and assessors), according to NCT page. Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial.	Low	Double blind (including investigator and assessors), according to NCT page. Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial.	Low	All randomised patients were included in the analysis	Low	All outcomes described in the methods are reported in the results.	Low	No other apparent sources of bias	NRinbiogendataextra

																		ction
ERG	OPERAI	**Low**	**Randomization was performed centrally with the use of an independent interactive Web-response system**	Low	Randomization was performed centrally with the use of an independent interactive Web-response system	**Low**	**Triple blind (participant, investigator, outcomes assessor). Patients in each group received a matching subcutaneous or intravenous placebo, as appropriate**	**Low**	**Triple blind (participant, investigator, outcomes assessor)**	**Low**	**Triple blind (participant, investigator, outcomes assessor)**	**Low**	**Efficacy analyses in the intention-to-treat population (all the patients who underwent randomization) or, for the end point of no evidence of disease activity, in a modified intention-to-treat population that excluded patients who were withdrawn from the trial for reasons other than efficacy failure or death and who had no evidence of clinical disease activity at the time of treatment discontinuation in the trial. Randomised: ocrelizumab 410, Interferon Beta-1a 411. All in efficacy outcomes. Safety (all patients who received any study treatment): ocrelizumab 408/410 (99.5%), Interferon Beta-1a 409/411 (99.5%)**	**Low**	**NCT record states that the outcomes are: Annualized Relapse Rate; Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 Weeks; Number of T1 Gadolinium (Gd)-Enhancing Lesions; Percentage of Participants With Confirmed Disability Improvement (CDI) for at Least 12 Weeks; Time to Onset of Confirmed Disability Progression (CDP) for at Least 24 Weeks; Number of T1 Hypointense Lesions; Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score; Percent Change in Brain Volume; Change From Baseline in Short Form Health Survey-36 (SF-36)**	**Low**	**No other apparent sources of bias**	Low

															Physical Component Summary (PCS) Score; Percentage of Participants Who Have No Evidence of Disease Activity (NEDA); Adverse Events; Exposure to Ocrelizumab (Area Under the Concentration - Time Curve, AUC); Number of Participants With Anti-Drug Antibodies (ADAs) to Ocrelizumab. All reported in Hauser 2017 except exposure to ocrelizumab (area under the concentration - time curve, AUC) not reported in Hauser 2017.			
CS	OPERAII	Low	Randomization was performed centrally with the use of an independent interactive Web-response system.	Unclear	Method of allocation concealment not reported	Low	Double blind (including patients), according to NCT page. Matching placebo	Low	Double blind (including investigator and assessors), according to NCT page. Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial.	Low	Double blind (including investigator and assessors), according to NCT page. Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial.	Low	All randomised patients were included in the analysis	Low	All outcomes described in the methods are reported in the results.	Low	No other apparent sources of bias	NRinbiogendataex

																		traction
ERG	OPERAII	**Low**	**Randomization was performed centrally with the use of an independent interactive Web-response system**	Low	Randomization was performed centrally with the use of an independent interactive Web-response system	**Low**	**Triple blind (participant, investigator, outcomes assessor). Patients in each group received a matching subcutaneous or intravenous placebo, as appropriate**	**Low**	**Triple blind (participant, investigator, outcomes assessor)**	**Low**	**Triple blind (participant, investigator, outcomes assessor)**	**Low**	**Efficacy analyses in the intention-to-treat population (all the patients who underwent randomization) or, for the end point of no evidence of disease activity, in a modified intention-to-treat population that excluded patients who were withdrawn from the trial for reasons other than efficacy failure or death and who had no evidence of clinical disease activity at the time of treatment discontinuation in the trial. Randomised: ocrelizumab 417, Interferon Beta-1a 418. All in efficacy outcomes. Safety (all patients who received any study treatment): ocrelizumab 417 (100%);**		**NCT record states that the outcomes are: Annualized Relapse Rate; Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 Weeks; Number of T1 Gadolinium (Gd)-Enhancing Lesions; Number of New, and/or Enlarging T2 Hyperintense Lesions; Percentage of Participants With Confirmed Disability Improvement (CDI) for at Least 12 Weeks; Time to Onset of Confirmed Disability Progression (CDP) for at Least 24 Weeks; Number of T1 Hypointense Lesions; Change From Baseline in Multiple Sclerosis Functional Composite**	**Low**	**No other apparent sources of bias**	Low

														Interferon Beta-1a 417/418 (99.8%)		**(MSFC) Score; Percent Change in Brain Volume; Change From Baseline in Short Form Health Survey-36 (SF-36) Physical Component Summary (PCS) Score; Percentage of Participants Who Have No Evidence of Disease Activity (NEDA); Adverse Events; Exposure to Ocrelizumab (Area Under the Concentration - Time Curve, AUC); Number of Participants With Anti-Drug Antibodies (ADAs) to Ocrelizumab. All reported in Hauser 2017 except exposure to ocrelizumab (area under the concentration - time curve, AUC) not reported in Hauser 2017.**			
CS	PRISMS	Low	The randomisation list was computer generated	Unclear	No description of allocation concealment.	Low	All personnel involved in the study were unaware of treatment allocation	Low	All personnel involved in the study were unaware of treatment allocation	Low	All personnel involved in the study were unaware of treatment allocation	Low	All randomised patients were analysed for efficacy and safety. A few patients did not have MRI scans at 2 years.	Low	All prespecified outcomes are presented in the results	Low	No other apparent sources of bias	Unclear
ERG	PRI	**Low**	**The randomisation list was**	**Unc**	**No description of**	**Low**	**Double-blind. The study drug was packed**	**Low**	**All personnel involved in the study were**	**Low**	**Patients were assessed by two physicians. A**	**Low**	**Analysis was by intention to treat. All outcome data**	Unc	Methods section states that outcomes were:	**Low**	**No other apparent**	**Unc**

	SMS		**computer-generated by Serono Biometrics and stratified by centre. Equal allocation of the three treatment groups was used with a block size of six.**	**lear**	**allocation concealment.**		**according to the randomisation schedule and delivered to the centres to maintain blinding; all treatments given three times weekly by subcutaneous injection**		**unaware of treatment allocation.**		**"treating" neurologist was responsible for overall medical management of the patient, including treatment of any side-effects, and an "assessing" neurologist was responsible for neurological assessments and follow-up of relapses. All injection sites were covered up at neurological examinations to ensure that masking was not compromised because of local reactions.**		**were included. The data from the few patients who withdrew from the study early were retained in the statistical analyses, if relevant, by use of a censoring mechanism, an offset for the time spent in the study, or calculation of a rate that was standardised for the time spent in the study. 560 patients randomised: 187 placebo; 189 interferon β-1a 22 µg and 184 interferon β-1a 44 µg; all included in clinical efficacy and safety analyses.**	lear	relapse, times to first and second relapse, proportion of relapse-free patients, progression in disability (an increase in EDSS of ≥1 point sustained over at least 3 months), ambulation index, arm-function index, need for steroid therapy and hospital admission, and disease activity under MRI and burden of disease. The authors also assessed the psychological status of a subset of 267 patients enrolled in English-speaking centres using the Beck's hopelessness scale, the Centre for Epidemiologic Studies' depression mood scale, and the general health questionnaire. Time to second relapse not reported in this paper; arm function and psychological status mentioned only briefly in results.		**sources of bias**	**lear**
CS	REGA	Low	Treatments were assigned by a computer-	Uncl	"Treatments were assigned by a	High	Neither the patients nor the treating physicians were	High	Neither the patients nor the treating physicians were	Low	"The physicians who assessed patients at regular intervals or at the	Low	True ITT	Low	All prespecified outcomes are presented in the results	Low	No other apparent sources of bias	High

	RD		generated randomisation list	ear	computer-generated randomisation list": theoretically, a computer-generated list could be present in plain view, therefore not enough information		blinded to treatment.		blinded to treatment.		time of a potential relapse were blinded to treatment". "Patients were asked not to discuss their treatment with the assessing physician and they covered their injection sites so that the physician could not guess which treatment they had received." "MRI evaluations were done blinded"							
ERG	REGARD	**Low**	**Computer-generated randomisation list that was stratified by centre**	**Unclear**	**Not stated**	**High**	**Neither the patients nor the treating physicians were blinded to treatment (different regimens: 44 µg subcutaneous interferon beta-1a three times per week or 20 mg subcutaneous glatiramer acetate once per day).**	**High**	**Neither the patients nor the treating physicians were blinded to treatment (different regimens: 44 µg subcutaneous interferon beta-1a three times per week or 20 mg subcutaneous glatiramer acetate once per day).**	**Low**	**The physicians who assessed patients at regular intervals or at the time of a potential relapse were blinded to treatment. Patients were asked not to discuss their treatment with the assessing physician and they covered their injection sites so that the physician could not guess which treatment they had received. MRI evaluations were done blinded at the Image Analysis Center, VU Medical Center, Amsterdam, Netherlands.**	**Low**	**The primary analysis was done on the intention-to-treat population, which included all randomly assigned patients. Patients who completed 96 weeks of treatment and assessments without any major protocol deviations were included in the per-protocol population. All patients who had at least one injection and had safety follow-up data were included in the safety analyses.**	**Low**	**The only outcome measure reported in the NCT record is Time to First Relapse (reported in the paper). The Methods section in the paper also states outcome measures of: Secondary endpoints included the mean number of T2 active lesions (defined as new or enlarging T2 lesions per patient per scan over 96 weeks), mean number of gadolinium-enhancing lesions per patient per scan, change in the volume of gadolinium-enhancing lesions, and changes in T2**	Unclear	Change in disability was defined in the protocol as a progression on the EDSS scale of one point that was confirmed after 3 months. Because progression data were collected at 6-month intervals, however, this pre-specified analysis could not be fulfilled. Instead, a	**High**

															lesion volume. Tertiary endpoints included CUA lesions, new T1 hypointensities, T1 hypointense lesion volume, brain volume, other relapse outcomes, and disability progression. These were all reported in the results section, plus adverse events.		post hoc analysis of the 6-month confirmed disability progression was done.	
CS	TEMSO	Unclear	Method of sequence generation not reported	Unclear	Method of allocation concealment not reported	Unclear	Reported as double blinded, but it is not specified whether placebo and study drug were of identical appearance	Low	Both treating and examining neurologists were unaware of treatment assignments	Low	Both treating and examining neurologists were unaware of treatment assignments	Low	The authors used a modified ITT and included all pts who received at least one dose of study drug	High	MSFC and EQ5D measured but not reported, as not significant findings!	Low	No other apparent sources of bias	high
ERG	TEMSO	**Unclear**	**Randomization was stratified according to the baseline EDSS score (≤3.5 or >3.5) and according to trial site, with a block size of 6; no further details.**	**Unclear**	**Method of allocation concealment not reported**	Low	O'Connor 2011 states the study was double-blind. NCT record states "Triple (Participant, Investigator, Outcomes Assessor)" and the placebo was film-coated like the active drug	**Low**	**Both treating and examining neurologists were unaware of treatment assignments**	**Low**	**Both treating and examining neurologists were unaware of treatment assignments**	**Low**	**All analyses were performed according to a modified intention-to-treat principle, i.e. patients who underwent randomization and were exposed to study medication for at least 1 day. 1088 randomised (placebo n=363; teriflunomide 7mg n=366; teriflunomide 14mg n=359); 1086 (99.8%)**	Low	Outcomes specified in the NCT record were: Annualized Relapse Rate; Time to 12-week Sustained Disability Progression; Change From Baseline in Total Lesion Volume (Burden of Disease); Changes From Baseline in Fatigue Impact Scale [FIS] Total Score; Number of Gd-enhancing T1-lesions Per Scan; Volume of Gd-	**Low**	**No other apparent sources of bias**	Unclear

														exposed to study medication. The safety population was all patients who underwent randomization and were exposed to study medication, regardless of the amount administered or the medication assigned at randomization. The safety analyses were conducted according to the treatment actually received: placebo n=360; teriflunomide 7mg n=368; teriflunomide 14mg n=358.		enhancing T1-lesions Per Scan. Outcomes reported in O'Connor 2011 were number of relapses, ARR, time to first relapse, number relapse-free; confirmed progression of disability sustained for at least 12 weeks, time to disability progression (shown graphically); change in FIS score; change from baseline in total lesion volume; number of Gd-enhancing T1-lesions per scan; volume of hypointense lesions on T1- or T2-weighted images; brain parenchymal fraction; and safety. No mention of MSFC or EQ5D in O'Connor 2011 or the NCT record			
CS	TENERE	Low	Assignment to groups was done centrally using an Interactive Voice Response System (IVRS] in a 1:1:1 ratio	Low	Assignment to groups was done centrally using an Interactive Voice Response System (IVRS] in a 1:1:1 ratio	High	Patients were not blinded. Teriflunomide was given orally. IFN beta-1a was subcutaneous	High	The treating neurologist was responsible for patient selection, medication administration, managing AEs, and relapse and safety assessments	High	A blinded examining neurologist scored FS and EDSS. The unblinded treating neurologist was responsible for relapse and safety assessments	Low	All randomised patients were included in the analysis	Low	All outcomes described in the methods are reported in the results.	Low	NR in biogen data extraction	High

			after confirmation of the selection criteria.		after confirmation of the selection criteria.													
ERG	TENERE	Unclear	Randomisation stratified by country (Americas, Eastern Europe, Western Europe and Africa) and baseline EDSS score (≤3.5 or >3.5); no further details	Unclear	Not stated	**High**	**Patients were randomised 1:1:1 to teriflunomide 7 mg or 14 mg (double-blind) or IFNβ-1a (open-label)**	**High**	**The treating neurologist was responsible for patient selection, medication administration, managing AEs, and relapse and safety assessments**	**High**	**An examining neurologist scored the Functional Systems (FS) and EDSS. The examining neurologist remained blinded to treatment and associated AEs. The unblinded treating neurologist conducted relapse and safety assessments**	**Low**	**Efficacy analyses were conducted on the intent-to-treat (ITT) population, which included all randomised patients (n=104 for IFNβ-1a, 109 for teriflunomide 7 mg and 111 for teriflunomide 14 mg). The safety analysis included all randomised patients exposed to study medication (n=101 [3 patients in the IFNβ-1a group were never treated, and were therefore excluded from the safety analysis], 110 and 110, respectively [1 patient in the teriflunomide 14 mg group received teriflunomide 7 mg for 3 months, and was therefore included in the teriflunomide 7 mg group for the safety analysis).**		NCT record states outcome measures as: Failure (the first occurrence of confirmed relapse or permanent treatment discontinuation for any cause, whichever came first); Time to Failure; Annualized Relapse Rate; Change From Baseline in Fatigue Impact Scale (FIS) Total Score; Treatment Satisfaction Questionnaire for Medication [TSQM] Scores; Adverse Events. All reported in the paper.	**Low**	No other apparent sources of bias	**High**
CS	TOW	Low	Randomisation was done centrally, via an	Low	Randomisation was done centrally,	Low	Patients, individuals administering the	Low	Patients, individuals administering the	Low	Patients, individuals administering the interventions, and	Low	The authors used a modified ITT and included all pts who received at	Low	All outcomes described in the methods are	Low	NR in biogen data extraction	low

	ER		interactive voice recognition system that generated an allocation sequence using a permuted-block randomisation schedule with stratification according to study site and baseline EDSS		via an interactive voice recognition system that generated an allocation sequence using a permuted-block randomisation schedule with stratification according to study site and baseline EDSS		interventions, and those assessing the outcomes were masked to treatment assignment.		interventions, and those assessing the outcomes were masked to treatment assignment.		those assessing the outcomes were masked to treatment assignment.		least one dose of study drug. The number of patients not analysed was extremely small, 1-2 per arm		reported in the results.			
ERG	TOWER	**Low**	**Randomisation was done centrally, via an interactive voice recognition system that generated an allocation sequence using a permuted-block randomisation schedule with stratification according to study site and baseline EDSS score**	**Low**	**The interactive voice recognition system was run by an independent company**	**Low**	**Patients, individuals administering the interventions, and those assessing the outcomes were masked to treatment assignment.**	**Low**	**Patients, individuals administering the interventions, and those assessing the outcomes were masked to treatment assignment.**	**Low**	**Patients, individuals administering the interventions, and those assessing the outcomes were masked to treatment assignment.**	**Low**	**1169 randomised: placebo (n=389), teriflunomide 7 mg (n=408), teriflunomide 14 mg (n=372); 1165 (>99%) were exposed to study drug or placebo (modified intention-to-treat population); 1, 1 and 2 patients not exposed, respectively. Safety analyses included all patients who underwent randomisation and were exposed to study drug or placebo, classified according to the treatment that**	**Low**	**The NCT record states the following outcome measures: Annualized Relapse Rate; Time to Disability Progression; Time Without Relapse; Change From Baseline to Week 48 in EDSS Total Score; Change From Baseline to Week 48 in Fatigue Impact Scale (FIS) Total Score; Change From Baseline to Last Visit in Fatigue Impact Scale (FIS) Total Score; Change From Baseline to Week 48 in Short**	Unclear	TOWER did not include any MRI endpoints; about 30% of participants discontinued study treatment before study end.	Unclear

			(≤3·5 or >3·5).									**they received (some patients received a dose other than that assigned by randomisation): n=385, 409 and 371, respectively.**		**Form Generic Health Survey - 36 Items (SF-36) Summary Scores; Change From Baseline to Last Visit in Short Form Generic Health Survey - 36 Items (SF-36) Summary Scores; Change From Baseline to Last Visit in Short Form Generic Health Survey - 36 Items (SF-36) Summary Scores; Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA). These were reported.**			

Italic = new information (from Biogen data extraction), **BOLD** = agree with Biogen data extraction, Normal font – differ from Biogen data extraction
NR = not reported in Biogen data extraction sheet

Appendix C. ERG quality appraisal of the CS MTC

Table 3C. Appraisal of methodological reporting of the MTC (based on the CS)

	ERG findings
Rationale and searches	
1. Are the rationale for the MTC and the study objectives clearly stated?	Yes Overall objective of appraisal: "The objective of this appraisal is to assess the clinical and cost-effectiveness of pegylated interferon β-1a (pegIFNβ-1a, Plegridy®) within its marketing authorisation for the treatment of adults with relapsing-remitting multiple sclerosis (RRMS)." (CS Document B, pg.12) Clinical evidence: "This systematic review aimed to evaluate available evidence in the literature on pegIFNβ-1a relative to other approved DMTs for RRMS or placebo." (CS Document C, pg.5) Cost effectiveness: "The primary objective of this SLR was to identify all economic evidence relevant to the development of an economic model that will evaluate treatments for MS." (CS Document C, pg.149)
2. Are searches stated and do they appear appropriate?	Yes "Electronic databases and grey literature sources, including trial registries and conference abstracts, were originally searched up to October 2014, with seven subsequent update searches carried out up to December 2018 to identify relevant studies on specified Biogen Idec products and all potentially relevant comparators for the treatment of MS" (CS Document C, pg.3) Databases and search terms listed (CS Document C, D.1.1)
3. Are inclusion/exclusion criteria adequately reported?	Yes Inclusion criteria stated in Table 22, CS Document C, page 30
4. Is the quality of the included studies assessed?	Yes Quality assessment of the ADVANCE study presented in CS Document C, page 31, Table 24 Quality assessment of the other studies in the MTC in the Biogen Data Extraction excel spreadsheet dated August 2018
Model methods	
1. Is the statistical model described?	Yes "Mixed-treatment comparison was performed using a Bayesian approach using the gemtc package…The gemtc package implements the models

	recommended by the NICE Decision Support Unit using Just Another Gibbs Sampler (JAGS) to provide the underlying Markov Chain Monte Carlo simulations. A burn-in of 50,000 simulations was used, followed by an additional run of 50,000 simulations to obtain parameter estimates. Model convergence was assessed using the Brooks-Gelman-Rubin statistic, and if there were any doubts about convergence of the estimates, additional simulations were run. Model fit was assessed using residual deviance and the Deviance Information Criterion" (CS Document B, pg.66)
2. Is there a justification for the choice of outcome measure provided?	Yes "Data were extracted for all outcomes identified in Appendix D; however, MTC and supporting analyses … focus on the following key outcomes: ARR…, CDP3M…, CDP6M…, relapses requiring hospitalisation, relapses requiring IV corticosteroids, mortality, NEDA, symptoms of MS [cognition, fatigue, and visual impairment], QOL, any adverse event [AE], any serious adverse event [SAE], treatment discontinuation due to any cause, or treatment discontinuation due to AE" (CS Document B, pg.66) This list does not include "CDP sustained for 12 months" which was also listed as an outcome in CS Document C, Table 22.
3. Has a structure of the networks been provided?	Yes Document CS B page 78 for ARR, page 80 for CDP3M, and page 82 for CDP6M
4. Has the choice of fixed or random effects model been justified?	Yes "The primary analysis used random-effects models. A sensitivity analysis using fixed effect models was also performed." (CS Document B, pg. 66) "…in a standard meta-analysis of randomised trials it is assumed that different trials are sufficiently (not necessarily completely) homogeneous and that they estimate the same single treatment effect (fixed effect model) or different treatment effects distributed around a typical value (random effects model)." (Cs Document C, pg.33)
5. Is any of the programming code used in the statistical programme provided?	Yes The run analysis code used in R for estimating ARR in base case is in CS Document C, pages 434-438.

6. Is a sensitivity analysis presented, is this appropriate?	Yes "A sensitivity analysis using fixed effect models was also performed." (CS Document B, pg.66) "Sensitivity analyses were conducted using alternative prior distributions for the between-trials SD in networks with fewer than 10 studies." (CS Document C, pg.34) The Biogen Plegridy Full Report Appendices document (pg.266) reports the sensitivity analysis to assess the impact of using a random effects model versus a fixed effects model on the MTC for ARR (which showed similar effects). The authors reported that they "observed high heterogeneity in the comparison of GA 20 mg qd versus placebo (I2 = 86%)… The Bornstein 1987 study appears to be the outlier in this analysis as the rate ratio from this study does not overlap with the confidence intervals of the other two included studies" (pg.260). They conducted a sensitivity analysis excluding this study (pg.274). The Biogen Plegridy Full Report Appendices document (pg.284) reports the sensitivity analysis to assess the impact of using a random effects model versus a fixed effects model, and the choice of prior distribution, on the MTC for CDP3M, with similar results between the analyses. Also, for CDP6M, the relative effects for all treatment comparisons were similar in the random effects and fixed effects models (pg.304), and for alternative prior distributions (pg.304). For adverse events, the Biogen Plegridy Full Report Appendices document (pg.317) states that in sensitivity analyses, the relative effects of all treatments compared to placebo were similar in the random effects and fixed effects models. Odds ratios were similar using alternative prior distributions (pg.317). For serious adverse events, CS Document B page 66 stated that the authors "analysed SAE excluding MS relapses where data were available and performed sensitivity analyses of SAE, including MS relapses"; however, the Biogen Plegridy Full Report Appendices document (Table 12, pg.236) shows the data for SAE with and without relapses included, but an odds ratio graph was only shown for the data excluding relapses (Figure 21, pg.234) The Biogen Plegridy Full Report Appendices document (pg.322) states that in sensitivity analyses of serious adverse events, the relative effects of all treatments compared to placebo were similar in the random effects

	and fixed effects models. Odds ratios were similar using alternative prior distributions (pg.322). For treatment discontinuation due to any cause, the Biogen Plegridy Full Report Appendices document (pg.327) shows sensitivity analysis results for the fixed and random effect models.
Results	
1. Are the results of the MTC presented?	Yes CS Document B, page 67-92
2. Does the study describe an assessment of the model fit?	Yes CS Document B, page 66 states "Model fit was assessed using residual deviance and the Deviance Information Criterion." The Biogen Plegridy Full Report main document page 123 states: "The model fit statistics indicated that there was little difference between the alternative models except for the change in the between trials standard deviation." Model fit statistics were shown in the Biogen Plegridy Full Report Appendices for ARR page 270, CDP3M page 290, CDP6M page 309, adverse events page 318, SAE page 323, treatment discontinuation due to any cause page 328
3. Is the evidence combined and the results presented?	Yes CS Document B, page 67-92
4. Has there been any discussion around the model uncertainty?	Yes The Biogen Plegridy Full Report stated that "There was substantial uncertainty associated with all of the estimated treatment effects" for CDP3M page 88, CDP6M page 89, any AE page 114, any SAE page 114 and treatment discontinuation due to any cause page 119, although this was not found in CS Documents B or C.
5. Are the point estimates of the relative treatment effects accompanied by some measure of variance?	Yes The OR (for dichotomous outcomes), HR (for time-to-event outcomes), rate ratios (for rate outcomes) are reported with either 95% credible intervals (CrI, Bayesian methods) or 95% CI (frequentist methods) (CS Document B, pg.67).

