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Dimethyl fumarate for the treatment of adult patients with relapsing remitting multiple sclerosis

Submitted by Biogen Idec Ltd.

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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Abbreviations

9-HPT	9-hole peg test
ACB	Atrioventricular conduction block
ACTH	Adrenocorticotrophic hormone
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ARR	Annualised relapse rate
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CSR	Clinical study report
CT	Computed tomography
DMT	Disease modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOD	Every other day
EQ-5D	European Quality of Life 5 dimensions
GA	Glatiramer acetate
GCP	Good clinical practice
GLMM	Generalised linear mixed model
GP	General Practitioner
HARRMS	Highly active relapsing-remitting multiple sclerosis
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HRQL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
Ig	Immunoglobulin
IM	Intramuscular
INEC	Independent neurology examination committee
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system

LOCF	Last observation carried forward
MCS	Mental component score
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSM	Multi-state Markov
MTC	Mixed treatment comparison
MTR	Magnetization transfer ratio
NA	Not applicable/available
NABT	Normal appearing brain tissue
NHS	National Health Service
NOCB	Next observation carried backwards
OD	Once daily
OM	Once monthly
OR	Odds ratio
OW	Once weekly
PAS	Patient Access Scheme
PASAT-3	Paced audio serial addition test 3
PCS	Physical component score
PPMS	Primary-progressive multiple sclerosis
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RES	Rapidly evolving severe
RR	Relative risk
RRMS	Relapsing remitting multiple sclerosis
RTI	Respiratory tract infection
SA	Sensitivity analysis
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short-form 36
SMC	Scottish Medicines Consortium
SOC	System organ class
SPC	Summary of product characteristics

SPMS	Secondary-progressive multiple sclerosis
SR	Systematic review
SSP	Statutory sick pay
SUR	Seemingly unrelated regression
T25FW	Timed 25-foot walk test
TID	Three times daily
TIW	Three times weekly
UTI	Urinary tract infection
VAS	Visual analogue scale
WMD	Weighted mean difference

Executive summary

Biogen Idec request that dimethyl fumarate is accepted for use in the NHS in England and Wales within its full licenced indication for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS). An unmet need currently exists amongst RRMS patients for an effective, orally administered first-line treatment that reduces the frequency of relapses and slows progression of RRMS disability without significant side effects. A number of treatment options are currently available for RRMS patients; however, patients are often required to switch between these treatments in order to achieve a balance of efficacy and tolerability. All adult RRMS patients are eligible for dimethyl fumarate, including naïve patients (newly diagnosed or those who have not received treatment), those who have failed previous treatment (for example discontinued due to lack of efficacy or tolerability), and patients who are sub-optimally treated or dissatisfied with their current therapy.

Background

Multiple sclerosis (MS) is a chronic, progressive, lifelong disease with no cure. It results in the accumulation of irreversible disability and is the leading cause of non-traumatic CNS morbidity and mortality in young adults. The majority of patients (85%) experience RRMS during their initial disease course, which is characterised by episodes of neurological deterioration (relapses), separated by periods of prolonged stability (remission). These patients can experience significant physical and mental impairment during relapses which may not be recovered during remission. As a result, approximately 42% of patients experience a residual deficit of ≥0.5 EDSS points after a relapse.

The exact pathogenesis of MS is unknown; however, it has been suggested that both genetic and environmental factors play a role. The prevalence of MS in England and Wales is 74–140 per 100,000.

There is no cure for MS. The goal of treatment is to decrease the frequency and severity of relapses, diminish the accumulation of lesions as observed on brain and spinal MRIs, slow the accumulation of physical disability, and maintain or improve patient quality of life (QoL).

Disease Modifying Therapies (DMTs) currently licensed for the treatment of RRMS in England and Wales are:

- Avonex® – Intramuscular (IM) interferon (IFN) β-1a 30 µg once weekly (OW)
- Copaxone® – Subcutaneous (SC) glatiramer acetate (GA) 20 mg once daily (OD)
- Extavia/Betaferon® – SC IFNβ-1b 250 µg every other day (EOD)
- Rebif® – SC IFNβ-1a 22 µg or 44 µg three times weekly (TIW)
- Gilenya® – Oral fingolimod 0.5 mg OD
- Tysabri® – Intravenous natalizumab 300 mg once monthly (OM)

Despite the availability of a range of DMTs, there are significant needs that are not fully met by current treatments. The majority of DMTs for RRMS patients require self-injection, which can be burdensome for many patients and in itself could affect compliance. Injection site reactions, permanent skin alteration due to lipoatrophy, injection fatigue and injection anxiety have been shown to impact adherence to

treatment. Injectable DMTs are associated with tolerability issues such as persistent flu-like symptoms and injection site reactions, which commonly lead to discontinuation.