Appendix D: Baseline characteristics of participants in the randomised controlled trials across randomised groups

Table 4D. Baseline characteristics of participants in the randomised controlled trials across randomised groups

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
ADVANCE	pegIFNβ-1a 125 mcg Q2W	512	151 (29) 361 (71)	36.9 (9.8)	2.47 (1.26)	6.9 (6.6) (first MS symptoms)	1.6 (0.67)
	pegIFNβ-1a 125 mcg Q4W	500	148 (30) 352 (70)	36.4 (9.9)	2.48 (1.24)	6.5 (6.1) (first MS symptoms)	1.5 (0.62)
	Placebo	500	142 (29) 358 (71)	36.3 (9.7)	2.44 (1.18)	6.3 (6.3) (first MS symptoms)	1.6 (0.67)
APEX	Dimethyl fumarate 240 mg BID	56	NR	NR	NR	NR	NR
	Placebo	58	NR	NR	NR	NR	NR
BEYOND	GA 20 mg QD	448	142 (32) 306 (68)	35.2 (NR) Median (IQR) = 35 (27-43)	2.28 (NR) Median (IQR) = 2 (1.5-3)	5.1 (NR) Median (IQR) = 3 (1-7) (MS diagnosis)	1.6 (NR) Median (IQR) = 1 (1-2)
	IFNβ-1b 250 mcg QAD	897	270 (30) 627 (70)	35.8 (NR) Median (IQR) = 35 (28-43)	2.35 (NR) Median (IQR = 2 (1.5-3)	5.3 (NR) Median (IQR) = 3 (1-7) (MS diagnosis)	1.6 (NR) Median (IQR) = 1 (1-2)
	IFNβ-1b 500 mcg QAD	899	270 (30) 629 (70)	35.9 (NR) Median (IQR) = 36 (28-43)	2.33 (NR) Median (IQR = 2 (1.5-3)	5.4 (NR) Median (IQR) = 3 (1-8) (MS diagnosis)	1.6 (NR) Median (IQR) = 1 (1-2)
Boiko 2017	GA 20 mg QD (Copaxone, Teva)[a]	61	NR	NR	NR	Median = 3.0 (range: 1.0-21.0) (MS symptoms)	1.28 (95% CI, 1.12-1.44)
	GA 20 mg QD (Timexon, Biocad)[a]	61	NR	NR	NR	Median = 5.0 (range: 0.0-37.0) (MS symptoms)	1.28 (95% CI, 1.15-1.40)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
	Placebo	28	NR	NR	NR	Median = 4.0 (range: 2.0-18.0) (MS symptoms)	1.21 (95% CI, 1.05-1.38)
Bornstein 1987	GA 20 mg QD	25	11 (44) 14 (56)	30 (NR)	NR	4.9 (NR) (unclear)	2 years: 3.8 (unclear average)
	Placebo	25	10 (40) 15 (60)	31 (NR)	NR	6.1 (NR) (unclear)	2 years: 3.9 (unclear average)
BRAVO	IFNβ-1a 30 mcg QW	447	140 (31.3) 307 (68.7)	Median (IQR) = 38.5 (30.3-45.9)	Median (IQR) = 2.5 (1.5-3.5)	Median (IQR) = 1.4 (0.3-4.7) (MS diagnosis)	Median (IQR) = 1 (1-2)
	Laquinimod 0.6 mg QD	434	152 (35) 282 (65)	Median (IQR) = 36.7 (29.6-44)	Median (IQR) = 2.5 (1.5-3.5)	Median (IQR) = 1.2 (0.3-3.8) (MS diagnosis)	Median (IQR) = 1 (1-2)
	Placebo	450	129 (28.7) 321 (71.3)	Median (IQR) = 37.5 (30.3-45.4)	Median (IQR) = 2.5 (1.5-3.5)	Median (IQR) = 1.2 (0.3-4) (MS diagnosis)	Median (IQR) = 1 (1-2)
Calabrese 2012	GA 20 mg QD	48	13 (27.1) 35 (72.9)	38.9 (10.2)	Mean (range) = 2.1 (1-5)	Mean (range) = 5.5 (0-9) (unclear)	NR
	IFNβ-1a 30 mcg QW	47	15 (32) 32 (68)	34.8 (9.6)	Mean (range) = 1.9 (1-5)	Mean (range) = 5.3 (0-8) (unclear)	NR
	IFNβ-1a 44 mcg TIW	46	14 (30.5) 32 (69.5)	35.9 (9.1)	Mean (range) = 1.9 (1-5)	Mean (range) = 5.7 (0-9) (unclear)	NR
CAMMS223	Alemtuzumab 12 mg QD	112	39 (35.5) 71 (64.5)	31.9 (8) Median (range) = 31 (18-49)	2 (0.73) median (range) = 2 (0-3)	NR	NR
	Alemtuzumab 24 mg QD	110	40 (35.7) 72 (64.3)	32.2 (8.8) Median (range) = 31 (18-54)	2 (0.73) Median (range) = 2 (0-3.5)	NR	NR

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
	IFNβ-1a 44 mcg TIW	111	40 (36) 71 (64)	32.8 (8.8) Median (range) = 31 (18-60)	1.9 (0.81) Median (range) = 2 (0-3.5)	NR	NR
CARE MS I	Alemtuzumab 12 mg QD	376	132 (35) 243 (65)	33 (8)	2 (0.8) Median (range) = 2 (0-4)	2.1 (1.4) Median (range) = 1.7 (0.1-5.2) (first MS symptoms)	1.8 (0.8) Median (range) = 2 (0-5)
	IFNβ-1a 44 mcg TIW	187	65 (35) 122 (65)	33.2 (8.5)	2 (0.8) Median (range) = 2 (0-3.5)	2 (1.3) Median (range) = 1.5 (0.2-5) (first MS symptoms)	1.8 (0.8) Median (range) = 2 (0-5) 2 years: Mean (SD) = 2.4 (0.85)
CARE MS II	Alemtuzumab 12 mg QD	426	145 (34) 281 (66)	34.8 (8.36)	2.7 (1.26) Median (range) = 2.5 (0-6.5)	4.5 (2.68) Median (range) = 3.8 (0.2-14.4) (first MS symptoms)	1.7 (0.86) Median (range) = 1 (0-5)
	Alemtuzumab 24 mg QD	170	49 (29) 120 (71)	35.1 (8.4)	2.7 (1.17) Median (range) = 2.5 (0-6)	4.3 (2.77) Median (range) = 3.7 (0.2-16.9) (first MS symptoms)	1.6 (0.86) Median (range) = 1 (0-6)
	IFNβ-1a 44 mcg TIW	202	71 (35) 131 (65)	35.8 (8.77)	2.7 (1.21) Median (range) = 2.5 (0-6)	4.7 (2.86) Median (range) = 4.1 (0.4-10.1) (first MS symptoms)	1.5 (0.75) Median (range) = 1 (0-4)
CombiRx	IFNβ-1a 30 mcg QW	250	77 (30.8) 173 (69.2)	37.6 (10.2)	2.0 (1.2)	1.4 (4.0) (first MS symptoms)	1.7 (0.9)
	GA 20 mg QD	259	74 (28.6) 185 (71.4)	39 (9.5)	1.9 (1.2)	1 (2.9) (first MS symptoms)	1.6 (0.7)
CONFIRM	DMF 240 mg BID	359	114 (32) 245 (68)	37.8 (9.4)	2.56 (1.2)	4.9 (5.1) (MS diagnosis)	1.3 (0.6)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
	DMF 240 mg TID	345	95 (28) 250 (72)	37.8 (9.4)	2.52 (1.19)	4.6 (5.2) (MS diagnosis)	1.4 (0.7)
	GA 20 mg QD	350	103 (29) 247 (71)	36.7 (9.1)	2.57 (1.22)	4.4 (4.7) (MS diagnosis)	1.4 (0.6)
	Placebo	363	112 (31) 251 (69)	36.9 (9.2)	2.59 (1.17)	4.8 (5) (MS diagnosis)	1.4 (0.8)
Copolymer I Study	GA 20 mg QD	125	37 (29.6) 88 (70.4)	34.6 (6)	2.8 (1.2)	7.3 (4.9) (unclear)	2 years: mean (SD) = 2.9 (1.3)
	Placebo	126	30 (23.8) 96 (76.2)	34.3 (6.5)	2.4 (1.3)	6.6 (5.1) (unclear)	2 years: mean (SD) = 2.9 (1.1)
DEFINE	DMF 240 mg BID	410	114 (28) 296 (72)	38.1 (9.1)	2.4 (1.29)	5.6 (5.4) (MS diagnosis)	1.3 (0.7)
	DMF 240 mg TID	416	110 (26) 306 (74)	38.8 (8.8)	2.36 (1.19)	5.1 (5.3) (MS diagnosis)	1.3 (0.6)
	Placebo	408	102 (25) 306 (75)	38.5 (9.1)	2.48 (1.24)	5.8 (5.8) (MS diagnosis)	1.3 (0.7)
Etemadifar 2006	IFNβ-1a 30 mcg QW	30	6 (20) 24 (80)	28.1 (1.2)	1.9 (1.1)	2.9 (2.3) (unclear)	2 (0.8)
	IFNβ-1a 44 mcg TIW	30	7 (23) 23 (77)	27.4 (1.2)	2.1 (1)	3 (2.2) (unclear)	2.4 (1)
	IFNβ-1b 250 mcg QAD	30	9 (30) 21 (70)	29.9 (1.4)	1.9 (0.7)	3.7 (2.3) (unclear)	2.2 (0.7)
EVIDENCE	IFNβ-1a 30 mcg QW	338	86 (25.4) 252 (74.6)	Mean (range) = 37.4 (18-55)	2.3 (NR) Median (range) = 2 (NR)	6.7 (NR) Median (range) = 4.1 (NR) (unclear)	2 years: mean (SD) = 2.6 (NR) 2 years: Median (range) = 2 (NR)
	IFNβ-1a 44 mcg TIW	339	85 (25.1) 254 (74.9)	Mean (range) = 38.3 (18-55)	2.3 (NR) Median (range) = 2 (NR-NR)	6.5 (NR) Median (range) = 4 (NR-NR) (unclear)	2 years: mean (SD) = 2.6 (NR) 2 years: median (range) = 2 (NR)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
GALA	GA 40 mg	943	302 (32) 641 (68)	37.4 (9.4)	2.8 (1.2)	7.7 (6.7) (1st MS symptoms)	1.3 (0.6)
	Placebo	461	148 (32.1) 313 (67.9)	38.1 (9.2)	2.7 (1.2)	7.6 (6.4) (first MS symptoms)	1.3 (0.6)
IFNB MS study	IFNβ-1b 50 mcg QAD	125	40 (32) 85 (68)	Mean (SE) = 35.3 (0.7)	Mean (SE) = 2.9 (0.1)	Mean (SE) = 4.7 (0.4) (MS diagnosis)	2 years: mean (SE) = 3.3 (0.1)
	IFNβ-1b 250 mcg QAD	124	38 (30.6) 86 (69.4)	Mean (SE) = 35.2 (0.6)	Mean (SE) = 3 (0.1)	Mean (SE) = 4.7 (0.4) (MS diagnosis)	2 years: mean (SE) = 3.4 (0.2)
	Placebo	123	35 (28.5) 88 (71.5)	Mean (SE) = 36 (0.6)	Mean (SE) = 2.8 (0.1)	Mean (SE) = 3.9 (0.3) (MS diagnosis)	2 years: mean (SE) = 3.6 (0.1)
INCOMIN	IFNβ-1a 30 mcg QW	92	35 (38) 57 (62)	34.9 (7.9)	1.96 (0.7)	6.7 (5.4) (unclear)	NR
	IFNβ-1b 250 mcg QAD	96	30 (31) 66 (69)	38.8 (7.1)	1.97 (0.7)	5.9 (4.2) (unclear)	NR
MSCRG	IFNβ-1a 30 mcg QW	158	40 (25) 118 (75)	36.7 (7.16)	2.4 (0.75)	6.6 (NR) (MS diagnosis)	1.2 (0.63)
	Placebo	143	40 (28) 103 (72)	36.9 (7.65)	2.3 (0.84)	6.4 (NR) (MS diagnosis)	1.2 (0.6)
OPERA I	Ocrelizumab, 600 mg, Q24W	410	140 (34.1) 270 (65.9)	37.1 (9.3)	2.86 (1.24)	6.74 (6.37) (first MS symptoms)	1.31 (0.65)
	IFNβ-1a, 44 mcg, TIW	411	139 (33.8) 272 (66.2)	36.9 (9.3)	2.75 (1.29)	6.25 (5.98) (first MS symptoms)	1.33 (0.64)
OPERA II	Ocrelizumab, 600 mg, Q24W	417	146 (35.0) 271 (65.0)	37.2 (9.1)	2.78 (1.30)	6.72 (6.10) (first MS symptoms)	1.32 (0.69)
	IFNβ-1a, 44 mcg, TIW	418	138 (33.0) 280 (67.0)	37.4 (9.0)	2.84 (1.38)	6.68 (6.13) (first S symptoms)	1.34 (0.73)
PRISMS	IFNβ-1a 22 mcg TIW	189	62 (33) 127 (67)	Median (IQR) = 34.8 (29.3-39.8)	2.5 (1.2)	Median (IQR) = 5.4 (3-11.2) (unclear)	2 years: mean (SD) = 3 (1.1)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
	IFNβ-1a 44 mcg TIW	184	63 (34) 121 (66)	Median (IQR) = 35.6 (28.4-41)	2.5 (1.3)	Median (IQR) = 6.4 (2.9-10.3) (unclear)	2 years: mean (SD) = 3 (1.1)
	Placebo	187	47 (25) 140 (75)	Median (IQR) = 34.6 (28.8-40.4)	2.4 (1.2)	Median (IQR) = 4.3 (2.4-8.4) (unclear)	2 years: mean (SD) = 3 (1.3)
REGARD	GA 20 mg QD	378	106 (28) 272 (72)	36.8 (9.5)	2.33 (1.31) Median (range) = 2 (NR)	NR	NR
	IFNβ-1a 44 mcg TIW	386	119 (31) 267 (69)	36.7 (9.8)	2.35 (1.28) Median (range) = 2 (NR)	NR	NR
TEMSO	Teriflunomide 14 mg QD	359	104 (29) 255 (71)	37.8 (8.2)	2.67 (1.24)	8.7 (6.7) Median (range) = 7.2 (NR) (first MS symptoms)	1.3 (0.7) 2 years: median (range) = 2 (NR)
	Teriflunomide 7 mg QD	366	111 (30.3) 255 (69.7)	37.4 (9)	2.68 (1.34)	8.8 (6.8) Median (range) = 7 (NR) (first MS symptoms)	1.4 (0.7) 2 years: median (range) = 2 (NR)
	Placebo	363	88 (24.2) 275 (75.8)	38.4 (9)	2.68 (1.34)	8.6 (7.1) Median (range) = 6.3 (NR) (first MS symptoms)	1.4 (0.7) 2 years: median (range) = 2 (NR)
TENERE	Teriflunomide 14 mg QD	111	33 (29.7) 78 (70.3)	36.8 (10.3)	2.3 (1.4)	6.6 (7.6) (first MS symptoms)	1.4 (0.8)
	Teriflunomide 7 mg QD	109	39 (35.8) 70 (64.2)	35.2 (9.2)	2 (1.2)	7 (6.9) (first MS symptoms)	1.3 (0.8)
	IFNβ-1a 44 mcg TIW	104	33 (31.7) 71 (68.3)	37 (10.6)	2 (1.2)	7.7 (7.6) (first MS symptoms)	1.2 (1.0)

Study ID	Treatment	Total N	No. males (%) No. females (%)	Mean age in years (SD)	Mean EDSS score (SD)	Mean duration of disease in years (SD)	Mean no. relapses in previous year (SD)
TOWER	Teriflunomide 14 mg QD	372	114 (31) 258 (69)	38.2 (9.4)	2.71 (1.35)	8.18 (6.73) (first MS symptoms)	1.4 (0.7)
	Teriflunomide 7 mg QD	408	108 (26) 300 (74)	37.4 (9.4)	2.71 (1.39)	8.18 (6.75) (1st MS symptoms)	1.4 (0.7)
	Placebo	389	116 (30) 273 (70)	38.1 (9.1)	2.69 (1.36)	7.64 (6.7) (first MS symptoms)	1.4 (0.8)

Appendix E. ERG's individual parameter changes to the Company's base-case analysis.

Table E5. Summary of ERG changes made in the economic model in order to implement the ERG preferred base case

Description of ERG change to economic model	**Implementation of the change in the model**
Base-case model	
Mortality risk	Mortality worksheet, EDSS relative risk, Pokorski, 1997 interpolated
Caregivers utility decrement	Utilities worksheet, utility decrement for caregivers, Gani 2008
All-cause discontinuation risk	Treatment worksheet, Annual discontinuation risk select 'Parity Assumption (ID527)[4]' from the dropdown box
Annual relapse rates by EDSS (RRMS)	Natural History worksheet, Annual relapse rates by EDSS score, IDS527 Assessment
Annual relapse rates by EDSS (SPMS)	Natural History worksheet, Annual relapse rates by EDSS score, IDS527 Assessment
ERG's scenario analysis	
All-cause discontinuation	Treatment worksheet, Annual discontinuation risk select 'user inputs' from the dropdown box and insert in cells G18 to S18 the values weighted by person-time, then drag to cell G27 to S27
EDSS health state utility values	Utilities worksheet, Utility by EDSS score, select 'ID527[4] Assessment' from the dropdown box
Treatment waning	Treatment worksheet, Waning effect, select 'Assumption 100%' from the dropdown box
EDSS, expanded disability status scale; ERG, evidence review group; 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

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 23 August 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Transcription error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P15, first bullet point "Patients treated with pegIFNβ-1a every 2 weeks had fewer new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks than patients in the placebo group (0.256 [95% CI, 0.206, 0.318] versus 0.397 [95% CI, 0.328, 0.48] P=0.0007). The CS reported the adjusted lesion mean ratio as 0.33 (95% CI, 0.27,0.40; P < 0.0001) for pegIFNβ-1a every 2 weeks versus placebo. Lesions were significantly smaller for those patients taking pegIFNβ-1a compared to placebo (P <0.0001)"	"Patients treated with pegIFNβ-1a every 2 weeks had fewer new or newly enlarging hyperintense lesions on T2-weighted images at 48 weeks than patients in the placebo group (3.6 95% CI, 3.1, 4.2] versus 10.9 [95% CI, 9.6, 12. 5]). The CS reported the adjusted lesion mean ratio as 0.33 (95% CI, 0.27,0.40; P < 0.0001) for pegIFNβ-1a every 2 weeks versus placebo. Lesions were significantly smaller for those patients taking pegIFNβ-1a compared to placebo (P <0.0001)"	Transcription error for newly or enlarging T2 lesions at 48 weeks, data cited were for ARR at 48 weeks	The ERG agree this is a transcription error. We have amended the following text on page 15 *"(3.6 95% CI, 3.1, 4.2] versus 10.9 [95% CI, 9.6, 12. 5])."*

Issue 2 Transcription error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P18, second paragraph "Caregivers utility decrements were based on information obtained from Gani et al., (2008).[10]"	"Caregivers utility decrements were based on information obtained from Acaster et al., (2013).[113]"	Transcription error, Biogen used disutilities from Acaster in the base case; Gani et al 2008 was used in scenario analyses only. Note: reference to Acaster is currently number 113 – this may change when the error is corrected	The ERG agree this is a transcription error. We have amended the following text on page 18 *"Caregivers utility decrements were based on information obtained from Acaster et al., (2013).[113]"*

Issue 3 Wording revision

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P23 section 2.1.1.2 Epidemiology "In Document B, B.1.3.1.2, the CS references a significant amount of data from a website that does not cite any peer reviewed publications"	In Document B, B.1.3.1.2, the CS references a significant amount of data from the MS Trust website that does not cite any peer reviewed publications	Reference to "a website" is ambiguous, this website is for the MS Trust, a useful website widely used by patients suffering with MS. Later in the paragraph the MS Society is referenced so it is unclear why the MS Trust has not been named	The ERG consider this to be an appropriate amendment to the wording. We have changed the sentence on page 23 to *"from the MS Trust website"*

Issue 4 Wording Revision

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P25 section 2.1.1.5 Diagnostic criteria "The CS states the use of the McDonald criteria for diagnosis of RRMS and acknowledges the 2017 update.[19] However, the ERG note that the criteria provided in CS Document B, page 20 are for the 2005 McDonald criteria."	"The CS states the use of the McDonald criteria for diagnosis of RRMS and acknowledges the 2017 update which is provided in CS Document B, appendix L.[19] However, the ERG note that the criteria provided in CS Document B, page 20 are for the 2005 McDonald criteria, as these criteria were used for the pivotal trial for PegIFNβ-1a."	As stated in CS Document B, page 20 the 2005 criteria were provided as these reflect the criteria used in the pivotal trial for PegIFNβ-1a, the current wording is therefore ambiguous. The 2017 criteria were also provided in appendix L p 430.	The ERG do not consider this to be a factual error. No change has been made.

Issue 5 Confidential mark-up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P44 section 4.2.1. Figure 1 is currently marked AIC	Remove confidential mark-up	PRISMA flow diagram available in Kieseier et al 2015 publication (CS Document C ref number 115)	The ERG note that this confidential marking was used in the CS Document C Figure 2. However, the ERG consider it reasonable to remove the marking on page 44 as it has been published in Kieseier et al., 2015.

Issue 6 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 51 table 6 For: - Disability progression: Multiple Sclerosis Functional Composite - Visual function: Visual Function Test - Cognitive changes (Symbol Digit Modalities Test, SDMT) - Paced Audio Serial Addition Test 3 (PASAT 3) "Additional. The CS does not report results for this outcome. It is mentioned in a single sentence in Appendix L, with no associated numeric results data."	Suggest this wording is revised as numeric data were provided in addition to the text (see justification for location). Text preceding table 6 (e.g. "The CS does not provide data for three outcomes: • progression of disability as measured by MSFC • visual function measured by the VFT • cognitive changes measured by the SDMT. All of which did not show a positive effect at 1 year compared to placebo. These three outcome measures are not mentioned in the CS document B, and are referred to in a single sentence in Appendix L, without associated numeric data. These outcomes are reported in the CSR (pg.77,80,82)." Should be removed/ revised accordingly. Further the text proceeding table 6 (e.g. "but it is unclear why they have not reported data for all outcomes included in the CSR ", and references to PASAT from the CSR) should be removed/ revised accordingly	Data incorrectly stated as not provided were available in Document C, p432 Appendix L, table 106	The ERG agree with these changes. Page 49 has been amended to "*The CS provides data for progression of disability as measured by MSFC, visual function measured by the VFT and cognitive changes measured by the SDMT in Document C Table 106 page 430."* Table 6 on page 51 has been amended as suggested.

Issue 7 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 62 section 4.2.11 It is unclear to the ERG as to how reliable the estimates presented in ATTAIN are, for example the ARR by the end of year 5 in ATTAIN is based on only pegIFNβ-1a Q2W, which represents 185 subjects from the original 547 starting ATTAIN (33.8%) (and pegIFNβ-1a Q4W 170 subjects of the original 529 starting ATTAIN [32.1%]) (CS Document C, pg.425).	"ATTAIN was considered complete when the last person completed 96 weeks, meaning that all patients had the opportunity to complete Year 4 (ADVANCE/ATTAIN combined), but only those patients who had enrolled in ATTAIN earlier on had the opportunity to complete Year 5 or longer. It is unclear to the ERG as to how reliable the estimates presented in ATTAIN are, for example the ARR by the end of year 5 in ATTAIN is based on only pegIFNβ-1a Q2W, which represents 185 subjects from the original 547 starting ATTAIN (33.8%) (and pegIFNβ-1a Q4W 170 subjects of the original 529 starting ATTAIN [32.1%]) (CS Document C, pg.425), however it should be noted these results appear consistent with year 4 for which represent 337 subjects from the starting 547 (61.6%)."	Biogen believe this statement is ambiguous. Patients were only required to complete Year 4 (ADVANCE/ATTAIN) to be considered 'completers', A total of 61.6% (n = 337; Figure 3 Doc B, P50) of patients completed year 4. The ARR at Year 5 was only based on 33.8% of patients (n = 185 patients), however this does not mean the remaining 66.2% had stopped treatment due to lack of an adverse event or lack of efficacy. The year 5 estimates demonstrated a statistically significant reduction in ARR vs. pegIFNβ-1a Q4W, aligned with the year 4 results.	The ERG do not consider this to be a factual error. No change made. Note: From Newsome 2018: p2, right hand column, top paragraph: "The study was considered complete when the last patient completed 96 weeks in the ATTAIN study." i.e. 2 years in ATTAIN, end of Year 4 altogether. From Newsome 2018: p3: Results; 1st para: "Of the 1332 patients who completed ADVANCE, 1076 (81%) were dosed in ATTAIN, and 842 patients (78% of those dosed in ATTAIN; 56% of the original ADVANCE study population) completed the ATTAIN study." So even of those completing the 96 weeks of the ATTAIN study (Year 4 compared with those starting Year 3) have still lost >20% of the sample and representing only just over half the original

			ADVANCE population. So although the year 5 results appear consistent with year 4, year 4 have lost lots of participants compared with year 3 and year 1

Issue 8 Transcription error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 66 table 10 For Discontinuations of treatment due to AE in the PegIFNß-1a Q2W group (ADVANCE year 2) is 41 (16%)	Figure within table should be amended to: For Discontinuations of treatment due to AE in the PegIFNß-1a Q2W group (ADVANCE year 2) is 41 (6%)	Transcription error – see Table 19, Doc B	The ERG agree with this transcription error. The text on page 66 has been amended to "*6%"*

Issue 9 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P77 section 4.3.1.7 last paragraph "Based on visual inspection of network plots for ARR, CDP3, and CDP6, the ERG…"	Based on visual inspection of network plots for ARR, CDP3M, and CDP6M, the ERG…	Typographical error Confirmed disability progression at 3 months abbreviated to CDP3M throughout document Confirmed disability progression at 6 months abbreviated to CDP6M throughout document	The ERG agree with this transcription error. The text has been amended on page 77 *"CDP3M, and CDP6M"*

Issue 10 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 80, "For completeness and to allow for external comparison with results that were used for decision making by NICE recently, the ERG have reported the main results from the MTC undertaken as part of the MTA (reported in Melendez-Torres et al 20176) for ARR, CDP3, and CDP6 within beta-interferons and GA (see Table 14) (see Section 6.2.3) "	"For completeness and to allow for external comparison with results that were used for decision making by NICE recently, the ERG have reported the main results from the MTC undertaken as part of the MTA (reported in Melendez-Torres et al 20176) for ARR, CDP3, and CDP6 within beta-interferons and GA (see Table 14) (see Section 6.2.3). It should be noted these results are not directly comparable as the comparators in the decision problem are different which leads to a differential number of studies informing the networks and comparative effectiveness e.g. for IFNbeta 1a 44, the CS includes additional studies including OPERA I & II, CARE MS-I & II."	Although Biogen agree that the comparison of the two MTC's seems reasonable, additional context is required. The MTC conducted by Biogen has additional comparators and additional studies, resulting in bigger network, e.g. studies such as OPERA I and OPERA II, CARE MS I and CARE MS-II.	The ERG do not consider this to be a factual error. No change made.

Issue 11 Transcription error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 81, Table 14: CDP3 and CDP6 headings CDP6 for IFN beta-1a 30, CS Doc B is [redacted] ARR for GA 20mg, MTA Table 8 is 0.65 (0.59 – 0.72)	CDP3M and CDP6M [redacted] [redacted]	CDP3M and CDP6M headings – abbreviations inline with rest of document. CDP6 for IFN beta-1a 30, CS Doc B should be [redacted] ARR for GA 20mg, MTA Table 8 should be 0.66 (0.54 – 0.80) as per	The ERG agree that table 10 headings should be changed to "*CDP3M and CDP6M*" and the IFN beta-1a 30 should be changed to [redacted] The ERG have not changed ARR for GA 20mg, MTA Table

		the committee papers	8, as this is the figure stated in Table 8 of the HTA (as per the reference, Melendez-Torres et al 2017[6])

Issue 12 Wording revision

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 82 section 4.3.1.9 NEDA The CS Document C (pg.451) states that "pegIFN beta-1a increased NEDA compared to GA 40 mg tiw, and this difference was statistically significant." Later, in Table 113 (CS Document C) a HR for pegIFN beta-1a 125 mcg q2w of 1.703 (95% CI 1.100,2.635) versus GA 40 mg tiw is reported. This suggests that treatment favours pegIFN beta-1a. However, the Biogen Plegridy Full Report document (pg.121) states that "For NEDA, an indirect comparison of pegIFN beta-1a and GA 40 mg tiw (via placebo) showed a statistically significant difference between these treatments (in favour of GA 40 mg tiw)." It is therefore unclear the direction of benefit between the two drugs	The CS Document C (pg.451) states that "pegIFN beta-1a increased NEDA compared to GA 40 mg tiw, and this difference was statistically significant." Later, in Table 113 (CS Document C) a HR for pegIFN beta-1a 125 mcg q2w of 1.703 (95% CI 1.100,2.635) versus GA 40 mg tiw is reported. This suggests that treatment favours pegIFN beta-1a.	Biogen would like to clarify the results are in favour of pegIFN beta-1a	The ERG do not consider this to be a factual error. No change made. The information provided in the Biogen Plegridy Full Report document (pg.121) has been checked and is correct.

Issue 13 Wording revision / Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 82 section 4.3.1.9 NEDA	Biogen propose this statement is removed.	Reference no. 71 (Rieckmann et al 2013 poster) indicates what is being	The ERG do not consider this to be a factual error. No

The GALA study does not refer to NEDA, nor does the Biogen Report indicate what is being referred to as NEDA so the ERG is not able to identify whether the report or the appendices are correct		referred to as NEDA. Although the term “NEDA” is not mentioned within Rieckmann et al 2013. (Reference number 71), the poster summarises definitions of NEDA: - disease free (no relapses, no EDSS progression, no gadolinium or T2 lesions at months 6 or 12) - clinical disease free (no relapses, no EDSS progression), MRI disease free (no gadolinium, no T2 lesions at months 6 and 12), and - disease activity free (no relapses, no Gadolinium or T2 lesions at months 6 or 12)	change made.

Issue 14 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 89 The ERG note that with so many characteristics not reported, and the differences between the studies even when they were reported, it is difficult to assess heterogeneity of patient characteristics. The ERG agrees that the clinical similarity of study populations was often unclear.	The ERG note that many trials did not report characteristics (however these were often limited to the smaller studies, reported only in abstract publications) and the differences between the studies even when they were reported, it is difficult to assess heterogeneity of patient characteristics. The ERG agrees that the clinical similarity of study populations was often unclear.”	Whilst we agree – the studies referred to are smaller and often only report in abstract – therefore we expect these to have a low relative contribution to any analysis	The ERG do not consider this to be a factual error. No change made.

Issue 15 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 95 "Transitivity of the MTCs included in the CS is unclear. The ERG note systematic differences between the comparisons being made other than the treatments that are being compared."	"Transitivity of the MTCs included in the CS is unclear. The ERG note systematic differences between the comparisons being made other than the treatments that are being compared. However, it should be noted that transitivity has not been cited in any prior NICE appraisal, many of which include the same studies and networks (e.g. TA312, TA5527, TA533)"	Biogen searched for the term "Transitivity" in all prior NICE MS appraisals and found no hits, many of these appraisals compare the same studies in similar networks. Where possible statistical heterogeneity was explored through the presentation of direct meta-analyses (the I^2 was either 0 or low [38%]).	The ERG do not consider this to be a factual error. No change made.

Issue 16 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 95 last bullet point There was a lack of rationale for why some study arms were included in the MTC but not others. For example, the BEYOND54 trial includes 3 arms: GA 20 mg QD, IFNβ-1b 250 mcg QAD, and IFNβ-1b 500 mcg QAD . Only GA 20 mg QD and IFNβ-1b 250 mcg QAD were included in the MTC of ARR. There might have been good explanations for this, but it was not made explicit in the CS	Suggest this bullet point is deleted	Document C, appendix D2.3 p34 states "Only treatments using the included interventions at EU licensed doses were included in the final networks." Hence why IFNβ-1b 500 mcg QAD is not included in the networks. A table of licensed doses were provided in appendix D1.2, table 23 Biogen acknowledge this could have been more explicit in Document B, however in	The ERG have made the suggested amendment to page 95. The ERG note that this sentence "*Biogen acknowledge this could have been more explicit in Document B, however in*" is not complete so not action was taken.

Issue 17 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 96 first bullet point Multi-arm studies were sometimes included in the MTC (e.g. Calabrese 201258 in the ARR MTC) with no explanation of how (or if) correlations between the outcomes were accounted for in the models	Multi-arm studies were sometimes included in the MTC (e.g. Calabrese 201258 in the ARR MTC) with only brief explanation correlation between the outcomes, however the ERG note the MTC code provide evidence that correlation was indeed accounted for.	Correlation is briefly described in Document C section D2.8. For clarify, correlation was accounted for using standard methods in NICE TSD 2, We acknowledge this should have been described in more detail. Additionally, the MTC code provided was based on the example code given in the appendix of NICE TSD 2	The ERG has made the following amendment to the text on page 96 "*Multi-arm studies were sometimes included in the MTC (e.g. Calabrese 201258 in the ARR MTC) with a brief explanation of how correlations between the outcomes were accounted for in the models provided in CS Document C section D2.8*"

Issue 18 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 96 second bullet point There were few eligible studies. Some of the assessment of whether an MTC is appropriate is reliant upon multiple trials for each comparison. First, prior to conducting an MTC, pairwise meta-analyses of all interventions that have been directly compared should be carried to examine statistical heterogeneity. Confidence in the MTC will be low in the presence of high	There were few eligible studies. Some of the assessment of whether an MTC is appropriate is reliant upon multiple trials for each comparison in order to assess statistical heterogeneity. First, prior to conducting an MTC, pairwise meta-analyses of all interventions that have been directly compared should be carried to examine statistical heterogeneity. Confidence in the MTC will be low in the presence of high heterogeneity.	Having 2 or more studies for each treatment comparison is not a prerequisite for conducting a network meta-analysis, they can still be conducted if there are only single studies for each comparison, but this removes the possibility of assessing statistical heterogeneity. There is more than 1 direct comparison in the ARR network – see Document B figure 14 (p78) Pairwise meta-analyses are	The ERG have amended the text on page 96 to add the following text "*2 direct comparisons with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo, 2 studies comparing GA 20mg versus IFN beta 1-a 30 mcg),"*

heterogeneity. In the CS, the MTC for ARR included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo), the MTC for CDP3M included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo), and the MTC for CDP6M included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo). No other comparisons could be assessed for heterogeneity.	In the CS, the MTC for ARR included 2 direct comparisons with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo, 2 studies comparing GA 20mg versus IFN beta 1-a 30 mcg), the MTC for CDP3M included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo), and the MTC for CDP6M included only 1 direct comparison with more than 1 study (2 studies comparing dimethyl fumarate 240 mg bid versus placebo). No other comparisons could be assessed for heterogeneity.	available in the Biogen Plegridy Full Report Appendices document for dimethyl fumarate 240 mg bid versus placebo ARR (Figure 26 in Appendix) – I^2=0% ARR (Figure 28 in Appendix) – I^2=0% ARR (Figure 30 in Appendix) – I^2=0% Furthermore, IFN beta-1a 30 mcg qw versus GA and placebo, respectively: ARR (Figure 32 in Appendix) – I^2=38% ARR (Figure 33 in Appendix) – I^2=0% These I^2 statistics would suggest no or low evidence of heterogeneity.	

Issue 19 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 99 section 5.1.1.1 The health outcome reported were EDSS changes, relapses, SPMS, reasons for discontinuation, YR and QALYs	The health outcome reported were EDSS changes, relapses, SPMS, reasons for discontinuation, LY and QALYs	Typographical error for life years	The ERG agree with this typographical error. “YR” has been amended to “LY” on page 99

Issue 20 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
100 & 101 section 5.2.1, section 5.2.1 Searches were limited to records published after 1 February 2018, in English The current systematic review updated this previous search from February 2018-November 2018	Should be: Searches were limited to records published after 1 February 2016, in English The current systematic review updated this previous search from February 2016 - November 2018	Factual inaccuracy in the dates for the searches	The ERG agree this is incorrect. We have amended page 100 and 101 as requested. "*1 February 2016"* and "*February 2016 - November 2018"*

Issue 21 Wording revision / clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
101 section 5.2.1 After clarification, it was confirmed that Econlit was used in preference to EconLit with Full Text as the company claims that the latter is restricted to full text only, which is not the case	Biogen suggest this sentence is removed.	The EconLit website states: "EconLit with Full Text is the full-text counterpart to EconLit, the American Economic Association's authoritative index for economic literature. In addition to all of the indexing available in EconLit, this database provides full text for key economic journals and books." Our understanding of the definition on their website is that EconLit and EconLit with Full Text both provide the same sources/indexing; however, EconLit with Full Text provides not only the indexing but	The ERG agree with the second paragraph in the justification column but note that this is not what the stated in response to clarification question B1. Therefore, the ERG's original statement is correct. However, we consider this to be a genuine misunderstanding therefore, we will remove this sentence as requested on page 101

		also the full text of the sources indexed.	

Issue 22 Wording revision / factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 108 section 5.3.4 The ERG also agree that it was appropriate to exclude DMTs that are used for treating people with highly active RRMS and RES-RRMS, as pegIFNβ-1a does not have marketing authorisation for these populations	"The ERG also agree that it was appropriate to exclude DMTs that are used for treating people with highly active RRMS and RES-RRMS, as pegIFNβ-1a is not used in clinical practice for these populations, in-line with the NHSE DMT algorithm."	The marketing authorisation supports the use in these population, however it is not used in clinical practice.	The ERG agree and have changed the text on page 108 to *"The ERG also agree that it was appropriate to exclude DMTs that are used for treating people with highly active RRMS and RES-RRMS, as pegIFNβ-1a is not used in clinical practice for these populations."*

Issue 23 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 108 Table 18 P 140 Table 41 P 147 Table 47 Dimethyl fumerate	Dimethyl fumarate	Typographical error	The ERG note the typographical error. We have corrected the spelling of dimethyl fumarate in these tables.

Issue 24 Suggestion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 110 – Table 19	Reduce font size or adjustment of columns	The values in the first column are rounded to 3 decimal places (EDSS 5-5.5 = 0.000) whereas it should be 0.0005	The ERG agree, thank you. We have adjusted the column width in Table 19 so that the hidden values can be seen.

Issue 25 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 123 – last paragraph & P 146 – Table 46 Though there may be some explanation for this, the ERG consider it more appropriate to use the disutilities from Gani et al.	"Though this could be partially explained as care requirements and intensity for when patients become wheelchair or bed bound (EDSS 7 and 9, respectively) the ERG consider it more appropriate to use the disutilities from Gani et al."	Carer disutility from Acaster et al. 2013 has been used in the base case for the last three appraisals; NICE TA 493 (cladribine), NICE TA 527 (Beta interferons), and NICE TA 533 (ocrelizumab). Biogen would request clarification as to why Gani et al. would be more appropriate. Carer requirements and intensity are vastly different at EDSS 5-6.5 when patients are increasingly disabled, whereas they could lower at higher EDSS scores when patients are wheelchair or bedbound. Thus, it would be possible to have a higher carer disutility in patients with an EDSS 5-6.5 compared to an EDSS 8.0.	The ERG does not consider this an inaccuracy. Here, the company elaborates/explains why the disutilities in less severe health states may be higher than those in more severe health states. No change required.

Issue 26 Transcription error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P 146 Table 46 Table 46: Caregivers utility decrements obtained from Ganie et al., (2008) EDSS 4-4.5 – Acaster value: -0.4050 EDSS 6-6.5 – Acaster value: -0.1620	P 146 Table 46: Caregivers utility decrements obtained from Gani et al., (2008) EDSS 4-4.5 – Acaster value: -0.0405 EDSS 6-6.5 – Acaster value: -0.1670	Typographical error in table title Transcription error in utility decrement values	The ERG agree these are transcription errors. We have amended the title to '*Caregivers utility decrements obtained from Gani et al., (2008)'* and disutility decrements *EDSS 4-4.5 – Acaster value: -0.0405 and EDSS 6-6.5 – Acaster value: -0.1670.*

NICE National Institute for Health and Care Excellence

Technical engagement response form

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

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

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments – end of **24 October 2019**

Thank you for your time.

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

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

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

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

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

About you

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

Questions for engagement

Issue 1: Use of peginterferon beta-1a in clinical practice	
Several options are available for treating relapsing-remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) at first line including interferon beta-1a, interferon beta-1b, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Are the patients who are likely to be treated with peginterferon beta-1a in the NHS the same as those who would have all these treatments, including the recently approved options, alemtuzumab and ocrelizumab?	As discussed at the NICE Technical engagement call, Biogen agree with the recommendations made by the clinical expert that patients should have the option to choose their disease modifying therapy (DMT) based on factors such as risk-benefit profile of the DMT, patient lifestyle (including pregnancy considerations), route and frequency of administration. Patients with relapsing remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) could present with either mild or more severe disease activity. Thus, treatment options would vary from patient to patient based on the factors mentioned above (risk-benefit profile, route & frequency of administration and patient lifestyle). The clinical expert on the technical engagement call mentioned that even though his recommendation for patients with more severe disease would be to consider escalation to higher efficacy DMTs, patients may still opt for a treatment option with a more tolerable and well-established safety profile such as an interferon. Biogen agree with the recommendations made by the clinical expert that that all treatments should be available as an option; the choice of treatment should be tailored to each patient's need after shared conversations between clinician and patient.
If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	Biogen believe peginterferon beta-1a should be considered in the same position as currently recommended within the NHS England DMT algorithm (1): • first-line treatment option for RRMS, and • alternative first-line treatment option for patients who are intolerant to their initial DMT. Biogen would like to highlight that there are >1,400 patients currently being treated with peginterferon beta-1a in-line with the NHS England DMT algorithm (2).

	We do not foresee any reason why the data from ADVANCE trial can't be extrapolated to first-line treatment for patients who are intolerant to their initial DMT. The technical engagement clinical expert recommended that peginterferon beta-1a would be considered for efficacy switch (e.g. from glatiramer acetate to interferon) as some patients prefer switching therapy between the lower efficacy DMTs, considering their established safety profile, before potentially initiating on a higher efficacy treatment. Biogen has a marketing authorisation for patients with RRMS (3), and thus would support its use in efficacy switch patients as described by the clinical expert.
Is alemtuzumab an appropriate comparator?	Alemtuzumab is currently being reviewed by the EMA safety committee (PRAC) following safety concerns and is currently restricted in adults with RRMS that is highly active despite treatment with at least two DMTs or where other DMTs cannot be used (4). Biogen has agreed to include alemtuzumab within the appraisal as a comparator (in-line with the scope) in the interim whilst a decision by the EMA is pending. In the event that alemtuzumab is no longer recommended as a first-line DMT, Biogen would suggest alemtuzumab is removed as a comparator. Biogen has already provided comparisons against all other comparators, including ocrelizumab, and thus no new analyses should be required in the event that alemtuzumab is removed as a comparator.
Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	Biogen were not able to identify any published literature that measures the minimum clinically significant reduction (MCID) of annualised relapse rate (ARR) or confirmed disability progression (CDP) in patients with multiple sclerosis. This must therefore be deferred to clinical expert opinion. It should also be acknowledged that Biogen is not aware that this question regarding the MCID of ARR or CDP has been raised in previous NICE multiple sclerosis appraisals.

Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	Biogen believe the patients in the ADVANCE trial do reflect the people who would be eligible for peginterferon beta-1a in NHS practice. Peginterferon beta-1a is currently being used in NHS practice and has been available since August 2015 (5). Unfortunately, Biogen could not provide a comparison of the geographical locations or ethnicity of patients included in the pivotal studies as this information is either not published or categorised differently within the comparator pivotal studies (e.g. rest of world).
If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	Based on the above, Biogen would argue that the baseline characteristics from the ADVANCE trial are reflective of the UK MS population and thus should be used in the economic model. Biogen demonstrated within our original submission that using the baseline characteristics from the UK MS Risk Sharing Scheme (RSS) in the economic model do not alter the cost-effectiveness results. **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS irrespective of whether the baseline characteristics from ADVANCE or the RSS are used in the economic model.**
Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	Biogen believe all the relevant data to model the clinical effectiveness has been included within the network meta-analysis in our submission. The ERG noted some inconsistencies in our submission with regards to the choice of studies used to derive the effectiveness for the comparators in the economic model. Biogen has provided a rationale for the inconsistency described below: • For interferon beta-1a, Biogen's submission excluded the PRISMS (1998) trial for the network for ARR. This was because the PRISMS study does not report the ARR within the publication (mean relapses per patient and proportion of relapse free reported).

	Biogen do not believe calculating the ARR based on the mean number of relapses per patient (as done so by Melendez-Torres et al - ID 527) is a justified assumption. As a result, this study was excluded from the ARR network. Nevertheless, we have conducted a further scenario analysis to include PRISMS into the NMA (Figure 1) showing minimal differences in the results (Table 1). **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS regardless of whether PRISMS study is included within the ARR network or not using Biogen's base case (Table 3) as well as the ERG's preferred assumptions (Table 4)** • For interferon beta-1a, Biogen's submission excluded the MSCGR (1996) trial from the network for CDP-6M. This was because the hazard ratio needed to include in this network was not reported in the publication or the CSR. The NICE MTA included this trial within the network as they included a hazard ratio using the method described in Tierney et al. (2007). Biogen avoided estimating the hazard ratio from the reported risk ratio as it would increase uncertainty and thus decided to exclude this study from the network. Nevertheless, we have conducted a further scenario analysis to include MSCGR into the NMA (Figure 2) showing minimal differences in the results (Table 2). **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS regardless of whether MSCGR study is included within the ARR network or not using Biogen's base case (Table 3) as well as the ERG's preferred assumptions (Table 4)** • A discrepancy between the number of studies used for the analyses of stopping treatment because of any reasons for the clinical section (3 trials), and in the economic models (18 trials) For the clinical section, the NMA restricted stopping treatment because of any reason to a 12-months follow-up which resulted in the reduction in number of trials within the network (3 trials). Most trials used a 22 to 24 months follow-up, however as we wanted to include the ADVANCE trial (pivotal trial for peginterferon beta-1a)

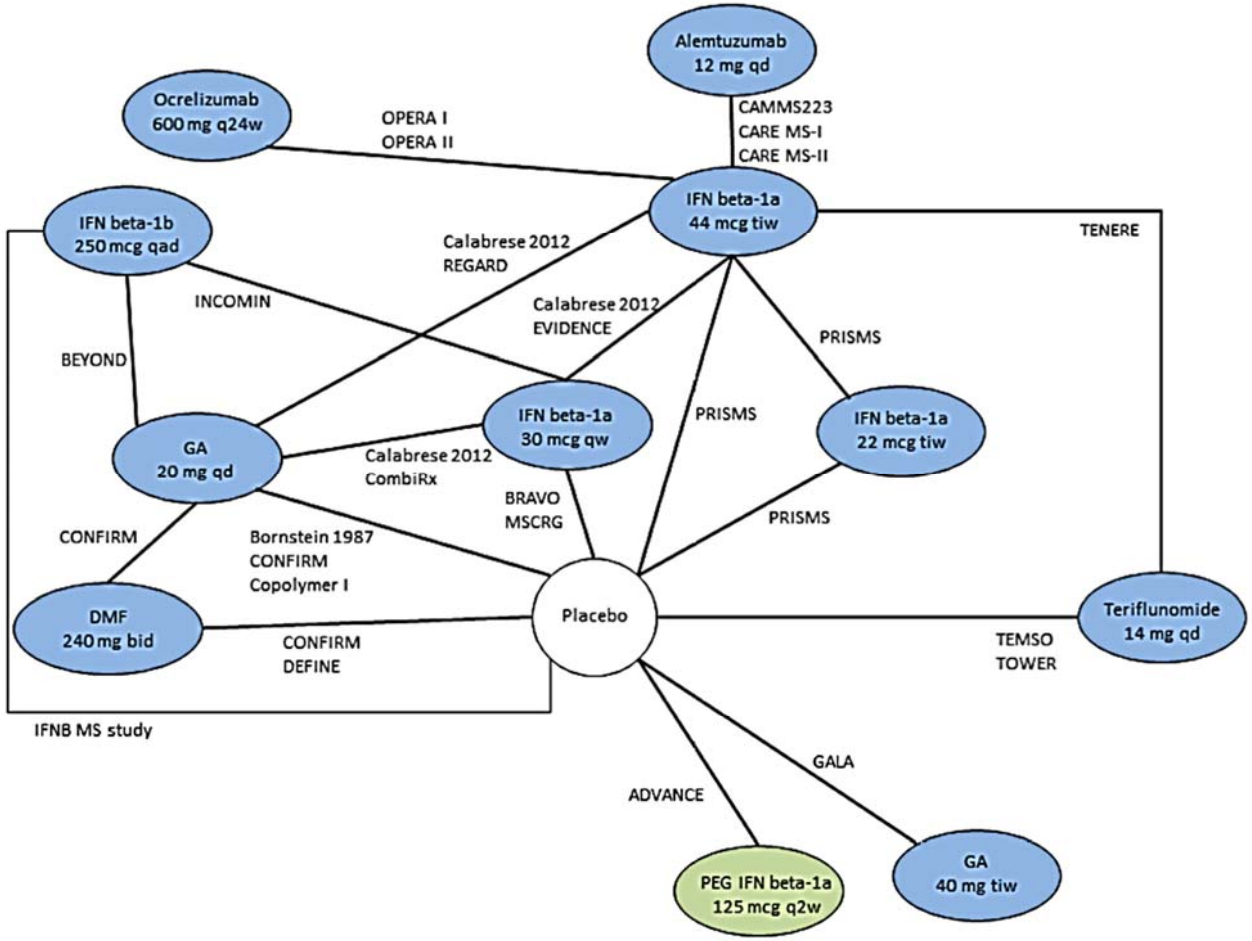
	into our analysis we focused on trials with a 12-month follow up. There was also significant variation in the definitions of stopping criteria between trials which would have increased uncertainty. The inputs used in the economic model were derived from the individual DMT's pivotal trials, and hence resulted in a larger number of studies (18 trials). This is consistent with the previous appraisals, and thus Biogen would not consider this issue as an inconsistency. **Biogen presented a suite of scenario analyses varying discontinuation rates within our original manufacturer submission demonstrating that peginterferon beta-1a remained a cost-effective options for the treatment of patients with RRMS.**
Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	There is a dearth of available literature in regard to treatment waning for DMTs, and current waning assumptions applied to the economic model are arbitrary. However for consistency with prior technology appraisals, we have applied the same step-change in hazard ratio for disability progression across all comparators. The development of neutralising antibodies (NAbs) against beta-interferons can reduce the efficacy of treatment, and has been a theory postulated in prior NICE appraisals to be directly linked to treatment waning. The incidence of NAbs with peginterferon beta-1a is <1%, considerably lower compared to its comparators such as interferon-beta 1a 30mcg (5-8%) (6), interferon beta-1a 44mcg (13-24%)(7), and interferon beta 1-b (23-41%)(8). Glatiramer acetate is not associated with Nabs (9). Thus, having the same waning effect for peginterferon beta-1a as the other interferons could be underestimating effect size. **Nevertheless, Biogen would like to iterate that peginterferon beta-1a remains to be a cost-effective treatment option when the same waning effects are used for peginterferon beta-1a and its comparators.**
Is it clinically plausible that the waning effects are the same for all treatments?	Different mechanisms of actions of the MS therapies would likely pertain to alternative waning effects – e.g. immune reconstitution therapies vs maintenance therapies.