Dimethyl fumarate

Dimethyl fumarate is a novel RRMS treatment which fulfils the unmet need for an effective, convenient and well tolerated oral therapy which can be used first line (no oral therapy is currently licensed for first line use). Dimethyl fumarate consequently represents a step-change in how RRMS is managed, and can therefore be considered innovative under the terms of the Kennedy report. While the mechanisms of action of dimethyl fumarate are not fully known, it is thought that activation of the Nrf2 transcriptional pathway plays a significant role. The Nrf2 pathway is the primary cellular defence system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes. Dimethyl fumarate is the first RRMS treatment to exhibit pharmacological activity on the Nrf2 pathway, and consequently has an innovative and unique mechanism of action.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion on 22nd March 2013, recommending the granting of a marketing authorisation for dimethyl fumarate for the treatment of adult patients with RRMS. A final decision on the European Commission ratification of the UK Marketing Authorisation is expected on imminently (A positive CHMP Opinion was received on 22nd March). Dimthyl fumarate is administered twice daily as gastro-resistant hard capsules, costing £343 for the first week starter pack (14 x 120 mg) and £1,373 for the standard 4 week pack, thereafter (56 x 240 mg). Biogen Idec intend to use a Patient Access Scheme that will reduce the price to £ (*Commerical in confidence information removed)* for the first week starter pack (14 x 120 mg) and £ (*Commerical in confidence information removed*) for the standard 4 week pack, thereafter (56 x 240 mg). Details of this scheme have been submitted to the minister for final ratification, and we would ask that NICE use the PAS price in this assessment.

Efficacy and safety

The efficacy and safety of dimethyl fumarate have been demonstrated in two large, double-blind, placebo-controlled, international, randomised controlled trials (RCTs) DEFINE and CONFIRM. Results from DEFINE and CONFIRM demonstrated that dimethyl fumarate:

- Significantly reduced frequency and risk of relapses, compared with placebo
    - Proportion of patients relapsing at 2 years significantly reduced, by 49% ($p<0.0001$) and 34% ($p=0.002$), respectively
    - Annualised relapse rate (ARR) significantly reduced at 2 years, by 53% ($p<0.0001$) and 44% ($p<0.0001$), respectively
- Significantly reduced risk of sustained disability progression, compared with placebo
    - In DEFINE, the risk of confirmed expanded disability status scale (EDSS) disability progression sustained for 3 months at 2 years reduced by 38% ($p=0.005$).

    - Disability progression was reduced by 21% in CONFIRM, although this was not statistically significant (p=0.25)
- Significantly reduced inflammatory disease (as measured by MRI), compared with placebo
    - 85% (p<0.0001) and 71% (p<0.0001) fewer T2 lesions, respectively, at 2 years
    - 72% (p<0.0001) and 57% (p<0.0001) fewer T1 lesions at 2 years, respectively
    - 90% (p<0.0001) and 74% (p<0.0001) fewer Gd+ lesions at 2 years, respectively
- Significant improvements in quality of life, compared with placebo
    - Significant improvements in global well-being visual analogue scale (VAS) after 2 years, p=0.0031 and p=0.0003, respectively
    - Significant changes in Short-form 36 (SF-36) from baseline
        - In physical functioning (p=0.0011) and (p=0.0250)
        - Role-physical (p=0.0001) and (p=0.0348)
        - General health (p=0.0006) and (p=0.0243)
    - Significant improvement in European Quality of Life 5 dimensions (EQ-5D) VAS score from baseline (p=0.0008) in the DEFINE study

The safety profile of dimethyl fumarate has been shown to be favourable, with no difference in the proportion of serious adverse events compared with placebo (DEFINE - 17% vs 21%; CONFIRM - 18% vs 22%). The most frequently reported adverse events were flushing and gastrointestinal side effects. Less than 3% of patients discontinued dimethyl fumarate due to flushing and 4% due to gastrointestinal tolerability issues.

Indirect comparisons also demonstrate that dimethyl fumarate is more effective than current first line injectable treatments. Dimethyl fumarate was found to be statistically significantly more effective than all IFNs and GA for ARR and proportion of patients relapsed at 24 months in a mixed treatment comparison. Dimethyl fumarate was not significantly different to fingolimod for the majority of outcomes, with the exception of proportion of patients relapsed at 24 months. Natalizumab was more effective than dimethyl fumarate for ARR, ARR requiring steroids, and proportion of patients relapsed at 24 months.