	However, as Biogen believe that current evidence in this area is limited, Biogen would suggest that this questions is most appropriately answered by the clinical experts.
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies? b) all years, that is at the start of treatment and after many years on treatment?	There are significant differences between the DMTs with regards to safety and adverse event profile. As a result, Biogen's preference is to use discontinuation rates obtained from the pivotal trials of each DMT, as opposed to the same probability for each DMT. This has been reflected within our base case analysis. However, Biogen has also conducted a scenario analysis where the same probability has been applied to all DMTs (5% discontinuation rate), maintaining consistency with previous appraisals. **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS even when the same probability of stopping treatment is applied to the economic model.**
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	Biogen has already submitted three scenarios where the different stopping criteria is used in the economic model. 1. Discontinuation rates obtained from the pivotal trials of each DMT, weighted by sample size 2. Discontinuation rates obtained from the pivotal trials of each DMT, weighted by person time 3. Same probability of stopping rates for all DMTs (5% applied to all DMTs) **Across all analyses peginterferon beta-1a was demonstrated to be a cost-effective option for the treatment of patients with RRMS regardless of which stopping criteria is used.**
Issue 7: Utility values	

Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	Biogen has used utility data derived from Orme et al. (2007) in the economic model for its base case. This is consistent with the previous appraisals. Biogen has already submitted a scenario analysis using utility data using Thompson et al. (2017). Biogen would like to iterate that the Thompson et al. (2017) study used the same data as the Orme et al. (2007) study (obtained from the MS Survey in 2006). However, the Orme paper has a much larger sample size (n=2,048) across all MS types (RRMS, PPMS, SPMS) (10), whereas the Thompson paper is restricted to a much smaller sample size (n=779) (11). Therefore, Biogen believe utility data obtained from the Orme paper would be more plausible, and also maintains consistency with the previous appraisals. **Regardless of whether utility data is obtained using the Orme et al (2007) study or the Thompson et al. (2017) study, peg-interferon beta-1a remains a cost-effective option for patients with RRMS.**

ARR = annualised relapse rate; CDP = confirmed disability progression; CDP 6M = confirmed disability progression at 6-months; DMT = disease modifying therapy; EMA = European Medicines Agency; ERG = Evidence Review Group; MCID = minimum clinically significant decrease; MS = multiple sclerosis; RES = rapidly evolving severe MS; RRMS = relapsing remitting multiple sclerosis; RSS = risk sharing scheme; Nabs = neutralising antibodies.

Figure 1: Network for annualised relapse rate including PRISMS trial



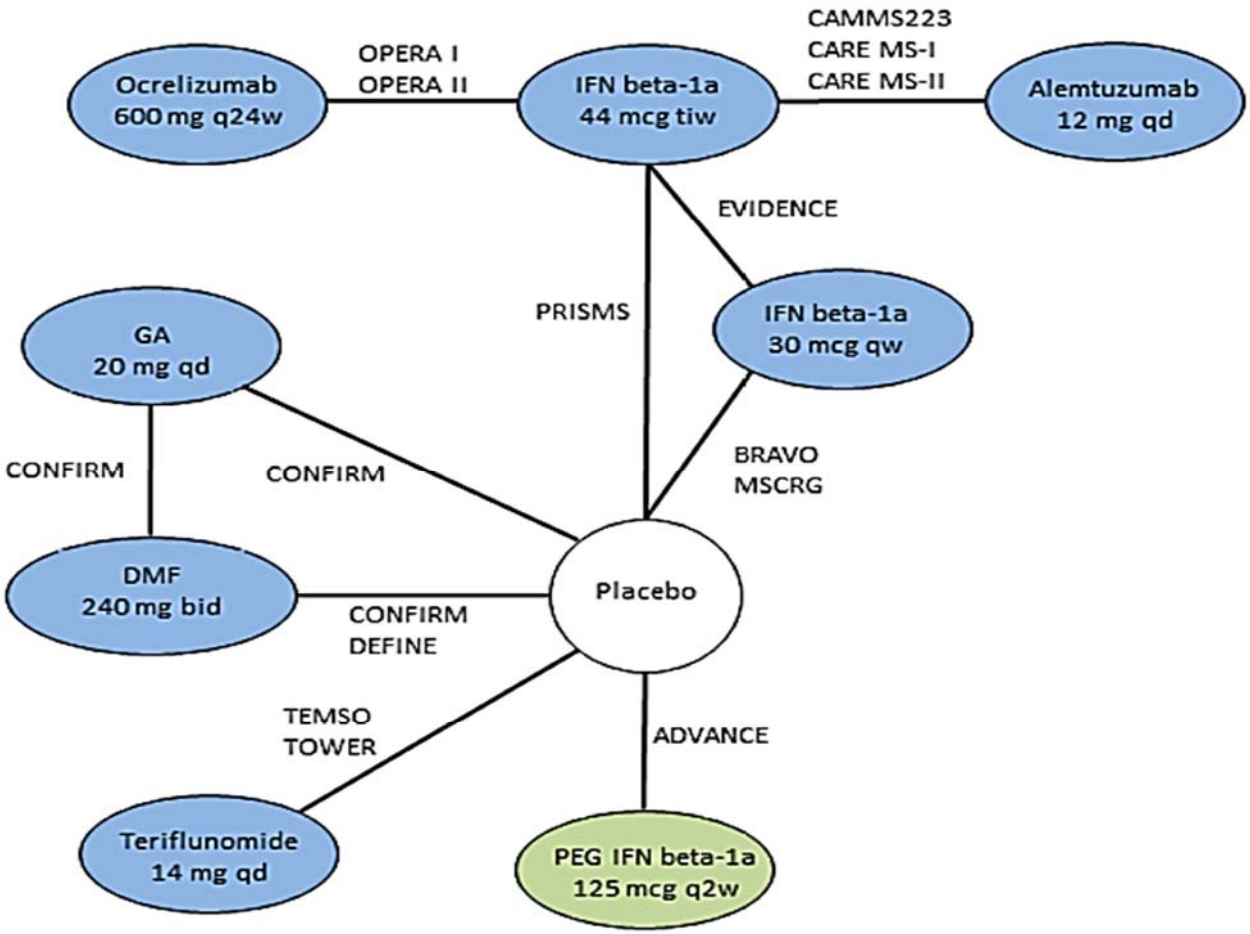
DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly.

Table 1: Rate ratio on ARR versus placebo including PRISMS study in the network

Treatment	Rate ratio for ARR from original submission	95% CI	Rate ratio for ARR including PRISMS	95% CI
PegIFNβ-1a	[redacted]	[redacted]	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]	[redacted]
GA 40	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 20	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 40	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

DMF = dimethyl fumarate; PEG IFN = pegylated interferon; GA = glatiramer acetate; genGA = generic glatiramer acetate; IFN = interferon

Figure 2: Network for confirmed disability progression at 6-months including MSCRG trial



bid = twice daily; DMF = dimethyl fumarate; PEG IFN = pegylated interferon; qad = every other day; q24w = once every 24 weeks; qd = once daily; tiw = 3 times a week.

Table 2: Hazard ratio on CDP at 6 months versus placebo including MSCRG study

Treatment	Hazard ratio for CDP-6M from original submission	95% CI	Hazard ration for CDP-6M including MSCRG	95% CI
PegIFNβ-1a	[redacted]	[redacted]	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]	[redacted]
GA 40	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 20	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 40	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

DMF = dimethyl fumarate; PEG IFN = pegylated interferon; GA = glatiramer acetate; genGA = generic glatiramer acetate; IFN = interferon

Table 3: Cost-effectiveness results using Biogen's base case of two additional scenario analyses using list prices.

Scenario	pegIFNβ-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	ocrelizumab	alemtuzumab
Base case - discounted												
QALY	4.39	0.75	0.74	0.75	0.74	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£273,641	-£11,423	-£14,035	-£8,701	-£11,033	-£19,328	NA	-£20,557	-£23,796	-£34,865	-£66,027	-£1,250
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
Scenario: Including PRISMS study for ARR												
QALY	4.394	0.75	0.74	0.75	0.74	0.17	N/A	0.47	0.60	0.45	-0.50	-1.08
Costs	£273,621	-£11,449	-£14,068	-£8,727	-£11,066	-£19,380	N/A	-£20,592	-£23,837	-£34,903	-£66,064	-£1,294
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
Scenario: Including MSCRG study for CDP-6M												
QALY	4.39	0.74	0.73	0.74	0.73	0.12	#N/A	0.26	0.59	0.44	-0.55	-1.13
Costs	£273,641	-£11,259	-£13,860	-£8,534	-£10,855	-£18,601	#N/A	-£17,369	-£23,747	-£34,771	-£65,629	-£424
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
Scenario: Including PRISMS study for ARR & MSCRG study for CDP-6M												
QALY	4.39	0.74	0.73	0.74	0.73	0.12	#N/A	0.26	0.60	0.44	-0.55	-1.13
Costs	£273,621	-£11,285	-£13,893	-£8,561	-£10,888	-£18,654	#N/A	-£17,404	-£23,788	-£34,809	-£65,667	-£468
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE

CDP-6M= confirmed disability progression at 6-months; DMF = dimethyl fumarate; DMT = disease-modifying therapy; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = , incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LCLE = less costly, less effective; MS = multiple sclerosis; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous

Table 4: Cost-effectiveness results using ERG preferred assumptions of two additional scenario analyses using list prices.

Scenario	pegIFNβ-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	ocrelizumab	alemtuzumab
ERG Base case - discounted												
QALY	5.41	1.24	1.25	1.24	1.25	0.50	N/A	0.95	0.91	0.65	-0.10	-0.22
Costs	£276,655	-£6,609	-£6,890	-£2,928	-£3,209	-£19,260	N/A	-£13,784	-£42,742	-£63,395	-£65,412	£5,727
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
Scenario: ERG base case including PRISMS study for ARR												
QALY	5.41	1.24	1.25	1.24	1.25	0.50	#N/A	0.95	0.91	0.65	-0.10	-0.22
Costs	£276,618	-£6,655	-£6,944	-£2,974	-£3,263	-£19,342	#N/A	-£13,839	-£42,821	-£63,468	-£65,469	£5,670
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
Scenario: ERG base case including MSCRG study for CDP-6M												
QALY	5.41	1.23	1.23	1.23	1.23	0.44	#N/A	0.71	0.90	0.64	-0.16	-0.26
Costs	£276,655	-£6,428	-£6,710	-£2,742	-£3,023	-£18,524	#N/A	-£10,663	-£42,690	-£63,315	-£65,123	£6,385
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
Scenario: ERG base case including PRISMS study for ARR & MSCRG study for CDP-6M												
QALY	5.41	1.23	1.24	1.23	1.24	0.44	#N/A	0.72	0.91	0.64	-0.16	-0.26
Costs	£276,618	-£6,474	-£6,763	-£2,788	-£3,077	-£18,606	#N/A	-£10,718	-£42,769	-£63,387	-£65,180	£6,328
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated

CDP-6M= confirmed disability progression at 6-months; DMF = dimethyl fumarate; DMT = disease-modifying therapy; ERG = Evidence review group; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = , incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LCLE = less costly, less effective; MS = multiple sclerosis; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous

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Technical engagement response form

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

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

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments – end of **24 October 2019**

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).

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- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	Declan Chard
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Clinical expert, nominated by the MS Trust, employed by UCL and UCLH. Please note that my opinions are not necessarily those of the MS Trust, UCL or UCLH.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None related to tobacco. Please note my previous declaration of anticipated future contracts with Biogen and Hoffmann-La Roche.

Questions for engagement

Issue 1: Use of peginterferon beta-1a in clinical practice	
Several options are available for treating relapsing-remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) at first line including interferon beta-1a, interferon beta-1b, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Are the patients who are likely to be treated with peginterferon beta-1a in the NHS the same as those who would have all these treatments, including the recently approved options, alemtuzumab and ocrelizumab?	Yes, I would consider the indications of this agent to be the same as for other first line agents. With regard to exclusion of patients with highly active (HA) or rapidly evolving severe (RES) multiple sclerosis (MS), for economic modelling this seems reasonable given that by far the majority of people with HA or RES MS are likely to opt for one of the treatments approved for this indication. However, I am concerned that this implies that people with HA or RES MS must not be prescribed such a first line treatment, and this will be codified in NHS guidance. While I would much prefer that someone with HA or RES MS chose one of the agents approved for this indication, some patients are very anxious about side effects, and in such a situation it makes clinical sense that they are at least allowed to start a first line treatment (which I would expect to have the same potential therapeutic effect in all people with relapsing remitting MS) than no treatment at all.
If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	I think the evidence of efficacy presented does support its use as an alternative first-line agent in those who are intolerant (due to side effects or mode of administration) of another first-line treatment. With regard to its use after treatment failure (where further relapses have occurred) with another first-line agent, for patients who do not wish to escalate to a more potent treatment due to concerns about side effects, then in clinical practice I think it would be reasonable to consider this in people who are not switching from another interferon.
Is alemtuzumab an appropriate comparator?	In terms of efficacy, I think alemtuzumab has been the benchmark for sustained treatment efficacy, but it has a substantially different side effect profile to interferons and, as already noted in the draft technical report, its use is limited while it undergoes a safety review. This leaves ocrelizumab (and natalizumab, albeit this would be prescribed in people with rapidly evolving severe multiple sclerosis). However, while I think it is a reasonable for economic models to compare efficacy relative to more potent treatments, the costs of monitoring and significant side effects also need to be realistically considered. As such, it would also make sense, for a clinical

	practice perspective, to compare peginterferon beta-1a with other interferons, as it is likely that these other treatment costs will be more comparable.
Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	a) With regard to annualised relapse rate, while a reasonable measure at a group level, in clinical practice I think this makes no real sense as an outcome. Firstly, relapses are essentially random, may substantially vary in frequency over years, and we cannot accurately predict them in a person with multiple sclerosis (MS). Given this, at an individual level we have no comparator against which to demonstrate efficacy. Secondly, annualised relapse rate does not take account of the severity of a relapse and the degree of recovery, and again these are unpredictable. I would consider any relapse that caused impaired function significant, and particularly so if a patient does not make a functionally full recovery. In practice treatment success is judged in retrospect by the absence of relapses. If a relapse occurs, then I would consider with the patient whether or not the current treatment is sufficient. b) Again, I think there is a difference between group level measures used in economic modelling and the individual consequences of any irreversible and functionally significant neurological impairment for a person with MS. As with relapses, at an individual level, there is a lot of variability in disability progression between MS patients, and we cannot predict with accuracy the likely future course against which to judge treatment efficacy. Further, confirmed disability progression as measured using the expanded disability status scale (EDSS) has different clinical implications at different points on the scale, for example progression from unimpaired walking to being limited to 500 m has different consequences when compared with progression from being able to walk 5 m with aids to essentially relying on a wheelchair for mobility. I would consider any persistent disabling symptoms or neurological deficits significant, but some have greater implications for care than others. In clinical practice it is relapses, and avoidance of relapse associated disability accrual, rather than disability progression per se, that underlies disease modifying treatment decisions in relapsing-remitting MS.

Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	The trial inclusion criteria do not appear to entirely match current NHS England criteria for other injectable treatments, in particular they do not include people with EDSS scores up to 6.5, and the study has been enriched on the basis of participants having had a relapse within the past year. With regard to regional differences in patients across Europe, there is some evidence that disease progression differs (Bovis et al. 2018 [https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.25323]). However, in terms of efficacy (relative reduction in risk of relapses), I am not aware of studies showing that Eastern and Western European populations would respond differently to treatment. With regard to care and treatment, there is also evidence that this differs across Europe (Berger et al. 2018 [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5826096/]).
If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	Please see my response to the previous question. If not already, I think the ADVANCE and UK MS Risk Sharing Scheme cohorts should be statistically compared, before assuming that the ADVANCE data can be directly extrapolated to people with MS in the UK.
Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	"Transition probabilities within SPMS": I think it is reasonable to assume that patients with secondary progressive (SP) multiple sclerosis (MS) are less likely to show improved expanded disability status scale (EDSS) scores, but not that they cannot improve. In all clinical subtypes of MS neurological impairments may vary significantly day to day, intercurrent illnesses (for example an infection) can cause a transient worsening of symptoms and neurological impairments, and people with SPMS may still, albeit less often that people with relapsing-remitting (RR) MS, have relapses. Further, EDSS scores are partly rater dependent. "Mortality: Same rate ratios for RRMS and SPMS phases": In practice, I would expect the mortality rate ratio to be higher in people with SP compared with RR MS. "Fatigue, injection-site reactions ... not associated with a disability": I can see why this has been omitted for lack of data, but in clinical practice both are significant and fatigue in particular can be associated with markedly impaired function.

Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	While it may make sense to economically model a diminishing potential for treatment efficacy, in clinical practice we do not make treatment decisions on this basis as, at an individual level, we can only judge efficacy through failure (further relapses) rather than success (the prevention of relapses). We reconsider treatment options when there is clear clinical evidence that relapses are still occurring on the current agent. We would also reconsider treatment in a person with multiple sclerosis (MS) who has entered a secondary progressive (SP) phase, although they may still have relapses that have functionally significant consequences. Indeed, in people who already have neurological impairments, even minor relapses may have marked functional effects. With regard to the timescales for diminishing potential treatment effects, in clinical practice I think the clearest indicator of this is the average time it takes a person with MS to develop SP disease, and it would be unusual for this to occur within a decade of the clinical onset of MS.
Is it clinically plausible that the waning effects are the same for all treatments?	In the absence of a specific reason (for example treatment neutralising antibodies), at a group level I think it is reasonable to assume that underlying relapse rate declines with disease duration and age (and so the potential for treatment efficacy wanes) in the same way for all treatments. However, as noted above, potentially waning treatment efficacy is not usually considered in clinical practice, rather treatments are reconsidered on the basis of clinical events, and more specifically if relapses occur, or a person with multiple sclerosis has clearly (and on clinical grounds it can take many years to be clear) entered a secondary progressive phase.
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies? b) all years, that is at the start of treatment and after many years on treatment?	a) In the absence of specific evidence to the contrary, I do not think it is plausible apply the same probability of stopping treatment to all therapies, as side effects differ substantially and some may be time-dependent (for example, as has been shown with natalizumab and the risk of developing progressive multifocal leukoencephalopathy). b) Initially I think the probability of stopping treatment will be relatively high as many side-effects declare themselves early on, and then will decrease for a while. However, recalling the natural history of multiple sclerosis (MS), and that over time increasing numbers of

	people with relapsing-remitting MS are likely to develop secondary progressive MS (leading to treatment being reconsidered), I think it likely that the probability of stopping treatment will, after several years, increase again.
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	Please see my response to the previous question.
Issue 7: Utility values	
Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	In both the cohorts studied by Orme et al. and Thompson et al. just over a third had relapsing-remitting (RR) multiple sclerosis (MS) and the rest progressive MS, and I think this is reflected in their expanded disability status scale (EDSS) score distributions. As such, neither is necessarily representative of patients likely to start interferons, although a subset (those with RRMS and lower EDSS scores) will be more so. Given that the transition from RRMS to secondary progressive (SP) MS is not necessarily clear, and can take years to become so, it seems reasonable to include data from people with SPMS. Both Orme et al. and Thompson et al. include data from people with primary progressive (PP) MS (about a quarter in both cohorts), who would not be prescribed interferons through the NHS. In the draft technical report it is noted that the Orme et al. study is a decade older than the Thompson et al. one. From a clinical perspective, there have been substantial changes in referral patterns and increasing treatment options, both of which may affect care cost estimates, and so it seems logical to use more recently acquired data.

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- 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

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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)	MS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to disclose

Questions for engagement

Issue 1: Use of peginterferon beta-1a in clinical practice	
Several options are available for treating relapsing-remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) at first line including interferon beta-1a, interferon beta-1b, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Are the patients who are likely to be treated with peginterferon beta-1a in the NHS the same as those who would have all these treatments, including the recently approved options, alemtuzumab and ocrelizumab?	Patients who are treated with peginterferon beta-1a would also be eligible for the drugs listed, as set out in the NHS England Treatment Algorithm for Multiple Sclerosis https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/. They are as likely to be treated with alemtuzumab and ocrelizumab as other highly efficacious treatments. Switching treatments should be a shared decision between clinicians and patient. Decisions on which DMT to take are determined by a variety of factors including the eligibility, efficacy, related side effects, the method and frequency of taking, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. Choosing which option to take requires access to evidence-based information, and support and advice from specialist health professionals. In 2014, the MS Society found that there is a lack of understanding and communication about what treatment options are currently available, with one in five people not having heard of any DMTs, or only heard of just one.[1] While MS nurses and neurologists are reported to be the most useful sources of evidence in aiding people to make a DMT decision, our research from last year showed that, of the people who are taking or are eligible for taking a DMTs, 13% had not met with a neurologist despite needing to and 14% had not met with an MS nurse despite needing to.[2] Of the 13 disease modifying therapies (DMTs) currently routinely available and reimbursed by NHS England, alemtuzumab and natalizumab are classified as 'high efficacy' by the Association of British Neurologists (ABN). Beta interferons, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod, are regarded as having 'moderate' efficacy. With the latter two drugs considered the more effective within this category. Cladribine and fingolimod, approved by NICE offer other options for good efficacy for people with highly active relapsing MS.

[1] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014
[2] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	The MS Society have produced a DMT booklet which outlines the impact each DMT has on MS (see page 33 and 34 for notes on efficacy). Link: https://www.mssociety.org.uk/about-ms/treatments-and-therapies/disease-modifying-therapies
If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	Those that do not response treatment are routinely referred to other treatment options, as per the NHS England Treatment Algorithm for Multiple Sclerosis Link: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/
Is alemtuzumab an appropriate comparator?	We agree with the MS Trust that although alemtuzumab is approved as a first-line treatment for relapsing remitting MS, we do not believe that it is an appropriate comparator for peginterferon.
Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	Any reduction in relapses and disability progression is significant for the patient, and can for people with relapsing-remitting MS compared to no treatment. The nature and impact of relapses are also highly individualised. A relapse is defined as an episode of neurological symptoms, lasting for at least 24 hours, that happens at least 30 days after any previous episode began. In relapses, symptoms usually come on over a short period of time and often remain for a number of weeks, but sometimes months. Relapses can vary from mild to severe. At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a GP, MS specialist nurse, and other care professionals. Due to the varied and unpredictable nature of MS, determining an “average” relapse rate is not straight forward; considering the number of people currently on disease modifying drugs it is likely that a significant proportion of people with relapsing remitting MS experience one or more relapses per year. However, the goal of any disease modifying treatment should be no evidence of disease activity (no relapses, no disability progression, and no new or active lesions on MRI scans).

	Alongside the reduction in relapses and disability progression both reduction on **brain atrophy** and improvement in **quality of life compared to alternative treatments** should be considered clinically meaningful.
Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	The ADVANCE trial applied inclusion and exclusion criteria which correspond to drug eligibility criteria in the UK. As such, we would expect the patients in ADVANCE recruited in Eastern Europe to be comparable to UK patients.
If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	We believe the risk sharing scheme data does not reflect the current population of people with RRMS who would be considered for peginterferon beta-1a. The drugs covered by the Scheme were Avonex (interferon beta-1a); Betaferon (interferon beta-1b); Copaxone (glatiramer acetate) and Rebif (interferon beta-1a).
Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	
Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	

Is it clinically plausible that the waning effects are the same for all treatments?	No, disease modifying treatments belong to different classes of drugs with different chemical structures and have different mechanisms of action, so we believe think it is highly unlikely that waning effects would be the same for all treatments.
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies? b) all years, that is at the start of treatment and after many years on treatment?	No, because disease modifying treatment belong to different classes of drugs and are administered differently and at difference times, responding to highly individualised circumstances. It is also important to note that treatment rates have increased sharply in recent years means that many people currently taking DMTs are relatively near the start of their treatment journey, notwithstanding the significant minority that will have been using peginterferon-beta 1a for a significant period. Link: https://www.mssociety.org.uk/about-ms/treatments-and-therapies/disease-modifying-therapies/early-treatment Stopping treatment can be an incredibly distressing experience for people with MS as for many this will signal a progression of a person's disease from relapsing-remitting MS to secondary progressive MS.
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	

Issue 7: Utility values	
Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

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Deadline for comments – end of **24 October 2019**

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- Do not use abbreviations.
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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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- 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

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About you

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

Questions for engagement

Issue 1: Use of peginterferon beta-1a in clinical practice	
Several options are available for treating relapsing-remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) at first line including interferon beta-1a, interferon beta-1b, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Are the patients who are likely to be treated with peginterferon beta-1a in the NHS the same as those who would have all these treatments, including the recently approved options, alemtuzumab and ocrelizumab?	In principle, the patients who are likely to be treated with peginterferon beta-1a would also be eligible for the drugs listed, as set out in the NHS England Treatment Algorithm for Multiple Sclerosis https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/. Ocrelizumab is a relatively new treatment so there is limited experience of long term use. On paper, it would appear to have a low risk of serious side effects; over time, as more experience is gained we would expect it to be offered more widely. Alemtuzumab has been used for a longer time and the side effect profile is well known and subject to monthly monitoring. In practice, some neurologists would view alemtuzumab and ocrelizumab as higher risk for first-line treatment and be more likely to offer interferon beta-1a or 1-b, glatiramer acetate, teriflunomide or dimethyl fumarate as first-line treatment. Some patients would also take this view.
If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	For patients who are intolerant to their initial disease-modifying treatment, it is routine clinical practice to switch them to an alternative first-line treatment as set out in the NHS England Treatment Algorithm for Multiple Sclerosis https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/. We cannot anticipate any reason why the same clinical practice should not apply to peginterferon as an alternative first-line treatment.
Is alemtuzumab an appropriate comparator?	No, although alemtuzumab is approved as a first-line treatment for relapsing remitting MS, we do not believe that it is an appropriate comparator for peginterferon. In clinical practice we would not expect peginterferon and alemtuzumab to be considered as equivalent, alternative treatment options either by clinicians or people with MS. People receiving alemtuzumab first-line tend to have more active disease and a less favourable baseline prognostic

	profile. For this group, the burden of side effects and monthly monitoring is balanced by the higher efficacy of alemtuzumab. This is reflected in the NHS England DMT treatment algorithm https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/: *For RRMS (that is not RES), alemtuzumab is an option that may be considered, but we note it is considerably more high-risk than the other options. It should be used only when the patient and MS specialists accept the significant risks and burden of monitoring.* Because of concerns about side effect risks, alemtuzumab is currently reserved for third line use pending the outcome of an ongoing EMA review.
Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	From the patient perspective, any reduction is clinically meaningful. Both relapses and disability progression have a significant impact on all aspects of life. Treatment goal is NEDA – no evidence of disease activity. As a minimum, this entails no relapses, no increase in disability, and no new or active lesions on MRI scans. Failing any one of these targets at an annual review should trigger a review of treatment and discussion with the patient. A growing number of neurologists with a specialist interest in MS are encouraging this early, proactive approach to managing RRMS.
Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	It is well-established that there are differences in health services for people with MS across Europe[1]. However, given that the ADVANCE trial applied inclusion and exclusion criteria which correspond to drug eligibility criteria in the UK, we would expect the patients in ADVANCE recruited in Eastern Europe to be comparable to UK patients. Baseline EDSS distribution (table 24, p114 of Technical engagement papers) confirms that the ADVANCE population covers people with RRMS with lower disease activity, comparable to the current use of disease modifying drugs in the UK.

[1] Kobelt G, Thompson A, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe. Mult. Scler. 2017;23(8), 1123-1136. www.ncbi.nlm.nih.gov/pubmed/28273775.

If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	No, we do not agree that the economic model should use baseline characteristics from the RSS. RSS data does not reflect the current population of people with RRMS who would be considered for peginterferon treatment.
Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	Yes, we believe the company has used all available data to model clinical effectiveness.
Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	We would question whether there is clinical evidence to support any waning effect. As noted in the MS Trust submission to this appraisal, one of the people we interviewed chose peginterferon over the other beta interferons because the incidence of neutralising antibodies is lower, making it less likely to lose efficacy over time[2]. This individual had identified this difference through their own in-depth research, highlighting the care taken and importance people place when making decisions about choosing a DMD. However, the approach taken by the company is consistent with waning effects applied in previous submissions.
Is it clinically plausible that the waning effects are the same for all treatments?	No, treatments belong to different classes of drugs with different chemical structures and have different mechanisms of action, so we would think it is highly unlikely that waning effects would be the same for all treatments. We have made this point in responses to previous ACDs, most recently in our response to the ocrelizumab RRMS ACD ID937: *The use of treatment waning in multiple sclerosis technology appraisals has become de facto, in the absence of clinical evidence or biological plausibility, the only purpose being to force an*

[2] White JT, Newsome SD, Kieseier BC, et al. Incidence, characterization, and clinical impact analysis of peginterferon beta1a immunogenicity in patients with multiple sclerosis in the ADVANCE trial. Ther Adv Neurol Dis 2016; 9(4): 239-249. www.ncbi.nlm.nih.gov/pubmed/27366230

	increase in the ICER. Unless this is a routine assumption for all drug technology appraisals, we consider this to be inequitable treatment for MS drugs and completely unjustified.
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies? b) all years, that is at the start of treatment and after many years on treatment?	No we would say it is not clinically plausible. Route of administration and dosing regimen have a major impact on stopping treatment. There are likely to be big differences in stopping between treatments which are self-injected, taken orally or administered by iv infusion. Side effects will also be a major cause of stopping treatment, but for alemtuzumab which is taken as two treatment courses, 12 months apart, the potential for stopping treatment as a result of side effects is limited. We would also argue that there are significant differences in motivation and compliance between people who choose treatment with alemtuzumab over beta interferon. The more risk-adverse patients who choose beta interferons may also be less tolerant of mild side effects. We would also expect to see a higher rate of stopping at the start of treatment, followed by a plateau of continued treatment, and then a further higher rate of stopping due to treatment burden or lack of perceived effect.
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	Table above is not referenced, so we are have not been able to respond to this question.
Issue 7: Utility values	
Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	Although Thompson et al (2017) is a more recent study, it is a smaller data set (n=779 vs n=2048) and has a higher mean age (56.7 years vs 51.4 years). Thompson et al acknowledge the older average age and note that this is associated with:

	more patients with severe disease, lower DMT usage, fewer patients of working age and actually working. Orme et al (2007) has been the standard for previous TAs so it would be more consistent to follow previous practice.

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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)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Use of peginterferon beta-1a in clinical practice	
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If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	**Yes this therapy has a role in people who have relative needle phobia given the infrequency of injections and who are intolerant to other first line oral therapies**
Is alemtuzumab an appropriate comparator?	**No, alemtuzumab would be considered a much more active therapy with significantly greater risk**
Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	**a) Minimum is a 30% reduction in ARR** b) No set consistent figure

Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	**The trial population is almost exclusively Caucasian and hence may not be representative of MS populations in certain parts of the UK. The skewing of recruitment to Eastern Europe is commonplace for trials in MS in the last 10 years**
If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	**On balance this is unnecessary**
Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	yes
Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	On balance yes although it is somewhat optimistic on the company's behalf as the therapy's efficacy is likely to be below the levels quoted. However, the therapy is usually well tolerated and has a less than 1% level of antibody formation.
Is it clinically plausible that the waning effects are the same for all treatments?	Partially dependent on antibody formation in the interferon beta group – beta 1-b and subcut beta 1-a approx. 20-30% antibody formation; peginterferon approximately 1%
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies?	No, therapies have different efficacies and tolerance. Additionally, two therapies: alemtuzumab and oral cladribine are time limited (18-24 months)

b) all years, that is at the start of treatment and after many years on treatment?	
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	This is an area of uncertainty and additional data is needed. The probabilities quoted are plausible
Issue 7: Utility values	
Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	Thompson et al 2017 on balance

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	NICE has not previously required separate evidence to be presented for the position of "alternative first-line treatment" in RRMS and Novartis would query whether it is *a priori* expected that relative efficacy would differ due to intolerance to first-line therapy. As such, Novartis does not consider it to be reasonable to require separate evidence for this position.
Is alemtuzumab an appropriate comparator?	No; both because of the current EMA safety restriction on alemtuzumab, but also as patients who would be considered for alemtuzumab are expected to be systematically different to those considering a first-line injectable, given the very different risk–benefit profiles of these two products.

Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	Novartis disagrees that the concept of a minimum clinically significant reduction is applicable to the direct clinical outcomes of annualised relapsed rate (ARR) and confirmed disability progression (CDP). These are major objective clinical events for patients and therefore any difference in relative treatment effect is important. Relapses have a direct impact on patients who may require sick leave and/or become hospitalised for a time; avoiding them is always meaningfully beneficial. This is even more evident with progression events, such as progression to being wheelchair-bound (Expanded Disability Status Scale, EDSS 7) or bed-ridden (EDSS 8), for which determining a minimum clinically significant reduction is impossible to determine objectively, complicated by the EDSS being a, non-continuous, ordinal scale. On the specific point noted by the Technical Team regarding variation in absolute ARR in placebo arms over time, Novartis would ask whether there is any evidence of relative relapse efficacy (that being what is modelled) varying over time in DMTs for which evidence for multiple trials may be available?
Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	
If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	In general, it is preferable to model interventions undergoing appraisal in the population in which their trial was undertaken. Analysis using Risk Sharing Scheme baseline characteristics may be an informative scenario analysis. As the Technical Report notes that the impact is not material to the incremental cost-effectiveness ratio (ICER), this issue does not seem pertinent.

Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	Novartis disagrees with the Technical Team suggestion that joint modelling of 3-month CDP and 6 month CDP should be undertaken: the reason why 6-month CDP has been preferred in previous NICE MS appraisals and regulatory authorities is that it is less likely to be subject to random bias than 3-month CDP which may be influenced by the residual effect of relapses. Given this rationale for preferring 6-month CDP, it is not expected that a consistent relationship between 3-month CDP and 6-month CDP exists between trials and therefore the effect of joint modelling will be to introduce the random bias of 3-month CDP into the 6-month CDP network, reducing its usefulness to guide decision making. Novartis would additionally note that RRMS trials may differ in their definition of 3-/6-month CDP and this should be explicitly addressed in considering whether the trials are sufficiently comparable to allow inclusion within an NMA. Notably, in NICE TA533 it is stated: “The committee noted that pegylated interferon beta-1a appeared to be an outlier in the updated mixed treatment comparisons because it appeared to be more effective than other beta interferons and high-efficacy treatments such as natalizumab. The committee heard that this was contrary to clinical experience, so it disregarded the comparison with pegylated interferon for this appraisal.” Novartis agrees with the Evidence Review Group (ERG) that all relevant trials should be included and that the influence of excluding trials for any specified reason may be tested in scenario analyses; given that it is noted that this issue does not materially affect the ICER, this may not be pertinent to the appraisal.
Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	Novartis notes that the Technical Report states that waning is line with TA527 – this is incorrect. In TA527 waning was assumed from 10 years only (at 50%). Instead, Novartis notes that the

	proposed waning assumptions are based on outdated appraisal assumptions made in 2014 for TA320 which were themselves based on assumption and not evidence. In contrast, in the more recent TA533, the Committee agreed that a separate waning effect should not be modelled – the Committee recognised that in clinical practice patients will not continue to be prescribed an ineffective therapy and will rather discontinue and switch to an alternative DMT. As such, the Committee agreed that all-cause discontinuation is a proxy for any waning of treatment effect. Therefore, to be consistent with the Committee in TA533 and in absence of evidence, Novartis does not consider it plausible that waning is applied in the model as arbitrary waning assumptions would introduce double-counting with all-cause discontinuation, including discontinuation due to lack of efficacy. A patient who is experiencing lack of efficacy will not remain on treatment (and the NHS should not incur costs of the treatment if efficacy would be waning). As such the appraisal should focus on the effect of discontinuation without introducing arbitrary waning assumptions that are not evidence-based.
Is it clinically plausible that the waning effects are the same for all treatments?	All waning assumptions are inherently arbitrary and do not reflect the clinical reality of switching treatments due to lack of efficacy. The issue of long-term differences in effectiveness between treatments ought to be captured through evidence-based modelling of time-dependent treatment discontinuation which does vary by DMT (see Issue 6). Importantly, Novartis notes that the practical effect of assuming differential waning for DMTs will be to bias appraisals against new products which will inevitably have shorter long-term follow-up data than the more established comparators. Novartis would caution that the potential ramifications of this issue are considered carefully in any situation where waning is modelled.
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies?	(a) It is implausible to model discontinuation being the same over time for all DMTs. Furthermore, if it remains in the appraisal, Novartis notes that alemtuzumab as an induction therapy cannot be meaningfully discontinued after year 2 as it is no longer taken,

b) all years, that is at the start of treatment and after many years on treatment?	but likewise is not expected to continue to be efficacious indefinitely as it is not curative. Further work would be needed to explore this issue for induction therapy such as alemtuzumab, if alemtuzumab remains a comparator in the appraisal. (b) Discontinuation is unlikely to be constant over time with early discontinuations being driven by intolerance, and later discontinuations reflecting lack of efficacy (see the response to Issue 5 above). In TA441 (now withdrawn) the Committee preferred a model with separate rates for Years 1, 2 and 3+.
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	As noted above, Novartis considers fixed proportional discontinuation to be inherently implausible as it mixes early discontinuation due to intolerance with later discontinuation arising from objective lack of efficacy (including any theoretical waning of effectiveness).
Issue 7: Utility values	
Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	The utility data from Orme et al. are based on over a two-and-a-half times larger number of survey responses (2,048) than Thompson et al. (779) and have been used in many previous MS appraisals, allowing consistency of decision making. Novartis would particularly highlight with respect to the plausibility of Thompson et al. that EDSS 7 represents people who have become wheelchair-bound and EDSS 8 those who have become bed-ridden for life: the higher values for these states reported by Thompson do not therefore seem to have face validity. In these most severe stages, Orme et al. is based on a 1.6x greater sample (391 vs 240). Orme et al. also provide utilities for SPMS and relapse whereas Thompson et al. do not and application of Thompson data by the ERG in fact continues to apply parts of the Orme et al. regression analysis directly to the Thompson data, which may not be valid.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis [ID1521]

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

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments – end of **24 October 2019**

Thank you for your time.

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

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

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

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

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

About you

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

Questions for engagement

Issue 1: Use of peginterferon beta-1a in clinical practice	
Several options are available for treating relapsing-remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) at first line including interferon beta-1a, interferon beta-1b, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Are the patients who are likely to be treated with peginterferon beta-1a in the NHS the same as those who would have all these treatments, including the recently approved options, alemtuzumab and ocrelizumab?	As discussed at the NICE Technical engagement call, Biogen agree with the recommendations made by the clinical expert that patients should have the option to choose their disease modifying therapy (DMT) based on factors such as risk-benefit profile of the DMT, patient lifestyle (including pregnancy considerations), route and frequency of administration. Patients with relapsing remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) could present with either mild or more severe disease activity. Thus, treatment options would vary from patient to patient based on the factors mentioned above (risk-benefit profile, route & frequency of administration and patient lifestyle). The clinical expert on the technical engagement call mentioned that even though his recommendation for patients with more severe disease would be to consider escalation to higher efficacy DMTs, patients may still opt for a treatment option with a more tolerable and well-established safety profile such as an interferon. Biogen agree with the recommendations made by the clinical expert that that all treatments should be available as an option; the choice of treatment should be tailored to each patient's need after shared conversations between clinician and patient.
ERG comment	**Nothing to add to this comment. The ERG clinical advisor's opinion aligns to this view.**
If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway?	Biogen believe peginterferon beta-1a should be considered in the same position as currently recommended within the NHS England DMT algorithm (1): • first-line treatment option for RRMS, and • alternative first-line treatment option for patients who are intolerant to their initial DMT.

	Biogen would like to highlight that there are >1,400 patients currently being treated with peginterferon beta-1a in-line with the NHS England DMT algorithm (2). We do not foresee any reason why the data from ADVANCE trial can't be extrapolated to first-line treatment for patients who are intolerant to their initial DMT. The technical engagement clinical expert recommended that peginterferon beta-1a would be considered for efficacy switch (e.g. from glatiramer acetate to interferon) as some patients prefer switching therapy between the lower efficacy DMTs, considering their established safety profile, before potentially initiating on a higher efficacy treatment. Biogen has a marketing authorisation for patients with RRMS (3), and thus would support its use in efficacy switch patients as described by the clinical expert.
ERG comment	**No further comment to make. The ERG did not appraise evidence for the use of peginterferon beta-1a outside of its position in NHS England DMT algorithm contained in the CS (as described above).**
Is alemtuzumab an appropriate comparator?	Alemtuzumab is currently being reviewed by the EMA safety committee (PRAC) following safety concerns and is currently restricted in adults with RRMS that is highly active despite treatment with at least two DMTs or where other DMTs cannot be used (4). Biogen has agreed to include alemtuzumab within the appraisal as a comparator (in-line with the scope) in the interim whilst a decision by the EMA is pending. In the event that alemtuzumab is no longer recommended as a first-line DMT, Biogen would suggest alemtuzumab is removed as a comparator. Biogen has already provided comparisons against all other comparators, including ocrelizumab, and thus no new analyses should be required in the event that alemtuzumab is removed as a comparator.
ERG comment	**No further comment. The ERG understand the current situation, and were asked by NICE to include it as a comparator as per the NICE final scope for this appraisal.**

Issue 2: Minimum clinically significant reduction in outcome measures	
In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?	Biogen were not able to identify any published literature that measures the minimum clinically significant reduction (MCID) of annualised relapse rate (ARR) or confirmed disability progression (CDP) in patients with multiple sclerosis. This must therefore be deferred to clinical expert opinion. It should also be acknowledged that Biogen is not aware that this question regarding the MCID of ARR or CDP has been raised in previous NICE multiple sclerosis appraisals.
ERG comment	**The ERG did not identify any published literature which measures the minimum clinically significant reduction of ARR or CDP in the SLR conducted for this appraisal. However, we have not conducted a full SLR to answer this particular question.**
Issue 3: Generalisability of ADVANCE population	
Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive?	Biogen believe the patients in the ADVANCE trial do reflect the people who would be eligible for peginterferon beta-1a in NHS practice. Peginterferon beta-1a is currently being used in NHS practice and has been available since August 2015 (5). Unfortunately, Biogen could not provide a comparison of the geographical locations or ethnicity of patients included in the pivotal studies as this information is either not published or categorised differently within the comparator pivotal studies (e.g. rest of world).
ERG comment	**The ERG refer to the statement made in the ERG report: page 21 "*only 14 patients were enrolled from the UK, therefore the generalisability to a UK population is unclear*" and page 60 "*The ERG suggests that there is potential variation geographically in outcomes and potentially in accompanying clinical practice, treatment physiotherapy and standards of care regimes*."**
If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?	Based on the above, Biogen would argue that the baseline characteristics from the ADVANCE trial are reflective of the UK MS population and thus should be used in the economic model.

	Biogen demonstrated within our original submission that using the baseline characteristics from the UK MS Risk Sharing Scheme (RSS) in the economic model do not alter the cost-effectiveness results. **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS irrespective of whether the baseline characteristics from ADVANCE or the RSS are used in the economic model.**
ERG comment	**The company demonstrated that the results remain unchanged irrespective of the choice of baseline characteristics from ADVANCE or the Risk Sharing Scheme.**
Issue 4: Clinical outcomes used in the economic model	
Has the company used all available data to model clinical effectiveness?	Biogen believe all the relevant data to model the clinical effectiveness has been included within the network meta-analysis in our submission. The ERG noted some inconsistencies in our submission with regards to the choice of studies used to derive the effectiveness for the comparators in the economic model. Biogen has provided a rationale for the inconsistency described below: • For interferon beta-1a, Biogen's submission excluded the PRISMS (1998) trial for the network for ARR. This was because the PRISMS study does not report the ARR within the publication (mean relapses per patient and proportion of relapse free reported). Biogen do not believe calculating the ARR based on the mean number of relapses per patient (as done so by Melendez-Torres et al - ID 527) is a justified assumption. As a result, this study was excluded from the ARR network. Nevertheless, we have conducted a further scenario analysis to include PRISMS into the NMA (Figure 1) showing minimal differences in the results (Table 1). **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS regardless of whether PRISMS study is included within the ARR network or not using Biogen's base case (Table 3) as well as the ERG's preferred assumptions (Table 4)**

	• For interferon beta-1a, Biogen's submission excluded the MSCGR (1996) trial from the network for CDP-6M. This was because the hazard ratio needed to include in this network was not reported in the publication or the CSR. The NICE MTA included this trial within the network as they included a hazard ratio using the method described in Tierney et al. (2007). Biogen avoided estimating the hazard ratio from the reported risk ratio as it would increase uncertainty and thus decided to exclude this study from the network. Nevertheless, we have conducted a further scenario analysis to include MSCGR into the NMA (Figure 2) showing minimal differences in the results (Table 2). **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS regardless of whether MSCGR study is included within the ARR network or not using Biogen's base case (Table 3) as well as the ERG's preferred assumptions (Table 4)** • A discrepancy between the number of studies used for the analyses of stopping treatment because of any reasons for the clinical section (3 trials), and in the economic models (18 trials) For the clinical section, the NMA restricted stopping treatment because of any reason to a 12-months follow-up which resulted in the reduction in number of trials within the network (3 trials). Most trials used a 22 to 24 months follow-up, however as we wanted to include the ADVANCE trial (pivotal trial for peginterferon beta-1a) into our analysis we focused on trials with a 12-month follow up. There was also significant variation in the definitions of stopping criteria between trials which would have increased uncertainty. The inputs used in the economic model were derived from the individual DMT's pivotal trials, and hence resulted in a larger number of studies (18 trials). This is consistent with the previous appraisals, and thus Biogen would not consider this issue as an inconsistency. **Biogen presented a suite of scenario analyses varying discontinuation rates within our original manufacturer submission demonstrating that**

	peginterferon beta-1a remained a cost-effective options for the treatment of patients with RRMS.
ERG comment	• **The ERG described the preferred NMA study inclusions in** Error! Reference source not found. **and Section** Error! Reference source not found. **of the ERG report. Biogen provided their rationale for the difference during clarification, and provided scenarios described above, and Fig 1 and 2 in this document. Despite preferring our own NMA, we consider the companies scenarios to be adequate.** • **To our knowledge, the company used all available evidence to model discontinuation rates. These approaches to modelling discontinuation all appear to be plausible. However, given the limitations outlined in issue 6, we preferred to use the 5% discontinuation rates that were observed in the Risk Sharing Scheme.** • **We thank the company for undertaking these additional analyses by considering the information from PRISMS and MSCGR for ARR and confirmed disability progression measured at six months. We have verified these results and they are in-line with the ERG's.**
Issue 5: Treatment waning	
Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect.	There is a dearth of available literature in regard to treatment waning for DMTs, and current waning assumptions applied to the economic model are arbitrary. However for consistency with prior technology appraisals, we have applied the same step-change in hazard ratio for disability progression across all comparators. The development of neutralising antibodies (NAbs) against beta-interferons can reduce the efficacy of treatment, and has been a theory postulated in prior NICE appraisals to be directly linked to treatment waning.