Health economics

An economic model has been developed to assess the cost-effectiveness of dimethyl fumarate, compared with the other available treatments for RRMS in the overall patient population. No subgroup analysis in other patient populations was performed due to a lack of data. This model demonstrated dimethyl fumarate to be a cost effective use of NHS resources. The base case analysis, with the list price for dimethyl fumarate resulted in incremental cost effectiveness ratios (ICERs) in the range £106,127 to £159,295 per QALY. However, Biogen Idec will provide dimethyl fumarate through a simple discount patient access scheme (PAS) which reduces the range of ICERs such that dimethyl

fumarate varies from dominance to £19,057 per QALY. The ICER for dimethyl fumarate vs natalizumab was £534,047; however this falls in the south-west quadrant of the cost effectiveness plane. This indicates that, while dimethyl fumarate may result in fewer QALYs (0.08 fewer), it incurred lower costs (£45,998 less expensive). Details of the PAS have been submitted to the minister for final ratification, and we would ask that NICE use the PAS price in this assessment.

The base case analysis with the PAS cost for dimethyl fumarate resulted in dimethyl fumarate dominating Gilenya® (fingolimod), Avonex® (IM IFNβ-1a 30 µg), Betaferon®/Extavia® (SC IFNβ-1b 250 µg), and Rebif® 44 µg (SC IFNβ-1a 44 µg), and producing ICERs below £20,000/QALY (quality adjusted life year) when compared with Copaxone® (glatiramer acetate) and Rebif® 22 µg (SC IFNβ-1a 22 µg) (Table 1). This was verified in scenario analysis and univariate sensitivity analysis, where dimethyl fumarate dominated the comparators in the majority of cases. As fingolimod is provided through a PAS (for which the price was not available) a scenario analysis was performed in which the cost of fingolimod was reduced by 5–95% from the list price in increments of 5%. Dimethy fumarate dominated fingolimod at discounts of 5-55%. Assuming a 60% discount of fingolimod generated an ICER of £3,951 per QALY. In probabilistic sensitivity analysis it was determined that the probability of dimethyl fumarate being cost effective, versus all comparators, was ≥70% at a willingness to pay threshold of £20,000/QALY (with the exception of glatiramer acetate).

Table 1: Base-case cost-effectiveness results (PAS price) ***(Commerical in confidence information removed)***

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SC IFNβ-1a 22 µg (Rebif® 22 µg)							£18,581
Glatiramer acetate (Copaxone®)							£19,057
Dimethyl fumarate (Tecfidera®)							-
IM IFNβ-1a 30 µg (Avonex®)							**Dominant**
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)							**Dominant**
SC IFNβ-1a 44 µg (Rebif® 44 µg)							**Dominant**
Fingolimod (Gilenya®)							**Dominant**
Natalizumab (Tysabri®)							£534,047

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

From a budget impact perspective (using prevalence and incidence data), adopting dimethyl fumarate would result in an additional cost to the NHS in England and Wales of £29,669,191 over 5 years based on the list price, and £4,570,619 based on the PAS price.

Conclusion

Dimethyl fumarate is a valuable additional therapy which fulfils an unmet need for a first-line oral treatment option for all patients with RRMS. There are no first-line oral treatment options currently licensed in the UK; dimethyl fumarate therefore fulfils the Kennedy criteria for innovation, representing a potential step-change in how RRMS is treated. As demonstrated by two RCTs, dimethyl fumarate is effective, reducing the frequency of relapses and slowing progression of RRMS disability without significant side effects. Economic analysis demonstrates the adoption of dimethyl fumarate with the NHS is a cost effective use of NHS resources.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Generic name: Dimethyl fumarate

Brand name: Tecfidera®

Approved name: Tecfidera® 120 mg or 240 mg hard capsules

Therapeutic class: Other nervous-system drugs ATC code: N07XX09

1.2 What is the principal mechanism of action of the technology?

Dimethyl fumarate pharmacodynamic responses appear to be exerted through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is the primary cellular defence system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes. Dimethyl fumarate reduces inflammatory responses in both peripheral and central cells, and promotes cytoprotection of central nervous system cells against toxic oxidative damage, demonstrating effects on pathways known to exacerbate multiple sclerosis pathology. Dimethyl fumarate has also been shown to up regulate Nrf2-dependent antioxidant genes in patients, confirming clinical pharmacodynamic activity in humans. However, the mechanism by which dimethyl fumarate exerts therapeutic effects in MS is not fully understood.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On 22nd March 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion, recommending the granting of a marketing authorisation for dimethyl fumarate for the treatment of adult patients with relapsing remitting multiple sclerosis. A final decision on the European Commission ratification of the Marketing Authorisation is expected immanently.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

During the assessment, the main issues discussed were the proposal for an indication for treatment in a broad RRMS disease population, impact of dimethyl fumarate on disability progression and potential monitoring requirements, which have been resolved and are reflected in the draft SmPC and in the Risk Management Plan. The draft EPAR is included in the reference pack, and a final version will be provided as soon as it

becomes available. There are not expected to be any special conditions attached to the marketing authorisation.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The anticipated indication for dimethyl fumarate in the UK is “For the treatment of adult patients with relapsing remitting multiple sclerosis.”