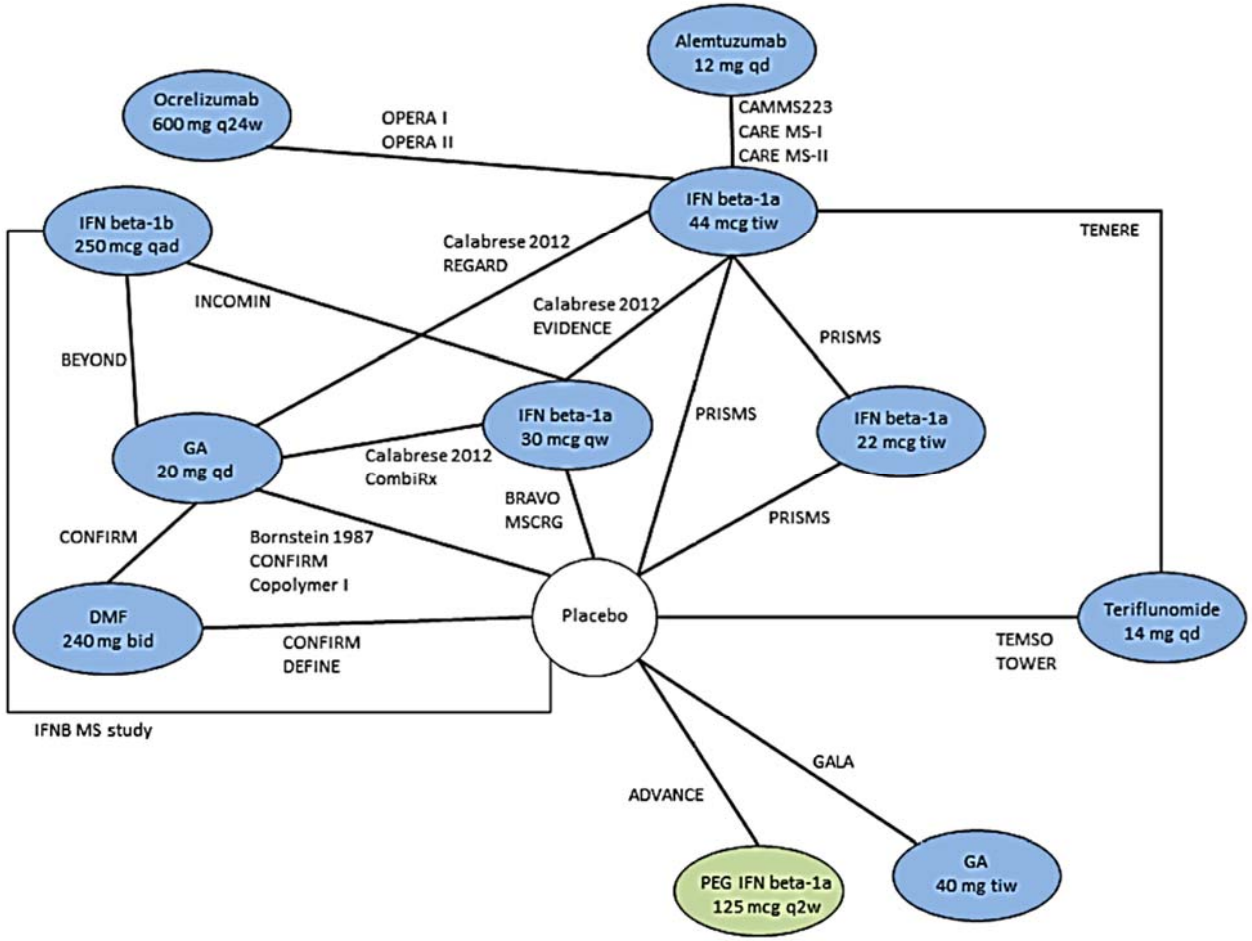
	The incidence of NAbs with peginterferon beta-1a is <1%, considerably lower compared to its comparators such as interferon-beta 1a 30mcg (5-8%) (6), interferon beta-1a 44mcg (13-24%)(7), and interferon beta 1-b (23-41%)(8). Glatiramer acetate is not associated with Nabs (9). Thus, having the same waning effect for peginterferon beta-1a as the other interferons could be underestimating effect size. **Nevertheless, Biogen would like to iterate that peginterferon beta-1a remains to be a cost-effective treatment option when the same waning effects are used for peginterferon beta-1a and its comparators.**
ERG comment	**The waning of treatment effects modelled by the company is plausible.**
Is it clinically plausible that the waning effects are the same for all treatments?	Different mechanisms of actions of the MS therapies would likely pertain to alternative waning effects – e.g. immune reconstitution therapies vs maintenance therapies. However, as Biogen believe that current evidence in this area is limited, Biogen would suggest that this questions is most appropriately answered by the clinical experts.
Issue 6: Stopping treatment	
Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies? b) all years, that is at the start of treatment and after many years on treatment?	There are significant differences between the DMTs with regards to safety and adverse event profile. As a result, Biogen's preference is to use discontinuation rates obtained from the pivotal trials of each DMT, as opposed to the same probability for each DMT. This has been reflected within our base case analysis. However, Biogen has also conducted a scenario analysis where the same probability has been applied to all DMTs (5% discontinuation rate), maintaining consistency with previous appraisals. **Peginterferon beta-1a remains a cost-effective option for the treatment of patients with RRMS even when the same probability of stopping treatment is applied to the economic model.**
ERG comment	**In Table 47 page 147 of the ERG's report, we provide justification for our use of the 5% discontinuation rate, which was applied in the recent health technology assessment monograph (Melendez-Torres et al, 2017). In summary, RCT's can be considered artificial, with highly selected/motivated participants, there may be**

	various non-clinical reasons for discontinuation (e.g. withdrawal of consent), and limited long-term follow-up.
Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?	Biogen has already submitted three scenarios where the different stopping criteria is used in the economic model. 1. Discontinuation rates obtained from the pivotal trials of each DMT, weighted by sample size 2. Discontinuation rates obtained from the pivotal trials of each DMT, weighted by person time 3. Same probability of stopping rates for all DMTs (5% applied to all DMTs) **Across all analyses peginterferon beta-1a was demonstrated to be a cost-effective option for the treatment of patients with RRMS regardless of which stopping criteria is used.**
ERG comment	**The ERG preference is 3, to use 'same probability of stopping rates for all DMTs (5% applied to all DMTs)'**
Issue 7: Utility values	
Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?	Biogen has used utility data derived from Orme et al. (2007) in the economic model for its base case. This is consistent with the previous appraisals. Biogen has already submitted a scenario analysis using utility data using Thompson et al. (2017). Biogen would like to iterate that the Thompson et al. (2017) study used the same data as the Orme et al. (2007) study (obtained from the MS Survey in 2006). However, the Orme paper has a much larger sample size (n=2,048) across all MS types (RRMS, PPMS, SPMS) (10), whereas the Thompson paper is restricted to a much smaller sample size (n=779) (11). Therefore, Biogen believe utility data obtained from the Orme paper would be more plausible, and also maintains consistency with the previous appraisals.

	Regardless of whether utility data is obtained using the Orme et al (2007) study or the Thompson et al. (2017) study, peg-interferon beta-1a remains a cost-effective option for patients with RRMS.
ERG comment	**We are in agreement with the company that the health state utility values obtained from Orme et al., 2007 should be used in the base-case.**

ARR = annualised relapse rate; CDP = confirmed disability progression; CDP 6M = confirmed disability progression at 6-months; DMT = disease modifying therapy; EMA = European Medicines Agency; ERG = Evidence Review Group; MCID = minimum clinically significant decrease; MS = multiple sclerosis; RES = rapidly evolving severe MS; RRMS = relapsing remitting multiple sclerosis; RSS = risk sharing scheme; Nabs = neutralising antibodies.

Figure 1: Network for annualised relapse rate including PRISMS trial



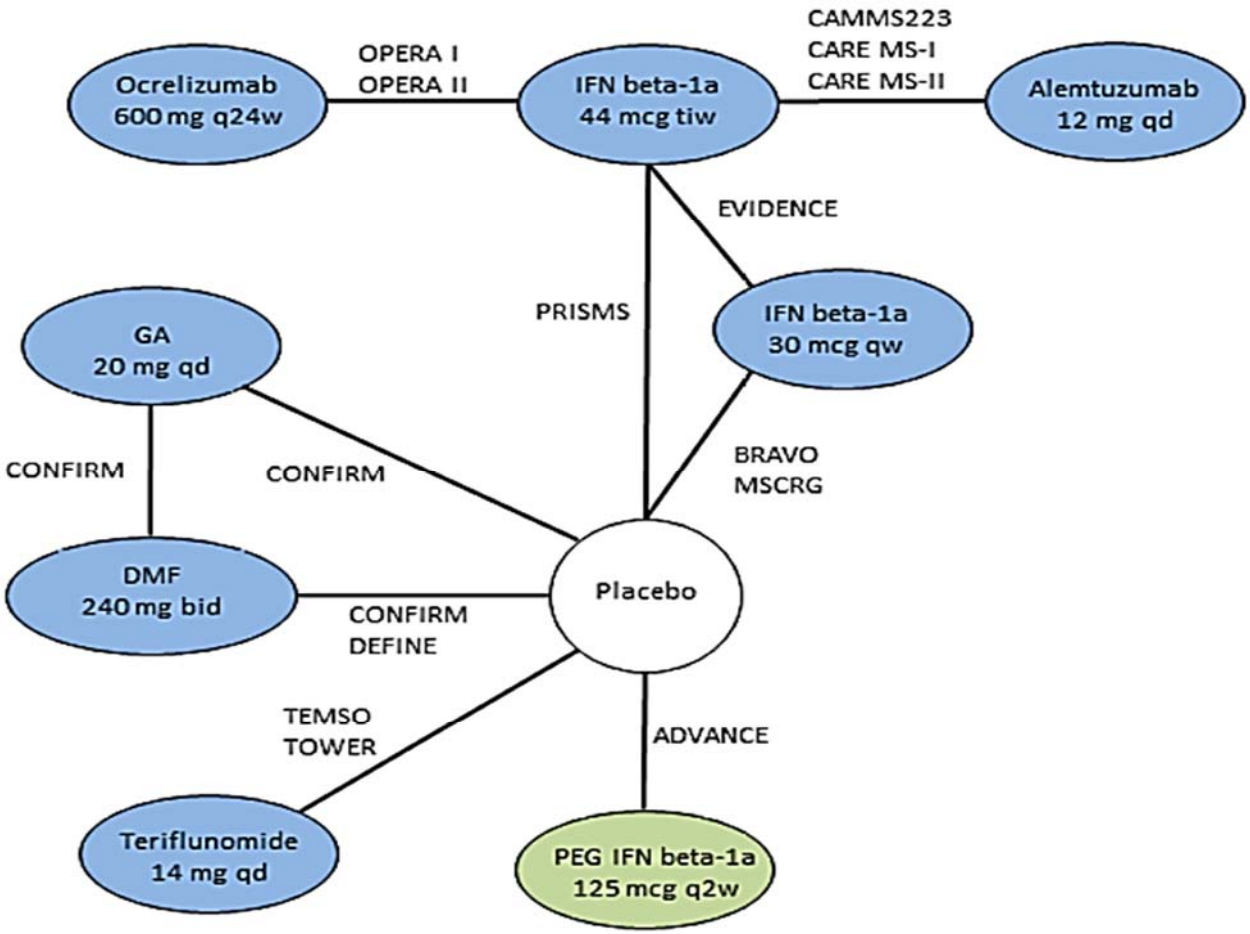
DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PEG IFN = pegylated interferon; q24w = every 24 weeks; qad = every other day; qd = once daily; qw = once weekly; tiw = three times weekly.

Table 1: Rate ratio on ARR versus placebo including PRISMS study in the network

Treatment	Rate ratio for ARR from original submission	95% CI	Rate ratio for ARR including PRISMS	95% CI
PegIFNβ-1a	[redacted]	[redacted]	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]	[redacted]
GA 40	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 20	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 40	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

DMF = dimethyl fumarate; PEG IFN = pegylated interferon; GA = glatiramer acetate; genGA = generic glatiramer acetate; IFN = interferon

Figure 2: Network for confirmed disability progression at 6-months including MSCRG trial



bid = twice daily; DMF = dimethyl fumarate; PEG IFN = pegylated interferon; qad = every other day; q24w = once every 24 weeks; qd = once daily; tiw = 3 times a week.

Table 2: Hazard ratio on CDP at 6 months versus placebo including MSCRG study

Treatment	Hazard ratio for CDP-6M from original submission	95% CI	Hazard ration for CDP-6M including MSCRG	95% CI
PegIFNβ-1a	[redacted]	[redacted]	[redacted]	[redacted]
IM IFNβ-1a 30	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]	[redacted]
GA 40	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 20	[redacted]	[redacted]	[redacted]	[redacted]
GenGA 40	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

DMF = dimethyl fumarate; PEG IFN = pegylated interferon; GA = glatiramer acetate; genGA = generic glatiramer acetate; IFN = interferon

Table 3: Cost-effectiveness results using Biogen's base case of two additional scenario analyses using list prices.

Scenario	pegIFNβ-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	ocrelizumab	alemtuzumab
Base case - discounted												
QALY	4.39	0.75	0.74	0.75	0.74	0.17	NA	0.46	0.60	0.44	-0.50	-1.08
Costs	£273,641	-£11,423	-£14,035	-£8,701	-£11,033	-£19,328	NA	-£20,557	-£23,796	-£34,865	-£66,027	-£1,250
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
Scenario: Including PRISMS study for ARR												
QALY	4.394	0.75	0.74	0.75	0.74	0.17	N/A	0.47	0.60	0.45	-0.50	-1.08
Costs	£273,621	-£11,449	-£14,068	-£8,727	-£11,066	-£19,380	N/A	-£20,592	-£23,837	-£34,903	-£66,064	-£1,294
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
Scenario: Including MSCRG study for CDP-6M												
QALY	4.39	0.74	0.73	0.74	0.73	0.12	#N/A	0.26	0.59	0.44	-0.55	-1.13
Costs	£273,641	-£11,259	-£13,860	-£8,534	-£10,855	-£18,601	#N/A	-£17,369	-£23,747	-£34,771	-£65,629	-£424
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE
Scenario: Including PRISMS study for ARR & MSCRG study for CDP-6M												
QALY	4.39	0.74	0.73	0.74	0.73	0.12	#N/A	0.26	0.60	0.44	-0.55	-1.13
Costs	£273,621	-£11,285	-£13,893	-£8,561	-£10,888	-£18,654	#N/A	-£17,404	-£23,788	-£34,809	-£65,667	-£468
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a LCLE

CDP-6M= confirmed disability progression at 6-months; DMF = dimethyl fumarate; DMT = disease-modifying therapy; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = , incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LCLE = less costly, less effective; MS = multiple sclerosis; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous

Table 4: Cost-effectiveness results using ERG preferred assumptions of two additional scenario analyses using list prices.

Scenario	pegIFNβ-1a	GA20	GA40	genGA 20	genGA 40	IFNβ-1b 44	IFNβ-1b	IFNβ-1a 30	teriflunomide	DMF	ocrelizumab	alemtuzumab
ERG Base case - discounted												
QALY	5.41	1.24	1.25	1.24	1.25	0.50	N/A	0.95	0.91	0.65	-0.10	-0.22
Costs	£276,655	-£6,609	-£6,890	-£2,928	-£3,209	-£19,260	N/A	-£13,784	-£42,742	-£63,395	-£65,412	£5,727
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
Scenario: ERG base case including PRISMS study for ARR												
QALY	5.41	1.24	1.25	1.24	1.25	0.50	#N/A	0.95	0.91	0.65	-0.10	-0.22
Costs	£276,618	-£6,655	-£6,944	-£2,974	-£3,263	-£19,342	#N/A	-£13,839	-£42,821	-£63,468	-£65,469	£5,670
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
Scenario: ERG base case including MSCRG study for CDP-6M												
QALY	5.41	1.23	1.23	1.23	1.23	0.44	#N/A	0.71	0.90	0.64	-0.16	-0.26
Costs	£276,655	-£6,428	-£6,710	-£2,742	-£3,023	-£18,524	#N/A	-£10,663	-£42,690	-£63,315	-£65,123	£6,385
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated
Scenario: ERG base case including PRISMS study for ARR & MSCRG study for CDP-6M												
QALY	5.41	1.23	1.24	1.23	1.24	0.44	#N/A	0.72	0.91	0.64	-0.16	-0.26
Costs	£276,618	-£6,474	-£6,763	-£2,788	-£3,077	-£18,606	#N/A	-£10,718	-£42,769	-£63,387	-£65,180	£6,328
ICER	-	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	NA	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a dominates	pegIFNβ-1a LCLE	pegIFNβ-1a dominated

CDP-6M= confirmed disability progression at 6-months; DMF = dimethyl fumarate; DMT = disease-modifying therapy; ERG = Evidence review group; GA = glatiramer acetate; genGA = generic glatiramer acetate; ICER = , incremental cost-effectiveness ratio; IFN = interferon; IM = intramuscular; LCLE = less costly, less effective; MS = multiple sclerosis; QALY = quality-adjusted life-year; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

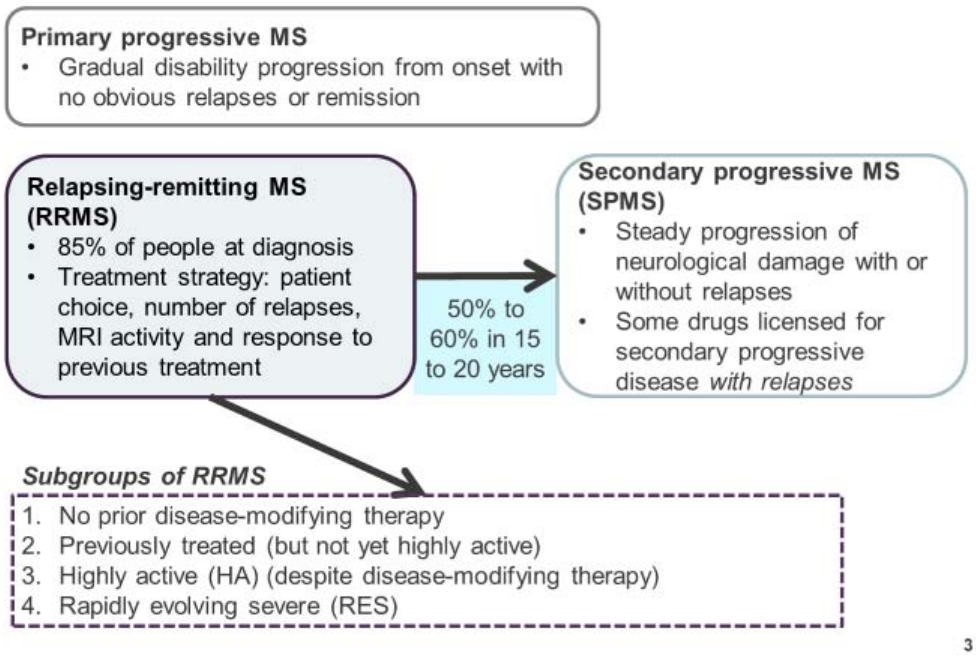
Issue date: November 2019

1. Topic background

1.1 Disease background: multiple sclerosis

- Chronic, lifelong, neurological disease with no cure. Results in progressive, irreversible disability. Affects central nervous system:
    - Immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves
- 85% of MS is relapsing-remitting (RRMS): episodes of relapses (neurological worsening) separated by remission (periods of stability)
- Associated with pain, disturbance to muscle tone, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Approximately 110,000 people in the UK have MS, and about 5,000 people are newly diagnosed each year
- Onset typically between 25 and 35 years of age
- Treatment (disease-modifying therapies): decrease frequency and severity of relapses, reduce accumulation of lesions, slow accumulation of physical and mental disability, maintain or improve patient quality of life

Types of multiple sclerosis

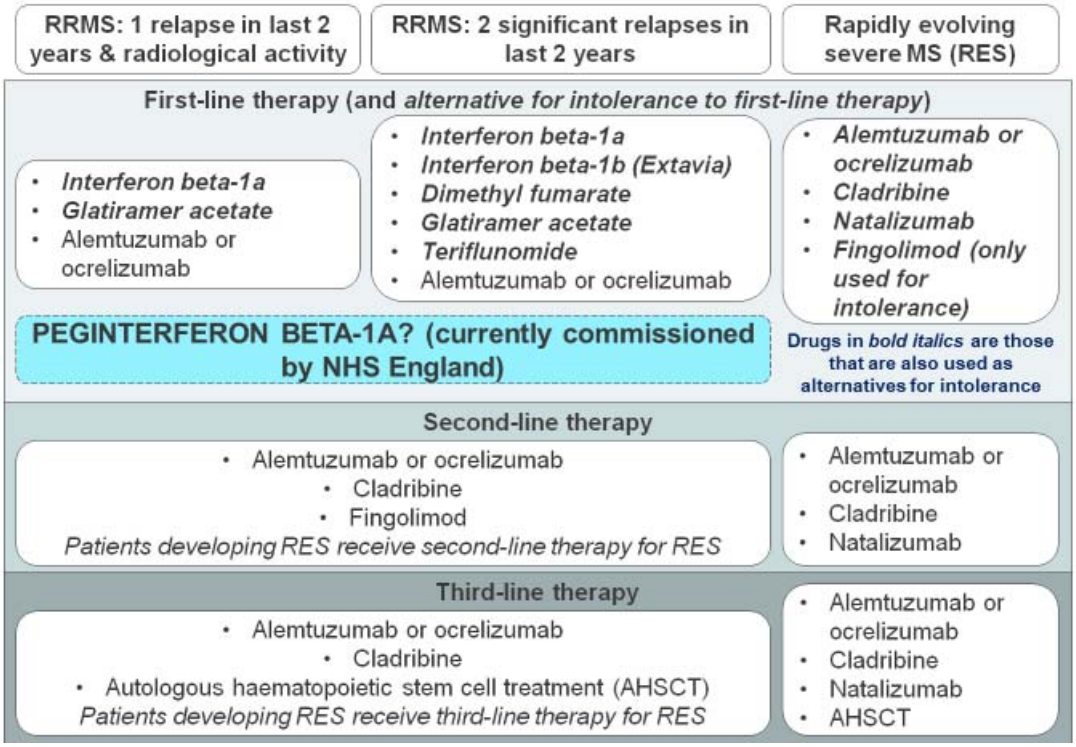


Peginterferon beta-1a (Plegridy)

- **Marketing authorisation**: "adult patients for the treatment of relapsing remitting multiple sclerosis" (obtained July 2014)
- **Mechanism of action**: a man-made version of naturally produced beta interferons, which help to reduce inflammation in the nerves. Reduces disease activity similar to non-peginterferon beta-1a. Pegylation increases circulation time of interferon (less frequent dosing) and decreases immunogenicity (reduced neutralising antibodies linked to treatment waning)
- **Administration and dose**: prefilled syringe/autoinjector administered subcutaneously every 2 weeks. 63µg dose 1, 94µg dose 2, 125µg dose 3+
- **Cost**: standard pack 2 injections £654. Annual cost: £8,502. No patient access scheme
- Currently commissioned by NHS England for RRMS first-line, not highly active (disease activity despite previous therapy) or rapidly evolving severe MS
- Originally included in the multiple technology assessment (TA527) on beta interferons and glatiramer acetate for MS. No recommendation because primary source of evidence preferred by committee in MTA was the UK MS Risk Sharing Scheme