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Completed studies are listed below:

DEFINE: A randomised, multicentre, double-blind, placebo-controlled, Phase III trial in RRMS patients (clinicaltrials.gov identifier NCT00420212). A total of 1,234 patients were included using proportion of relapsing patients at 2 years as the primary efficacy outcome. Multiple secondary and tertiary outcomes were included.

CONFIRM: A randomised, multicentre, double-blind, placebo-controlled, active-reference, Phase III trial in RRMS patients (clinicaltrials.gov identifier NCT00451451). A total of 1,417 patients were included using annualised rate of relapses at 2 years as the primary efficacy outcome. Multiple secondary and tertiary outcomes were included. Glatiramer acetate was included as a reference comparator, although this study was not statistically powered to detect a difference between dimethyl fumarate and glatiramer acetate.

Ongoing studies are listed below. However, neither of these will report within the 12 month time frame noted above.

Study 201: A Phase II IFN/GA 6 month add-on safety/MRI study with 108 patients.

Study 303: ENDORSE is the 5 year open-label extension study for DEFINE and CONFIRM, with 1,733 patients. Interim safety analyses are expected to be available on an annual basis.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of commercial availability in the UK is July 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Dimethyl fumarate was approved for use in the USA by the Food and Drug Administration on 27th March 2013 and in Canada by Health Canada on 3rd April 2013.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A technology appraisal for dimethyl fumarate has also been submitted to the Scottish Medicines Consortium (SMC). This was submitted on the 28th March 2013 and it is anticipated that a decision will be posted on the SMC website on 12th August 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	Gastro-resistant hard capsules
Acquisition cost (excluding VAT)	First week starter pack: 14 x 120 mg capsules in blister packs (£343) Standard 4 week pack: 56 x 240 mg capsules in blister packs (£1,373) A patient access scheme has been submitted to the DH PAS price First week starter pack: 14 x 120 mg capsules in blister packs £ *(Commerical in confidence information removed)* Standard 4 week pack: 56 x 240 mg capsules in blister packs £ *(Commerical in confidence information removed)*
Method of administration	Oral
Doses	120 mg or 240 mg per capsule
Dosing frequency	Twice daily
Average length of a course of treatment	Treatment should be continued as long as clinical benefit is observed, or until unacceptable tolerability issues become apparent
Average cost of a course of treatment	Treatment duration is likely to vary widely depending on each patient's disease progression and treatment preferences. The annual cost of treatment is £17,910 at list price, £*(Commerical in confidence information removed)* at PAS price (based on 730.5 doses per year)
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed. This dose reduction will not result in any change in cost

Abbreviations: PAS, patient access scheme; VAT, value added tax.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

NA

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigations are required.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Current first line treatments for RRMS require two to three neurologist visits, liver function tests, and full blood cell counts each year (Table 3). In addition to these, it is recommended that patients receiving dimethyl fumarate undergo renal function assessments (e.g. creatinine, blood urea nitrogen and urinalysis) prior to treatment initiation, after 3 and 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated (1). This additional test for renal function would be expected to be performed during routine examinations and would therefore incur no additional visits and minimal additional costs.

Table 3: Monitoring requirements for interferon and dimethyl fumarate

	All interferons	Glatiramer acetate	Dimethyl fumarate
Year 1	3 Neurologist visits 3 full blood counts 3 liver function tests	2 Neurologist visits 2 full blood counts 2 liver function tests	3 Neurologist visits 3 full blood counts 3 liver function tests 3 renal function tests
Subsequent years	1 Neurologist visit 2 full blood counts 2 liver function tests	1 Neurologist visit	1 Neurologist visit 2 full blood counts 2 liver function tests 2 renal function tests

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There are no specific therapies that need to be administered alongside dimethyl fumarate. Co-administration of acetylsalicylic acid has been found to reduce the occurrence and severity of flushing in healthy volunteers, and may consequently be of benefit to some patients (2).

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Multiple sclerosis (MS) is a progressive, chronic, disabling disease which attacks the central nervous system (CNS). MS is the leading cause of non-traumatic CNS morbidity and mortality in young and middle-aged adults, with a median age of onset of 30 years, and is two to three times more common in women than in men (3, 4).

MS is an autoimmune disease directed against myelin, the fatty sheath surrounding and insulating nerve fibres, resulting in inflammation and tissue damage (5). This impairs transmission of electrical impulses between the brain, spinal cord and other parts of the body, and causes the primary symptoms of MS, such as weakness, sensory loss, visual loss, cognitive dysfunction, and problems with memory and concentration (6).

In addition to inflammation, oxidative stress can also cause ongoing tissue damage in the CNS (7). High levels of reactive oxygen species such as superoxide have been shown to be present in spinal fluid from MS patients (7), which can overwhelm antioxidant mechanisms leading to tissue damage and cellular injury (7, 8). The CNS is equipped with an endogenous antioxidant defence mechanism, which is regulated by nuclear factor erythroid 2-related factor 2 (Nrf2) (8). Therapeutics designed to enhance the endogenous antioxidant potential could therefore have clinical value in MS.

The exact pathogenesis of MS is currently unknown; however, it has been suggested that both genetic and environmental factors play a role (9, 10). Smoking has been found to be a risk factor in developing MS (9, 11), and MS prevalence increases with distance from the equator, suggesting a role for ultraviolet radiation or vitamin D (9). Countries in the northern part of Europe therefore have higher rates of MS, and the prevalence in England and Wales has been estimated at 74–140 per 100,000 of population (12).

The most common form of MS is relapsing remitting (RRMS), which forms the initial disease course in 85% of all MS patients (13). RRMS is characterised by unpredictable episodes of neurological deterioration (relapses), separated by periods of prolonged stability (remission). Most patients with RRMS will eventually enter a period of steady progression of neurological damage with or without relapses, known as secondary-progressive MS (SPMS). Primary-progressive MS (PPMS) is the least common form of the disease (15%), and is characterised by gradual disability progression from onset with no discernible relapses or remissions (13).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

- The prevalence of MS in England and Wales has been estimated at 74–140 per 100,000 of population (12).

- Based on the 2011 census, the adult population of England and Wales is 43,486,200 (14); using the upper estimate of prevalence, the estimated number of MS cases is therefore 60,881.
- RRMS comprises 85% of all MS cases (13); using the upper estimate of prevalence, the total number of adults with RRMS is therefore estimated at 51,749.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Mortality has been shown to be significantly higher in patients with MS than in the general population (15-17), and increases with higher Expanded Disability Status Scale scores (16). No specific data were available on life expectancy in MS patients in England and Wales; however, standardised mortality rates from 1.4–2.89 have been reported in the USA, Austria, Canada, and Denmark, with life expectancy reduced by 5–10 years (15, 18).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

- **Beta interferon and glatiramer acetate for the treatment of multiple sclerosis, TA32 (2002):** Beta interferon and glatiramer acetate were not recommended for use in NHS England and Wales (19). Following this, beta interferon and glatiramer acetate were approved for use under the Risk Sharing Scheme by the Department of Health.
- **Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis, TA127 (2007):** Natalizumab was recommended for the treatment of patients with rapidly evolving severe (RES) RRMS. RES disease was defined as ≥2 disabling relapses in 1 year, and ≥1 Gd+ lesion on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI (20).
- **Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis, TA254 (2012):** Fingolimod was recommended for the treatment of patients with highly active disease despite treatment with a beta-interferon, provided the manufacturer provides fingolimod at a discount agreed as part of a patient access scheme (21).

In addition to these specific guidelines, NICE has also issued CG8: Management of multiple sclerosis in primary and secondary care in 2003, prior to the introduction of natalizumab and fingolimod (22). This document is currently undergoing review, with revised guidelines expected in 2014.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There is currently no well-defined treatment pathway for patients with MS. At present the majority of patients will initiate treatment with IFN or GA, while a minority of patients may initiate with natalizumab as a result of RES disease. Patients may switch between IFN and GA as a result of disease activity or tolerability issues, or their physician may decide to escalate them to fingolimod or natalizumab if their disease profile meets the criteria set out in the relevant NICE guidelines (20, 21). Patients may also switch from fingolimod or natalizumab to IFN or GA as a result of safety and/or tolerability issues. There is consequently no set pathway for treatment, and treatment choices are based on efficacy and safety concerns, as well as patient preference.

Dimethyl fumarate will be the only first-line oral treatment option for RRMS, and will provide enhanced efficacy, compared with IFN or GA. Dimethyl fumarate will also offer an alternative second-line treatment with fewer safety concerns than natalizumab and fingolimod. Dimethyl fumarate is likely to be used first-line in many patients, and will offer an alternative to injectable therapy for patients currently on IFN or GA or patients unwilling to self-inject. Dimethyl fumarate may also be considered as an alternative escalation option to natalizumab or fingolimod when treatment with IFN or GA is inadequate.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

As there is no well-defined treatment pathway the issues are discussed in the response to Section 2.5.