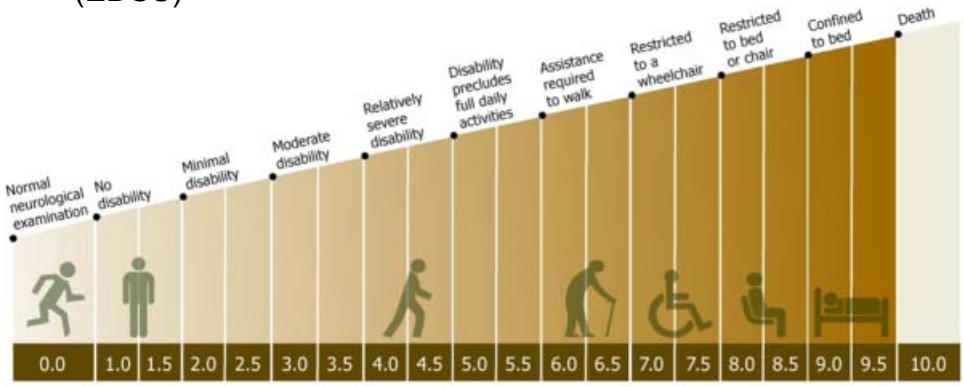
1.2 Treatment pathway

NHS England treatment algorithm and company positioning

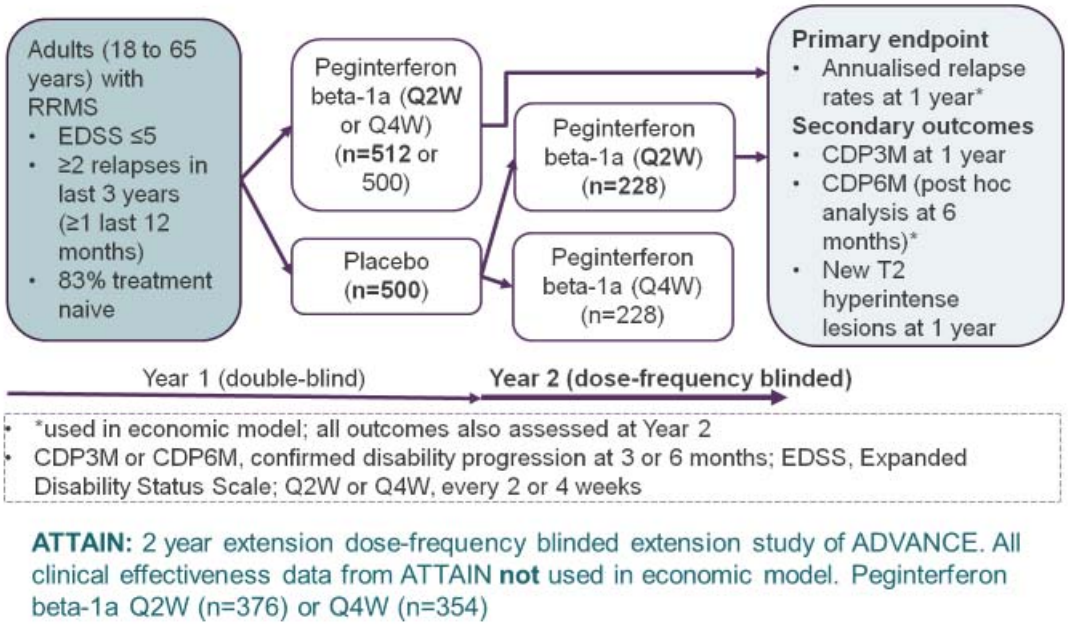


Aim of disease-modifying therapies

- Reduce frequency of relapse and slow disability
    - Relapse: new or recurrent neurological symptoms lasting ≥24 hours without fever or infection; separate events are at least 30 days apart
    - Disability: assessed using Expanded Disability Status Scale (EDSS)



1.3 Clinical evidence: ADVANCE trial



ATTAIN: 2 year extension dose-frequency blinded extension study of ADVANCE. All clinical effectiveness data from ATTAIN **not** used in economic model. Peginterferon beta-1a Q2W (n=376) or Q4W (n=354)

ADVANCE: baseline characteristics

Characteristic		Peginterferon beta-1a every 2 weeks (Q2W; n = 512)	Placebo (n = 500)
Age, mean ± SD		36.9 ± 9.8	36.6 ± 9.8
Female, n (%)		361 (71)	358 (72)
Race, n (%)	White	416 (81)	412 (82)
Region, n (%)	India	58 (11)	56 (11)
	North America	19 (4)	17 (3)
	Western Europe	41 (8)	38 (8)
	Eastern Europe	355 (69)	354 (71)
	Rest of world	39 (8)	35 (7)
Body mass index (kg/m^2), mean ± SD		24.6 ± 5.1	24.6 ± 4.9
EDSS score	Mean ± SD	2.5 ± 1.3	2.4 ± 1.2
Relapses in previous year, mean ± SD		1.6 ± 0.7	1.6 ± 0.7
Relapses in previous 3 years, mean ± SD		2.6 ± 1.0	2.6 ± 1.0
Time since MS diagnosis, years ± SD		4.0 ± 5.1	3.5 ± 4.63
Previous treatment, n (%)	Glatiramer acetate	27 (5)	24 (5)
	Interferon beta-1b	8 (2)	6 (1)
	Interferon beta-1a	4 (< 1)	5 (1)
	Other	58 (11)	58 (12)
Number of lesions, mean ± SD	T2	48.7 ± 36.8	50.6 ± 35.7
	Gd+	1.2 ± 3.4	1.6 ± 3.8

1.4 Key clinical effectiveness results

ADVANCE: key results at 1 year

Outcome	Peginterferon beta-1a every 2 weeks (Q2W; n = 512)	Placebo (n = 500)	Peginterferon beta-1a Q2W vs placebo
Annualised relapse rate (95% CI)	0.256 (0.21 to 0.32)	0.397 (0.33 to 0.48)	Rate ratio: 0.644 (0.50 to 0.83); p=0.0007
CDP3M (estimated proportion)	0.068	0.105	Hazard ratio: 0.62 (0.40 to 0.97); p=0.04
CDP6M	-	-	Hazard ratio: 0.46 (0.26 to 0.81); p=0.007
New T2 lesions (adjusted mean)	3.6	10.9	Lesion mean ratio: 0.33 (0.27 to 0.40); p<0.001

Subgroup analysis of annualised relapse rate showed efficacy of peginterferon beta-1a was similar in all patients regardless of sex, age, body weight or disease status

CDP3M or CDP6M, confirmed disability progression at 3 or 6 months; CI, confidence interval; Q2W or Q4W, every 2 or 4 weeks

Network meta-analysis: key results reported by company

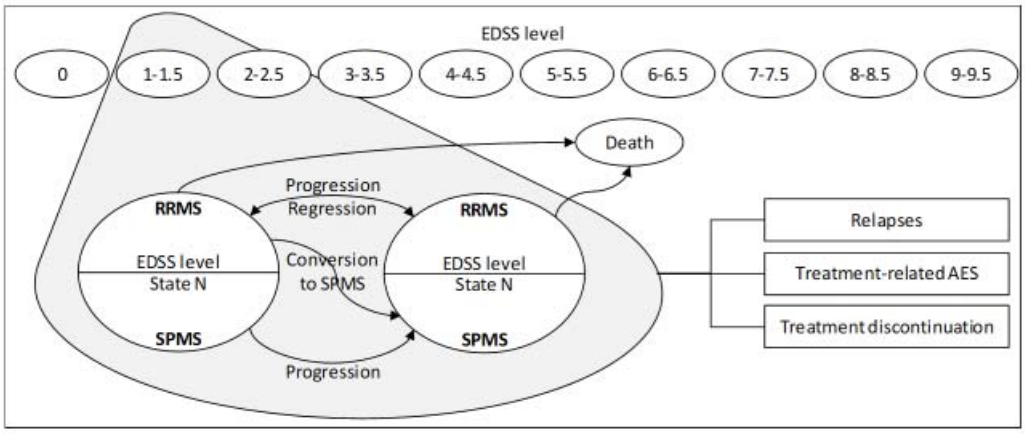
- **Annualised relapse rates (Company submission, Document B, Figure 15)**
  - Statistically significantly higher vs alemtuzumab and ocrelizumab
  - Statistically significantly lower vs placebo
  - No statistically significant differences vs any other treatments
- **Confirmed disability progression at 3 months (CDP3M; Company submission, Document B, Figure 17)**
  - No statistically significant differences vs placebo or any active treatment
- **Confirmed disability progression at 6 months (CDP6M; Company submission, Document B, Figure 19)**

- Statistically significantly lower vs placebo
- No statistically significant differences vs any active treatment

Statistically significant p<0.05

Note: The clinical significance of the results will be considered in more detailed by committee

1.5 Company's model structure



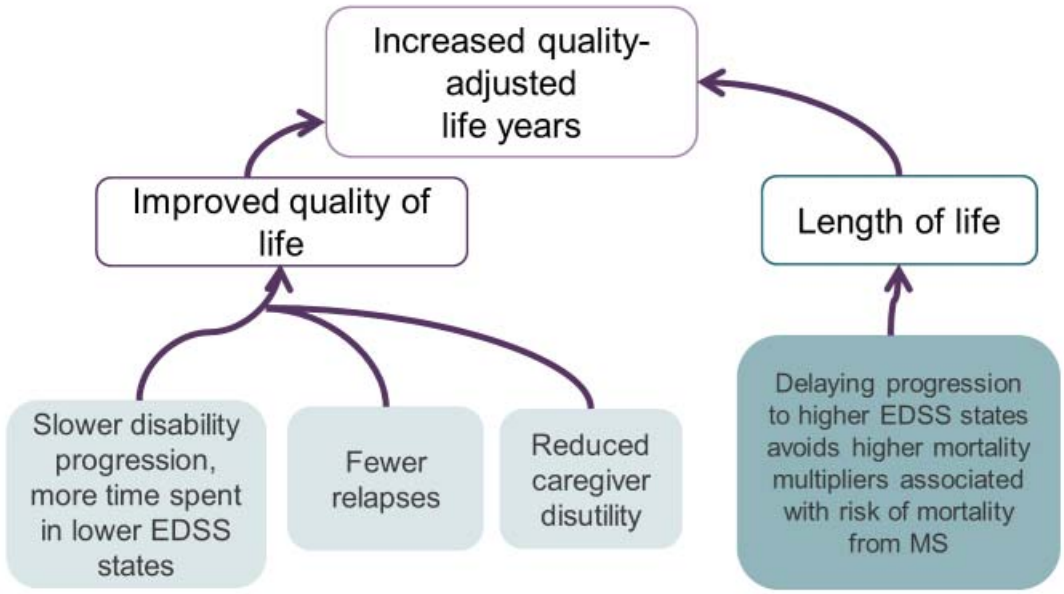
- Markov cohort model
- 20 EDSS health states (RRMS, SPMS)
- Annual cycle, 50-year time horizon
- Starting age 36 years; 29% men
- NHS/PSS perspective, 3.5% discount
- On-treatment effects (annualised relapse rates, disability progression, adverse events) taken from network meta-analyses
- Patients stop treatment after progression to EDSS ≥ 7 or on conversion to SPMS. Overall stopping risk applied for all treatments over lifetime horizon
- After stopping treatment, patients follow natural disease progression course based on British Columbia MS data set (n=898)

1.6 Key model assumptions

Parameter	Base-case assumption	Justification
Disability progression	Disability progression and relapses modelled independently, with independent treatment effects applied to each.	In line with previous appraisals. EDSS progression is a key driver of cost-effectiveness. This approach avoids potential double counting.
	Treatments had an indirect effect on the risk of progression to SPMS and mortality.	Delaying progression to higher EDSS levels avoids higher mortality multipliers associated with risk of mortality from MS and

		avoids higher probabilities of progression to SPMS.
	Transition probabilities within RRMS: patients can improve to a lower EDSS level in this phase. **Transition probabilities within SPMS**: patients cannot improve to a lower EDSS level in this phase.	As per the definition of RRMS, patients can regress (demonstrated in the British Columbia MS data set). As per the definition of SPMS, patients cannot regress (aligned with the London, Ontario data set).
	After stopping treatment, patients follow the natural disease progression course.	In line with previous appraisals. This approach underestimates cost-effectiveness estimates for treatments with the highest stopping rates as they are likely to transition to higher efficacy drugs.
Mortality	Same rate ratios for RRMS and SPMS phases.	Due to lack of data (conservative assumption)
Treatment waning	Treatment effect wanes over time; same decline for all disease-modifying therapies. • Years 1-2: no waning • Years 3-5: 75% of full treatment effect • Year 6 onwards: 50% of full treatment effect	In line with previous appraisals.
Health related quality of life	Fatigue, injection-site reaction (erythema, pain, pruritus) not associated with a disutility.	Due to lack of data.
	Patient who received treatment would incur the risk of disutility and costs associated with adverse effects for each year over.	Due to lack of data. This approach may overestimate impact of adverse effects, because patients with severe/frequent events likely to stop treatment early on.
Costs	Non-serious type of fatigue, injection-site reaction (erythema, pain, pruritus) and nasopharyngitis have no costs associated with them.	Injection-site reactions often do not lead to any resource use, particularly from NHS/PSS perspective.

1.7 **Overview of how quality-adjusted life years accrue in the model**



2. Summary of the technical report

After technical engagement, the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

2.1 In summary, the technical team considered the following:

Issue 1 **A. Population.** Peginterferon beta-1a is likely to be used in line with current NHS practice in accordance with NHS England's treatment algorithm for multiple sclerosis disease-modifying therapies, **that is, as first-line treatment for relapsing-remitting multiple sclerosis, and as an alternative first-line treatment for people who are intolerant of their initial disease-modifying therapy**.

B. Comparators. It is unclear whether alemtuzumab should be a comparator, however, if the European Medicines Agency (EMA) **restrictions remain in place, this would limit its relevance as a first-line treatment.** Ocrelizumab **should be**

included as a comparator, given that it is recommended if alemtuzumab is contraindicated or otherwise unsuitable.

Issue 2 **Minimum clinically significant reduction in outcome measures**. **The overarching view from most stakeholders appears to be that any relative reduction** in annualised relapse rates and confirmed disability progression is clinically meaningful.

Issue 3 **Generalisability of ADVANCE trial population**. **Although the baseline characteristics of patients from the ADVANCE trial are likely to be subject to some bias, they are broadly generalisable to the UK setting and should be used in the economic model**.

Issue 4 **Source of data**. The company **has adequately justified the** inconsistencies in study choice included in their analyses **in the clinical effectiveness section, which have little impact on the cost-effectiveness estimates**.

Issue 5 **Treatment waning**. It is likely that the waning effects of peginterferon beta-1a may be different to newer disease-modifying therapies such as alemtuzumab and ocrelizumab. **However, in the absence of supporting evidence, the same waning effects should be applied to all disease-modifying therapies**.

Issue 6 **Stopping treatment for any reason (for example, lack of effect, adverse effects)**. **It is clinically more plausible that individual disease-modifying therapies would have specific stopping rates, which will likely vary over time**.

Issue 7 **Utility values**. **The utility values used in Orme et al. (2007) and Thompson et al. (2017) are broadly similar. Using Orme et al. is consistent with previous appraisals.**

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The unknown impact of treatment sequencing from second line onwards on the cost-effectiveness estimates.
- The possibility of informative censoring. More patients in the peginterferon beta-1a arm (15%) stopped participating in the ADVANCE trial than in the placebo arm (9%) at 1 year. It is unclear whether patients who completed the trial were different in terms of baseline characteristics and outcomes than those who had stopped the study early.

2.3 Taking these aspects into account, the technical team's preferred assumptions result in alemtuzumab dominating peginterferon beta-1a (see table 1). These results do not take into account the commercial arrangements for interferon beta-1a (Avonex, Rebif), interferon beta-1b (Extavia), glatiramer acetate (Copaxone), dimethyl fumarate (Tecfidera), teriflunomide and ocrelizumab, because these are confidential and cannot be reported here.

2.4 The technology is unlikely to be considered innovative (see Table 3).

2.5 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Use of peginterferon beta-1a in clinical practice

Background/description of issue	The **company** positions peginterferon beta-1a as first-line therapy, excluding the 'rapidly evolving' and 'highly active' subgroups presented in the scope (because it is "unlikely to be used in this population in clinical practice", and because of "limited data", respectively). Peginterferon beta-1a is currently commissioned by NHS England as a first-line treatment. As such, the company has only presented clinical and cost-effectiveness analyses compared with all available first-line treatments. However, the scope and the licence do not restrict the use of peginterferon beta-1a to first-line treatment only. In addition, cost can affect the place in the treatment pathway (NICE technology appraisal, TA533 states ocrelizumab should only be used if alemtuzumab is contraindicated or otherwise unsuitable, "because it is more costly than alemtuzumab"). If committee's preferred model assumptions lead to cost-effectiveness results suggesting peginterferon beta-1a is not a cost-effective initial first-line treatment, can the evidence in the company submission be used to consider peginterferon beta-1a's use as an alternative first-line option in the event of intolerance or from second line onwards? • The main clinical evidence (from the ADVANCE trial) includes patients who were mostly treatment naïve (83%). • The company has focused the clinical and cost-effectiveness results on a first-line population, so they have omitted some scope comparators which would be used later in the pathway. Please note that in April 2019, the European Medicines Agency's pharmacovigilance risk assessment committee started a review of alemtuzumab. It advises that during the ongoing review, alemtuzumab should only be started in adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least 2 disease-modifying therapies, or when other disease-modifying therapies cannot be used. Alemtuzumab is frequently the most cost-effective treatment option, however given this restriction, it is unclear if it is an appropriate comparator.

Questions for engagement	1. Several options are available for treating relapsing-remitting multiple sclerosis (not highly active or rapidly evolving severe subgroups) at first line including interferon beta-1a, interferon beta-1b, dimethyl fumarate, glatiramer acetate, teriflunomide, alemtuzumab and ocrelizumab. Are the patients who are likely to be treated with peginterferon beta-1a in the NHS the same as those who would have all these treatments, including the recently approved options, alemtuzumab and ocrelizumab? 2. If peginterferon beta-1a is not a cost-effective first-line treatment, has enough evidence been presented to consider it as an alternative first-line treatment for patients who are intolerant to their initial disease-modifying therapy or later in the treatment pathway? 3. Is alemtuzumab an appropriate comparator?
Why this issue is important	The company have focused their analyses on the first-line population, however committee may recommend it later in the pathway. Whether alemtuzumab is an appropriate treatment option is important – this frequently dominates all other treatments, but it is undergoing a safety review, which limits its use to later in the pathway.
Technical team preliminary judgement and rationale	Given peginterferon beta-1a is already used at first line in NHS practice, this is the most likely place in the pathway. If committee choose to recommend it second line onwards, for example, because of cost, there is nothing in the licence to prevent this, although it should be noted that the ADVANCE trial included a population that was primarily treatment naïve (83%). It is unclear at this stage whether alemtuzumab should be a comparator, however if the EMA restrictions remain in place, this would limit its relevance as a first-line treatment. Ocrelizumab should be included as a comparator, given that it is recommended if alemtuzumab is contraindicated or otherwise unsuitable.
Summary of comments	**Comments received from company:** • Different factors affect the choice of disease-modifying therapies including patient preference, disease activity, risk-benefit profile of treatments, route and frequency of administration and patient lifestyle. All treatments should be available as options. • Peginterferon beta-1a should be considered in the same position as currently recommended in the NHS England disease modifying therapies algorithm: first-line treatment option for RRMS and an alternative first-line treatment option for patients who are intolerant of their

	initial disease modifying therapy. Data from ADVANCE trial can be extrapolated to first-line treatment for patients who are intolerant of their initial disease modifying therapy. • Peginterferon beta-1a could also be considered for efficacy switch among lower efficacy disease-modifying therapies with established safety profile, before starting higher efficacy treatments. • Alemtuzumab is a relevant comparator pending the decision of the EMA safety committee on its use. **Comments received from clinical expert:** • Peginterferon beta-1a would be considered at the same point in the treatment pathway as other first line agents. • Patients with highly active or rapidly evolving severe MS should be allowed to have these first line treatments as options. • The company's efficacy evidence does support peginterferon beta-1a's use as an alternative first-line agent in those who are intolerant (due to side effects or mode of administration) of another first-line treatment. • For patients not switching from another interferon, peginterferon beta-1a should be considered for patients whose first-line treatment is not effective (further relapses have occurred) but do not wish to escalate to a more potent treatment because of concerns about side effects. • Comparison of peginterferon beta-1a to other more potent treatments such as ocrelizumab should consider costs for monitoring and side effects. Because of comparable treatment costs, other interferons may be appropriate comparators. **Comments received from clinical organisation:** • Peginterferon beta-1a will mainly be considered in people with relatively low inflammatory activity (usually 1 relapse in last 2 months with minimal MRI changes), while ocrelizumab and alemtuzumab may be considered in people with greater inflammatory activity because of potentially greater risk.

	• Peginterferon beta-1a can be used for people who are intolerant to other first line oral therapies. • Alemtuzumab is not an appropriate comparator as it would be considered a much more active therapy with significantly greater risk. **Comments received from patient organisations:** • Patients eligible for peginterferon beta-1a are eligible for treatments set out in NHS England Treatment Algorithm for Multiple Sclerosis. They are as likely to be treated with alemtuzumab and ocrelizumab as other highly efficacious treatments. • For patients who are intolerant of their initial disease modifying therapy, it is routine clinical practice to switch to an alternative first-line treatment and this should apply to peginterferon beta-1a. • Although alemtuzumab is approved as a first-line treatment, it is not an appropriate comparator for peginterferon beta-1a. People receiving alemtuzumab first line tend to have more active disease and a less favourable baseline prognostic profile. **Comments received from comparator company:** • Patients considering peginterferon beta-1a would be the same as those who might consider one of the recently approved treatment options (not alemtuzumab). • NICE has not previously required separate evidence to be presented for the position of "alternative first-line treatment" in RRMS. It is unclear whether relative efficacy would differ due to intolerance to first-line therapy. • Alemtuzumab is not an appropriate comparator because of current EMA safety restriction and patients are expected to be systematically different to those considering a first-line injectable given the different risk-benefit profiles.
Technical team judgement after engagement	Peginterferon beta-1a is likely to be used in line with current clinical practice, as first-line treatment for relapsing-remitting multiple sclerosis, and as an alternative first-line treatment for people who are intolerant of their initial disease modifying therapy.

	It is unclear at this stage whether alemtuzumab should be a comparator, however if the EMA restrictions remain in place, this would limit its relevance as a first-line treatment. Ocrelizumab should be included as a comparator, given that it is recommended if alemtuzumab is contraindicated or otherwise unsuitable.

Issue 2 – Minimum clinically significant reduction in outcome measures

Background/description of issue	The primary endpoint in the ADVANCE trial was annualised relapse rate at 1 year. In addition, one of the key clinical outcomes in the company's model was confirmed disability progression, either at 3 or 6 months. The **Association of British Neurologists** commented that a clinically significant treatment response may be considered to be **"**Reduction of relative relapse rate compared to best supportive care." It further stated that "Relative reduction in confirmed disability progression compared to best supportive care is more difficult to ascertain due to the longer term nature of data needed to determine this in comparison to relapse rates.**"** The **technical team** notes that a systematic review of 26 randomised, placebo-controlled trials in relapsing-remitting multiple sclerosis showed that the annualised relapse rate for the placebo group that did not receive any active treatment had decreased by 6.2% per year ($p < 0.0001$; 95% CI 4.2%; 8.1%; Nicholas et al. 2011), which suggests that there may be natural variability in annualised relapse rates over time.
Questions for engagement	4. In clinical practice, what is considered a minimum clinically significant reduction for the following outcomes: a) annualised relapsed rate b) confirmed disability progression?
Why this issue is important	If the differences in outcome measures reported in the trials and network meta-analyses are not clinically meaningful, then the results of the economic model based on these effectiveness data may not be valid.
Technical team preliminary judgement and rationale	The minimum clinically significant change in outcome measures should consider natural variability in readings over time.
Summary of comments	**Comments received from company:**

	• Unable to identify any published literature that measures the minimum clinically significant reduction (MCID) of annualised relapse rate or confirmed disability progression in patients with multiple sclerosis. • This issue has not been raised in previous NICE multiple sclerosis appraisals. **Comments received from clinical expert:** • In clinical practice, treatment success is judged retrospectively by the absence of relapses Any relapse that caused impaired function is significant, particularly if the patient does not make a functionally full recovery. • In clinical practice, disease modifying treatment decisions in RRMS are based on relapses and avoidance of relapse associated disability accrual. Any persistent disabling symptoms or neurological deficits are significant, though there may be variations in their implication for care. **Comments received from clinical organisation:** • For annualised relapse rates, minimum is 30%. • For confirmed disability progression, there is no set consistent figure. **Comments received from patient organisations:** • Any reduction in relapses and disability progression is significant for the patient. • Reduction on brain atrophy and improvement in quality of life compared to alternative treatments should be considered clinically meaningful. • Treatment goal is no evidence of disease activity (no relapses, no increase in disability, no new or active lesions on MRI scans). **Comments received from comparator company:** • Minimum clinically significant reduction is not applicable to direct clinical outcomes of annualised relapse rate and confirmed disability progression because these are major

	objective clinical events for patients and any difference in relative treatment effect is important. • Regarding variation in absolute annualised relapse rates in placebo arms over time, is there evidence of relative relapse efficacy (that being what is modelled) varying over time in disease modifying therapies for which evidence for multiple trials may be available?
Technical team judgement after engagement	Although one clinical organisation suggested that a minimum 30% reduction in annualised relapse rate is clinically meaningful, no data or references were provided to support this figure, and the overarching view from most stakeholders appears to be that any relative reduction in annualised relapse rates and confirmed disability progression is clinically meaningful.

Issue 3 – Generalisability of ADVANCE population

Background/description of issue	The **company** stated that "The patient population in ADVANCE … is reflective of adult patients with relapsing-remitting multiple sclerosis (RRMS) in the UK" (Document B, section B.3.11). It highlighted that the baseline characteristics of patients in ADVANCE are similar to other comparator studies of relevant appraisals, which have previously been considered generalisable to the UK (Document B, section B.2.9.3, Table 17). In addition, a subgroup analysis showed that the efficacy of peginterferon beta-1a was broadly similar across all populations, regardless of geographical region (Company clarification response, A5). The **ERG** noted that ADVANCE was conducted across 26 countries and only enrolled 14 patients from the UK, with most participants from Eastern Europe (69%), followed by India (11%) and Western Europe (including the UK, 8%). It noted differences in efficacy of peginterferon beta-1a across the 3 geographical regions and highlighted that there may be differences in clinical practice, treatments and standards of care (ERG report, pages 60-61). The company presented a scenario analysis using data on the patient characteristics from the UK MS Risk Sharing Scheme, a 10-year observational study initiated in 2002 to assess the impact of disease-modifying therapies on disability progression in patients with relapsing-remitting multiple sclerosis. This was the population used in NICE technology appraisal 527. This increased the overall costs of peginterferon beta-1a, but it did not have a significant impact on cost-effectiveness results.