2.7 Please identify the main comparator(s) and justify their selection.

Based on the product indications (23-28) and the relevant NICE guidelines (19-21), the main comparators for the treatment of RRMS in England and Wales are:

- Avonex® – IM IFNβ-1a 30 µg OW
- Copaxone® – SC glatiramer acetate 20 mg OD
- Extavia/Betaferon® – SC IFNβ-1b 250 µg EOD
- Rebif® – SC IFNβ-1a 22 µg or 44 µg TIW
- Gilenya® – Oral fingolimod 0.5 mg OD
- Tysabri® – Intravenous natalizumab 300 mg OM

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Dimethyl fumarate is associated with few serious adverse events. Patients may experience flushing and gastrointestinal events (i.e. diarrhoea, nausea and abdominal pain) which tend to begin during the first month of treatment and may continue to occur

intermittently throughout treatment with dimethyl fumarate (29, 30). Co-administration of acetylsalicylic acid has been found to reduce the occurrence and severity of flushing in healthy volunteers, and may consequently be of benefit to some patients (2).

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Dimethyl fumarate is administered twice daily as an oral capsule, and will consequently incur no administration costs. Based on the indication, it is expected that patients will require three neurologist visits, three full blood counts, three renal function tests, and three liver function tests in the first year, and one neurologist visit, two full blood counts, two renal function tests and two liver function tests in each subsequent year (1). This results in monitoring costs of £1,780.55 in the first year, and £597.21 in each subsequent year, based on national tariffs and reference costs (31, 32). The same tests are required for IFN, with the exception of renal function tests; however, these can be performed during already required examinations and incur minimal additional costs

2.10 Does the technology require additional infrastructure to be put in place?

It is not anticipated that any additional infrastructure will be required for dimethyl fumarate treatment.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;***

- ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology***

- ***could lead to recommendations that have any adverse impact on people with a particular disability or disabilities***

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Not applicable.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

At present, most patients with RRMS will receive IFN or GA as their first treatment. These therapies provide only around a 30% reduction in relapse rate (33-36), and are associated with adverse events such as injection-site reaction, flu-like symptoms, and depression (33-36). The method of administration also represents a problem with these therapies, with up to 22% of patients afraid to receive injections (37). This can impact upon adherence, with 32% of non-adherent patients receiving IFN or GA citing injection related reasons for not taking their medication (38). Oral therapy for these patients may therefore alleviate anxiety and increase adherence.

Natalizumab and fingolimod offer greater efficacy, compared with IFN and GA; however, they are also associated with adverse events such as progressive multifocal leukoencephalopathy with natalizumab (23), and macular oedema and bradycardia with fingolimod (28). These therapies are restricted by NICE to patients with RES disease (natalizumab (20)) or patients with high disease activity despite treatment with beta-interferon (fingolimod (21)). Dimethyl fumarate has a favourable safety profile and eliminates side effects typically associated with injectable therapies; while flushing and GI events may occur, these are generally mild-to-moderate in severity. It has also been shown in mixed treatment comparison that dimethyl fumarate significantly reduces relapse rate, compared with IFN or GA.

Dimethyl fumurate is formulated as a multi-particulate dosage in which delayed-release microtablets are contained within a capsule. Each micro-tablet is formulated such that the active drug is not released in the stomach, but is rapidly released once the micro-tablet has entered the small intestine. This innovation avoids potential gastric irritation, whilst optimising the delivery of the active pharmacological agent into the bloodstream.

Dimethyl fumarate therefore represents a first-line treatment option with enhanced efficacy in an oral form, which is likely to provide patients with significant long-term benefits. A first-line oral treatment with a favourable safety profile may also in the future allow a change in the overall treatment pathways for RRMS, by facilitating "shared care" agreements and increasing primary care management. The introduction of first-line oral dimethyl fumarate consequently represents the 'step-change' in management of RRMS defined in the Kennedy report as a requirement for a product to be considered innovative (39).