Questions for engagement	5. Are the patients in the ADVANCE trial likely to reflect people who would be eligible for peginterferon beta-1a in NHS practice? For example, are patients in Eastern Europe likely to be comparable to the UK in characteristics and the care and treatment they receive? 6. If not, should the economic model use the baseline characteristics of the population from the UK MS Risk Sharing Scheme?
Why this issue is important	If the patients in ADVANCE do not have similar characteristics to those who would have peginterferon beta-1a in the NHS, some of these factors may influence how well the treatment works. This might mean that the safety and effectiveness results from the ADVANCE trial for peginterferon beta-1a do not accurately reflect how safe and effective the treatment would be in UK clinical practice.
Technical team preliminary judgement and rationale	For the purposes of interpreting the safety and effectiveness of the ADVANCE trial, the evidence is likely to be subject to some bias but broadly generalisable and relevant for this appraisal. For the purposes of the economic model, there is an alternative UK-based population that can be used. If patients in ADVANCE are unlikely to reflect people seen in the NHS, the company should use the baseline characteristics from the population in the UK MS Risk Sharing Scheme, as per NICE technology appraisal 527 (Beta interferons and glatiramer acetate for treating multiple sclerosis) for its base case analysis. However, this is not a salient issue because it has little impact on the cost-effectiveness results.
Summary of comments	**Comments received from company:** • Patients from ADVANCE trial reflect people in the NHS eligible for peginterferon beta-1a (already currently used in NHS practice since August 2015) and should be used in the economic model. • Geographical locations or ethnicity of patients in ADVANCE compared with comparator pivotal studies is not possible because the information is not published or categorised differently. **Comments received from clinical expert:**

	• ADVANCE trial inclusion criteria do not completely match current NHS England criteria for other injectable treatments, in particular, they do not include people with EDSS scores up to 6.5. • There is evidence of regional differences across Europe in disease progression, and care and treatment. • In terms of efficacy (relative reduction in risk of relapses), the clinical expert is not aware of any evidence to show differences in response to treatment between Eastern and Western populations. • ADVANCE and UK MS Risk Sharing Scheme cohorts should be statistically compared before assuming that data from ADVANCE can be directly extrapolated to people with MS in the UK. **Comments received from clinical organisation:** • ADVANCE trial population is almost exclusively "Caucasian" so may not be representative of MS populations in certain parts of the UK. Skewing of recruitment of study participants to Eastern Europe is commonplace for trials in MS in the last 10 years. • On balance, it is not necessary for the economic model to use the baseline characteristics of the population from the UK MS Risk Sharing Scheme. **Comments received from patient organisations:** • ADVANCE trial applied inclusion and exclusion criteria which correspond to drug eligibility criteria in the UK and therefore patients recruited in Eastern Europe should be comparable to UK patients. • The Risk Sharing Scheme data does not reflect the current population of people with RRMS who would be considered for peginterferon beta-1a. **Comments received from comparator company:** • It is preferable to model interventions in the population in which their trial was undertaken.

Technical team judgement after engagement	For the purposes of interpreting the safety and effectiveness of the ADVANCE trial, the evidence is likely to be subject to some bias but broadly generalisable and relevant for this appraisal. The baseline characteristics of patients from ADVANCE should be used in the economic model.

Issue 4 – Clinical outcomes used in the economic model

Background/description of issue	The **company** used the following clinical outcomes in its base case analysis: annualised relapse rate, confirmed disability progression at 6 months (CDP6M), mortality and stopping treatment for any reason. It conducted scenario analyses using confirmed disability progression at 3 months (CDP3M) and stopping treatment because of adverse events. The **ERG** noted that there were inconsistencies in the company's choice of studies used to derive the effectiveness values for comparators for these outcomes in the economic model, either when comparing the clinical and cost-effectiveness sections within the company submission, or when comparing this company submission to a previous appraisal. For example: • For interferon beta-1a, the company submission excluded the PRISMS (1998) trial (provided data on annualised relapse rate), and the MSCGR (1996) trial (provided data on disability progression at 6 months). However, NICE multiple technology appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis (TA527) included these trials. • The ERG noted a discrepancy between the number of studies used for the analyses of stopping treatment because of any reason undertaken for the clinical section (3 trials), and in the economic model (18 trials). • The ERG noted that for the analyses of stopping treatment because of adverse events, the company only included 2 studies, compared with 21 trials that were included in the network meta-analysis of this outcome at 24 months in TA527 (ERG report, pages 70-86 and 114). In addition, the **technical team** notes that the company's analysis for CDP3M included the BEYOND trial. However, BEYOND had not reported CDP6M and therefore was excluded from this analysis. The technical team notes that in the NICE technology appraisal on ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533), the committee preferred joint modelling of CDP3M and CDP6M, that is, using data from trials that report both data at 3 and 6 months to infer missing data at 6 months, rather than excluding trials.
Questions for engagement	7. Has the company used all available data to model clinical effectiveness?
Why this issue is important	These clinical outcomes are used in the economic model and therefore affect the cost-effectiveness estimates.

Technical team preliminary judgement and rationale	The ERG suggested that the discrepancies in the data included in the clinical effectiveness section of the company's submission does not have a large impact on the cost-effectiveness estimates. However, for completeness, the company should present clinical effectiveness results using all relevant studies and its impact on cost-effectiveness estimates using scenario analyses. Alternatively, the company should provide a clear justification for the inconsistencies in study choice.
Summary of comments	**Comments received from company:** • Reasons for inconsistencies in choice of studies: o For interferon beta-1a, company excluded PRISMS (1998) trial because this study does not report annualised relapse rate (ARR) and does not consider the method used by the NICE MTA (TA527; Melendez-Torres et al) to derive the ARR from mean number of relapses per patient is a justified assumption. However, a scenario analysis including PRISMS in the NMA showed minimal differences in the results and on the cost-effectiveness results. o For interferon beta-1a, company excluded MSCGR (1996) trial from the network for confirmed disability progression at 6 months (CDP6M) because the hazard ratio was not published or in the clinical study report. The company did not derive the hazard ratio from the reported risk ratio as undertaken in TA527 because it considered that this would increase uncertainty. However, a scenario analysis including MSCGR in the NMA showed minimal differences in the results and on the cost-effectiveness results. o Discrepancy in the number of studies used for the analyses of stopping treatment because of any reasons for the clinical section (3 trials) and in the economic model (18 trials): only data up to 12 months follow up were used in the clinical section (3 trials) to reduce uncertainty. Most trials used different definitions of stopping criteria and reported data at 22 to 24 months follow up which were incompatible with data from the ADVANCE trial. Inputs in economic model were from individual disease modifying therapy pivotal trials and is consistent with other appraisals. In its original submission, company provided different scenario analyses varying stopping rates for which peginterferon beta-1a was still a cost-effective option. **Comments received from clinical expert:**

	• Company used the same rate ratios for RRMS and SPMS phases for mortality: in clinical practice, mortality rate ratio should be higher in people with SPMS than people with RRMS. • Company excluded fatigue, injection site reactions not associated with a disability. This is reasonable given the lack of data, but in clinical practice, these side effects are significant, and in particular, fatigue can be associated with markedly impaired function. **Comments received from clinical organisation:** • Yes, the company has used all available data to model clinical effectiveness. **Comments received from patient organisation:** • Yes, we believe that the company has used all available data to model clinical effectiveness. **Comments received from comparator company:** • Does not agree that joint modelling of 3-month CDP and 6-month CDP data should be undertaken. Regulatory authorities and previous NICE MS appraisals preferred 6-month CDP data because it is less likely to be subject to random bias than 3-month CDP data which may be influenced by residual effect of relapses. Therefore, a consistent relationship between 3-month CDP and 6-month CDP data are not expected and joint modelling would introduce the random bias of 3-month CDP data reducing its usefulness to guide decision making. • RRMS trials may differ in their definition of 3/6-month CDP and should be explicitly addressed in considering whether trials are sufficiently comparable to allow inclusion in a network meta-analysis.
Technical team judgement after engagement	The company has adequately justified the discrepancies in the data included in the clinical effectiveness section in its submission, which have little impact on the cost-effectiveness estimates.

Issue 5 – Treatment waning

Background/description of issue	The **company** assumed that the same waning effects occurred for all treatments in line with some previous NICE technology appraisals (for example, TA527): • Years 1-2: no waning • Years 3-5: 75% of full treatment effect • Year 6 onwards: 50% of full treatment effect The **technical team** agrees that treatment waning should be modelled as in the NICE technology appraisal on beta interferons and glatiramer acetate for treating multiple sclerosis (TA527). However, it is concerned that the waning effects for the newer disease-modifying therapies such as alemtuzumab, dimethyl fumarate, teriflunomide and ocrelizumab may be different.
Questions for engagement	8. Are the waning effects modelled by the company clinically plausible? That is, from years 3 to 5, effect decreases to 75% of full treatment effect and from year 6 onwards, the effect decreases further to 50% of full treatment effect. 9. Is it clinically plausible that the waning effects are the same for all treatments?
Why this issue is important	Applying the same waning effects to all disease-modifying therapies does not affect the relative clinical effectiveness of the different treatments, which may effectively 'cancel out' the impact of treatment waning overall.
Technical team preliminary judgement and rationale	It is likely that the waning effects of peginterferon beta-1a may be different to newer disease-modifying therapies such as alemtuzumab and ocrelizumab. The company should provide alternative scenario analyses of waning specific to individual treatments based on available evidence, to explore how much impact this might have.
Summary of comments	**Comments received from company:** • Current waning assumptions in the economic model are arbitrary because of little published evidence on treatment waning for disease-modifying therapies. Consistent with previous NICE appraisals, the same step-change in hazard ratio for disability progression across all comparators has been applied. Peginterferon beta-1a may be associated with less treatment waning than interferon beta-1a and interferon beta-1b.

	Comments received from clinical expert: • In clinical practice, treatment decisions are based on failure (further relapses or progression to SPMS). • With regard to timescales for diminishing potential treatment effects, in clinical practice, the clearest indicator is the average time a person with MS develops SPMS which usually occurs over 10 years of clinical onset of MS. • In the absence of a specific reason (for example, treatment neutralising antibodies in interferons), at a group level, it is reasonable to assume that underlying relapse rate declines with disease duration and age (and so the potential for treatment efficacy wanes) in the same way for all treatments. **Comments received from clinical organisation:** • The modelled waning effects are clinically plausible but likely overestimated for peginterferon beta-1a because its efficacy is likely to be below the levels quoted although it is well tolerated and has less than 1% level of antibody formation. • Waning effects are partially dependent on antibody formation which is different for various interferons. **Comments received from patient organisations:** • It is not clinically plausible that waning effects are the same for all treatments because different classes of drugs have different chemical structures and mechanisms of action. • It is unclear whether there is any evidence to support any waning effect. **Comments received from comparator company:** • In TA527, waning was assumed from 10 years only (at 50%). • Waning assumptions are based on appraisals (TA320) conducted in 2014 which were based on assumptions and not evidence. • In the recent appraisal of ocrelizumab (TA533), the committee considered that a separate waning effect should not be modelled because all-cause stopping rate is a proxy for any

	treatment waning as in clinical practice patients would not continue an ineffective therapy and will discontinue and switch to an alternative disease modifying therapy. • It is not plausible to include waning in the model as arbitrary waning assumptions would introduce double counting with all-cause stopping rates which include stopping because of lack of efficacy. • Waning assumptions are inherently arbitrary and do not reflect clinical reality of switching treatments due to lack of efficacy. Long-term differences in effectiveness between treatments should be captured through evidence-based modelling of time-dependent stopping rates that do not vary by disease modifying therapies. The practical effect of assuming differential waning for disease modifying therapies will be to bias appraisals against new products that have shorter long-term follow up data than more established comparators.
Technical team judgement after engagement	It is likely that the waning effects of peginterferon beta-1a may be different to newer disease-modifying therapies such as alemtuzumab and ocrelizumab. However, in the absence of supporting evidence, the same waning effects should be applied to all disease modifying therapies.

Issue 6 – Stopping treatment

Background/description of issue

The **company** applied a probability of stopping treatment for any reason in its base case analysis (left column below). It used the annualised stopping rates from 18 trials and weighted these based on sample size to derive the risk of stopping treatment for any reason for each disease-modifying therapy.

Treatment	Annual probability of stopping treatment for any reason	
	Weighted by sample size (company base case)	Weighted by person time
Peginterferon beta-1a	15.6%	15.6%
Avonex (interferon beta-1a)	**7.9%**	**8.3%**
Rebif 22 mcg (interferon beta-1a)	6%	6%
Rebif 44 mcg (interferon beta-1a)	**10.5%**	**9.7%**
Extavia (interferon beta-1b)	**6.9%**	**7.5%**

	Copaxone 20 mg (glatiramer acetate)	**11%**	**8.1%**
	Copaxone 40 mg (glatiramer acetate)	8.9%	8.9%
	Generic glatiramer acetate 20 mg	**11%**	**8.1%**
	Generic glatiramer acetate 40 mg	8.9%	8.9%
	Teriflunomide	**18.6%**	**18.5%**
	Dimethyl fumarate	18%	18%
	Alemtuzumab	2.6%	2.6%
	Ocrelizumab	6.7%	6.7%

The **ERG** considered that deriving the stopping risk weighted by person time (right column above) may be more appropriate than using the trial sample size. It also had concerns that an annualised stopping rate would not capture changes over time, for example, early higher stopping rates because of tolerability or adverse effects and later higher stopping rates because of progression to secondary progressive or inactive multiple sclerosis (ERG report, page 22). In addition, it considered that the data from trials may not accurately reflect stopping treatment that would have been observed in a real-world setting over a longer time horizon (ERG report, page 147). Therefore, the ERG considered it more appropriate to use estimates from real life clinical studies, such as the UK MS Risk Sharing Scheme. In its base case, the ERG used a 5% stopping rate that was applied in the NICE multiple technology appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis (TA527) for all treatments. It acknowledged that the Risk Sharing Scheme did not include some of the newer disease-modifying therapies but noted the paucity of real-life studies following up people on newer treatments (ERG report, page 19).

Questions for engagement	10. Is it clinically plausible to apply the same probability of stopping treatment for any reason to: a) all disease-modifying therapies? b) all years, that is at the start of treatment and after many years on treatment? 11. Are the annual probabilities of stopping treatment for any reason for the different disease modifying therapies in the table above clinically plausible? If so, which values are most plausible – the company's base case weighted by sample size or the alternative values weighted by person time?

Why this issue is important	Probability of stopping treatment for any reason should reflect what would normally happen in clinical practice as closely as possible. Otherwise the length of time for which treatment is taken may not be accurate, which may affect the costs and effectiveness of treatment.
Technical team preliminary judgement and rationale	The 5% stopping rate used by the ERG is based on the UK MS Risk Sharing Scheme that only included beta-interferons and glatiramer acetate. It is unclear whether the same probability of stopping treatment for any reason should apply to newer disease-modifying therapies and for all years. The company should provide a scenario analysis altering the stopping rates for individual treatments based on available evidence.
Summary of comments	**Comments received from company:** • Company prefers stopping rates from pivotal trials for each disease modifying therapy because of significant differences between treatments with respect to safety and adverse event profile. A scenario analysis using the same probability of stopping for all therapies (5%) consistent with previous appraisals show that peginterferon beta-1a remains a cost-effective option. **Comments received from clinical expert:** • In the absence of evidence, it is not plausible to apply the same probability of stopping treatment for all therapies because side effects differ substantially and some may be time-dependent. • Probability of stopping treatment will be relatively high initially because of side effects but because of the disease progression to SPMS, probability of stopping treatment after several years will increase again. **Comments received from clinical organisation:** • It is not plausible to apply the same probability of stopping treatment because different treatments have different efficacies and tolerances and some therapies (alemtuzumab and cladribine) are time-limited (18 to 24 months). • The probabilities of stopping treatment in the table are plausible but this is an area of uncertainty.

	Comments received from patient organisations: • It is not clinically plausible to apply the same probability of stopping treatment because different disease modifying therapies are different classes of drugs, are administered differently and at different times. **Comments received from comparator company:** • It is not clinically plausible to model stopping rates being the same over time for all disease modifying therapies. Alemtuzumab cannot be meaningfully stopped after 2 years as it is no longer taken but it is not expected to be efficacious indefinitely as it is not curative. • Stopping rates are unlikely to be constant over time with early stopping driven by intolerance and later stopping reflecting lack of efficacy. In appraisal on daclizumab (TA441 now withdrawn), the committee preferred a model with separate rates for Years 1, 2 and 3+.
Technical team judgement after engagement	It is clinically more plausible that individual disease modifying therapies would have specific stopping rates, which will likely vary over time.

Issue 7 – Utility values

Background/description of issue	In its base case analysis, the **company** used the utility values from Orme et al. (2007) for consistency with previous technology appraisals. It also provided utility values from a more recent study, Thompson et al. (2017), although these were not used in any company analyses. The **ERG** provided a scenario analysis using Thompson et al. (2017). This study collected resource use, cost and health-related quality of life (EQ-5D) data in a cross-sectional retrospective study of 779 people living in the UK with multiple sclerosis. The ERG highlighted that this study includes information collected from people receiving treatment with more recent disease-modifying therapies, but that the participants were older than those in the Orme study and had fewer people. On the whole, the utility values in each health state are similar. However there are some health states where the differences are more pronounced, for example, Expanded Disability Status Scale (EDSS)

	7 has lower utility values in Orme et al., suggesting that people with more severe disease would accrue less utility than if using Thompson et al.

EDSS	Orme et al. (2007)				Thompson et al. (2017) – difference compared to Orme et al.			
	No relapse		Relapse		No relapse		Relapse	
	RRMS	SPMS	RRMS	SPMS	RRMS	SPMS	RRMS	SPMS
0	0.870	0.825	0.799	0.754	**0.028**	**0.028**	**0.028**	**0.028**
1-1.5	0.799	0.754	0.728	0.683	**-0.012**	**-0.012**	**-0.012**	**-0.012**
2-2.5	0.705	0.660	0.634	0.589	**-0.01**	**-0.01**	**-0.01**	**-0.01**
3-3.5	0.574	0.529	0.503	0.458	**-0.001**	**-0.001**	**-0.001**	**-0.001**
4-4.5	0.610	0.565	0.539	0.494	**-0.005**	**-0.005**	**-0.005**	**-0.005**
5-5.5	0.518	0.473	0.447	0.402	**0.051**	**0.051**	**0.051**	**0.051**
6-6.5	0.460	0.415	0.389	0.344	**-0.004**	**-0.004**	**-0.004**	**-0.004**
7-7.5	0.297	0.252	0.226	0.181	**0.076**	**0.076**	**0.076**	**0.076**
8-8.5	-0.049	-0.094	-0.120	-0.165	**0.206**	**0.206**	**0.206**	**0.206**
9-9.5	-0.195	-0.240	-0.266	-0.311	**0.085**	**0.085**	**0.085**	**0.085**

Questions for engagement	12. Which utility value data set, Orme et al. (2007) or Thompson et al. (2017), is more plausible for patients likely to have peginterferon beta-1a?
Why this issue is important	Orme et al. (2007), used in the company base case, is a decade older than Thompson et al (2017), therefore the associated utility values in Orme may be out of date. The choice of source of utility values may have a large impact on cost-effectiveness results.
Technical team preliminary judgement and rationale	Utility values are broadly similar between the 2 studies, and using Orme et al. is consistent with previous appraisals. Using Orme et al. in the base case is reasonable, however the company should explore the impact of using the utility values from Thompson et al.
Summary of comments	**Comments received from company:** • Thompson et al (2017) used the same data from the MS Survey in 2006 as Orme et al (2007). Orme has a larger sample size (n=2,048) across all MS types (RRMS, PPMS, SPMS) whereas Thompson's paper is restricted to a smaller sample of 779 people. Company considers utility data from Orme is more plausible and consistent with previous

	appraisals. A scenario analysis using Thompson study showed that peginterferon beta-1a remains a cost-effective option. **Comments received from clinical expert:** • Just over 30% of patients in the cohorts included in Orme and Thompson had RRMS and the rest had progressive MS; 25% have primary progressive MS and would not be prescribed interferons. Neither cohorts are representative of patients likely to start interferons, although a subset (patients with RRMS and lower EDSS scores) will be more representative. • From a clinical perspective, there have been substantial changes in referral patterns and increasing treatment options, both of which may affect care cost estimates, and so it seems logical to use more recently acquired data. **Comments received from clinical organisation:** • On balance, Thompson et al is the preferred study for utility data. **Comments received from patient organisation:** • Orme has been the standard for previous appraisals so it would be more consistent to follow previous practice. **Comments received from comparator company:** • The sample size in Orme is 2.5 times larger than Thompson. Orme has been used in many previous MS appraisals allowing for consistency in decision making. • There are issues regarding face validity of the higher utility values for patients in EDSS 7 health state (people who have become wheelchair bound) and EDSS 8 health state (people who have become bed-ridden for life) reported by Thompson. • Orme also provides utilities for SPMS and relapse, whereas Thompson does not. The ERG applies Thompson data and continues to apply parts of the Orme regression analysis directly to the Thompson data which may not be valid.

Technical team judgement after engagement	Utility values are broadly similar between the 2 studies, and using Orme et al. is consistent with previous appraisals.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER^ vs alemtuzumab (all at list price**)	Change from base case
Company base case	**–**	**£1,155***	**–**
Mortality rates: ERG's interpolated disease-specific relative risk from Pokorski et al. (1997)	Previous technology appraisals (for example, TA527) highlighted that the standardised mortality ratios from Pokorski et al. overestimated mortality, especially in the lower EDSS health states. The interpolated values better reflect the increased risk of mortality compared to the general population as EDSS levels increase.	£2,019*	+£864
Carer utility decrements: ERG's values from Gani et al. (2008)	Values from Gani et al. (2008) provide more plausible utility decrements, that is, utility decrements increase as EDSS levels rise.	£1,149*	-£6
RRMS relapse frequency: ERG's values from NICE multiple technology appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis (TA527)	The values reported in TA527 based on the British Columbia cohort provide more plausible changes in annual relapse rates because they decrease as EDSS levels increase.	£1,284*	+£129
SPMS relapse frequency: ERG's values from NICE multiple technology appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis (TA527)	The values reported in TA527 provide more plausible changes in annual relapse rates because they decrease as EDSS levels increase and they are less than the relapse rates for people with RRMS.	£1,297*	+£142
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	Dominated^	-
^ICERs are costs saved per QALY lost.			

Alteration	Technical team rationale	ICER^ vs alemtuzumab (all at list price**)	Change from base case
*Peginterferon beta-1a dominates all other comparators. **All incremental cost-effectiveness ratios (ICERs) are reported at list price. This is because several comparators have confidential discounts. The ICERs are therefore currently confidential to protect these discounts. ***Alemtuzumab dominates all other comparators. Please note that alemtuzumab is currently undergoing a safety review by the EMA, please see Issue 1 p.13 above for more details. There are patient access schemes for interferon beta-1a (Avonex, Rebif), interferon beta-1b (Extavia), glatiramer acetate (Copaxone), dimethyl fumarate (Tecfidera), teriflunomide and ocrelizumab.			

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
The model assumes that people do not receive other disease-modifying therapies when they stop treatment. Once treatment is stopped, people do not have any residual benefit from treatment and follow the British Columbia natural history cohort.	The model should generally try to accurately map out the patient journey through the treatment pathway, for a lifetime time horizon. There are several treatments available for people with MS from second line onwards, but these have not been captured in the model. Instead, the British Columbia natural history cohort has been used a proxy, and this does not reflect the range of treatments which are available second line and onwards for MS. This may influence cost-effectiveness results.	Unknown, but this is in line with the approach taken in previous NICE technology appraisals on relapsing-remitting multiple sclerosis.
The ERG noted that more patients in the peginterferon beta-1a arm (15%) stopped participating in ADVANCE than in the placebo arm (9%) at 1 year. However, because the company had not provided demographic data of patients who stopped participating in the trial, the ERG was not able to determine whether these patients were different from those who had completed the trial.	The results obtained in ADVANCE could potentially be biased.	Unknown.

Table 3: Other issues for information

Issue	Comments
Stopping rules	In line with TA527 and TA533, the company applied the following stopping rule in its model for all disease-modifying therapies: stop treatment upon progressing to EDSS ≥7 and/or progressing to secondary progressive multiple sclerosis.
Adverse events	For its base case analysis, the company included the disutility of serious and non-serious adverse events and the costs related to managing these events.
Innovation	The technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company and consultees.

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