While the mechanisms of action of dimethyl fumarate are not fully known, it is though that activation of the Nrf2 transcriptional pathway plays a significant role. The Nrf2 pathway is the primary cellular defence system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes. Dimethyl fumarate is the first RRMS treatment to exhibit pharmacological activity on the Nrf2 pathway, and consequently has an innovative and unique mechanism of action.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related

benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Patients receiving IFN or GA often experience treatment anxiety as a result of self-injection, and may find their administration schedule burdensome (38, 40). This may impact upon adherence to therapy, and up to 25% of patients receiving IFN or GA are estimated to be non-adherent to therapy (38). Of these patients, 32% cited injection related reasons for non-adherence (38). Providing these patients with an oral treatment option is therefore likely to improve adherence, and may result in improved clinical outcomes.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Adherence in second-line RRMS patients has been examined by Halpern et al (41). No studies have specifically examined the link between adherence and clinical outcomes; however, this has been extensively examined in patients with HIV. These studies concluded that higher adherence was linked to fewer hospitalisations (42, 43), less disease progression (44), and greater virological control (45, 46).

5 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with relapsing-remitting multiple sclerosis	Adult patients (≥18 years old) with relapsing-remitting multiple sclerosis	The indicated population for dimethyl fumarate is patients aged ≥18 years
Intervention	Dimethyl fumarate	As per scope	NA
Comparator(s)	• Beta-interferon • Glatiramer acetate • Natalizumab (for patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon)	As per scope	NA
Outcomes	• 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 of disease activity • Mortality • Adverse effects of treatment • Health-related quality of life	Relapse rate Disability progression MRI outcomes Symptoms of multiple sclerosis Freedom from disease activity Mortality Adverse effects of treatment Health-related quality of life	MRI parameters may be indicative of disease activity in the absence of relapses or disability progression, and are therefore included in the clinical results; however, these are not included in the economic model. Severity of relapse was not evaluated in the pivotal dimethyl fumarate trials, and was therefore not considered in this submission.

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis in the NHS.	As per scope	NA

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Subgroups to be considered	If evidence allows subgroups according to the following will be considered: • Patients with relapsing-remitting multiple sclerosis whose disease has inadequately responded to treatment with disease modifying therapy • Patients with relapsing-remitting multiple sclerosis whose disease is intolerant to treatment with disease modifying therapy • Patients with highly active relapsing-remitting multiple sclerosis • Patients with rapidly evolving severe relapsing-remitting multiple sclerosis	No subgroups considered	Dimethyl fumarate is indicated for all adult patients with RRMS; consequently, no subgroup analysis of patients by disease activity has been performed.
Special considerations, including issues related to equity or equality	NA	NA	NA

Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NA, not applicable.

Section B – Clinical and cost effectiveness

6 Clinical evidence

Summary of evidence

The efficacy of dimethyl fumarate has been demonstrated in two pivotal Phase III studies (DEFINE and CONFIRM). These studies included both BID (twice daily) and TID (three times daily) dosing for dimethyl fumarate. The licensed dose of dimethyl fumarate is BID; the results for dimethyl fumarate TID will therefore be presented, but not discussed in detail.

The DEFINE and CONFIRM studies demonstrate that:

- **Dimethyl fumarate significantly reduces the frequency and risk of MS relapses over 2 years compared with placebo**

  In the DEFINE and CONFIRM studies respectively:

  - The proportion of patients relapsing at 2 years were significantly reduced with dimethyl fumarate BID, corresponding to a 49% (p<0.0001) and 34% (p=0.002) relative reduction in the risk of relapse compared with placebo
  - Dimethyl fumarate BID also significantly reduced the frequency of relapses (ARRs) by 53% (p<0.0001) and 44% (p<0.0001) at 2 years compared with placebo

- **Dimethyl fumarate reduces the risk of sustained disability progression over 2 years compared with placebo**

  In the DEFINE and CONFIRM studies respectively:

  - Dimethyl fumarate BID reduced the risk of confirmed expanded disability status scale (EDSS) disability progression, sustained for 3 months, at 2 years by 38% (p=0.005) and 21% (p=0.25), compared with placebo

  In a pre-specified integrated analysis of DEFINE and CONFIRM dimethyl fumarate BID significantly reduced the risk of confirmed EDSS disability progression by 32% (p=0.0034) compared with placebo

- **Dimethyl fumarate significantly reduces inflammatory disease activity as measured by MRI (magnetic resonance imaging) in patients with RRMS compared with placebo**

  Dimethyl fumarate BID reduced the number of lesions in the DEFINE and CONFIRM studies at 2 years respectively by:

  - 85% (p<0.0001) and 71% (p<0.0001) for T2 lesions compared to those treated with placebo and 72% (p<0.0001) and 57% (p<0.0001) for T1 lesions compared to those treated with placebo
  - Gd+ lesions were also significantly reduced at 2 years with dimethyl fumarate BID by 90% (p<0.0001) and 74% (p<0.0001) compared to placebo

- **Dimethyl fumarate significantly improves the quality of life (general well-being, physical health and functioning and self-reported heath status) of patients with RRMS**

  In the DEFINE and CONFIRM studies respectively:

- Significant results in favour of dimethyl fumarate BID were observed in the change in global well-being VAS (visual analogue scale) from baseline (p=0.0031) and (p=0.0003) compared with placebo
- Significant changes in SF-36 (Short-form 36) from baseline
    - In physical functioning (p=0.0011) and (p=0.0250)
    - Role-physical (p=0.0001) and (p=0.0348)
    - General health (p=0.0006) and (p=0.0243)
- Significant improvement in EQ-5D (European Quality of Life 5 dimensions) VAS score from baseline (p=0.0008) in the DEFINE study

The efficacy of dimethyl fumarate BID is generally consistent across a variety of subgroups defined by baseline disease characteristics, including prior relapse rate, previous treatment status, and lesion type and volume. In particular, efficacy was generally consistent irrespective of patients' previous treatment history. This indicates that dimethyl fumarate is likely to be effective in the subgroups set out in the NICE scope, where patients are likely to have more relapses, higher EDSS scores, and greater previous use of MS treatments.

The relevance of these results to clinical practice is reinforced by the performance of the GA (glatiramer acetate) arm in CONFIRM, where patients had outcomes which were consistent with previous clinical trials of GA (34, 47, 48).

Safety

Dimethyl fumarate demonstrated a favourable safety profile. The results for the relevant BID dose are summarised below:

- The overall incidence of adverse events was similar across dimethyl fumarate and placebo groups (96% vs 95% in DEFINE and 94% vs 92% in CONFIRM)
- The most common adverse events included flushing and gastrointestinal (GI) events. The incidence of these events were highest in the first month and decreased thereafter
    - Vascular disorders – flushing (38% and 31%, vs 5% and 4% for placebo) and hot flush (8% and 5%, vs 2% for placebo) in DEFINE and CONFIRM respectively
    - GI events – abdominal pain upper (10% and 10%, vs 5% and 4% for placebo), nausea (13% and 11%, vs 9% and 8% for placebo) and vomiting (10% and 7%, vs 6% and 4% for placebo), in DEFINE and CONFIRM respectively
    - Most reported adverse events were mild to moderate in severity, transient in nature and manageable
- The incidence of adverse events leading to discontinuations is low with dimethyl fumarate (DEFINE, 16%; CONFIRM, 12%) and comparable with placebo (DEFINE, 13%; CONFIRM, 10%)
- Discontinuations due to flushing or GI problems occurred in 8% and 7% of patients in DEFINE and CONFIRM, respectively (vs 2% and <1% with placebo)
- The incidence of serious adverse events was low with dimethyl fumarate (DEFINE 18%; CONFIRM 17%) and comparable to placebo (DEFINE 21%; CONFIRM 22%)
- Many MS treatments have a detrimental effect on the rate of infections as a result of their mechanism of action; however, dimethyl fumarate is not associated with an increased risk

of serious infections; 2% with dimethyl fumarate in both studies comparable with placebo; 1-2%

- No instances of opportunistic infections were noted with dimethyl fumarate treatment

Decreased white blood cell and lymphocyte counts were observed; however, mean values remained within normal limits.

Statistical analyses: meta-analysis

- Dimethyl fumarate was significantly better than placebo for all efficacy outcomes in the meta-analysis of DEFINE and CONFIRM
- Dimethyl fumarate was significantly better than GA for ARR and rate of relapses requiring steroids in the direct comparison from CONFIRM

Statistical analyses: mixed treatment comparison

In the mixed treatment comparison, dimethyl fumarate was found to be:

- Significantly better than all IFNs, GA, and both doses of teriflunomide for ARR
- Significantly better than IM IFNβ-1a 30 µg, SC IFNβ-1a 22 µg, SC IFNβ-1a 44 µg, IFNβ-1b 250 µg, GA and teriflunomide 7 mg for proportion of patients relapsed at 24 months
- Significantly better than IM IFNβ-1a 30 µg for annualised steroid treated relapse rate and patients remaining relapse free at 24 months
- Significantly better than SC IFNβ-1a 22 µg TIW for annualised steroid treated relapse rate

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.2, appendix 2.

Two systematic reviews (SRs) of the literature were conducted to identify relevant RCT and non-RCT evidence regarding the efficacy and safety of dimethyl fumarate for the treatment of relapsing-remitting MS (RRMS). These were performed in October/November 2012 and we are not aware of any additional relevant publications since this SR. The following section describes the methodology for the RCT and the non-RCT searches. Critical appraisals and descriptions of each relevant RCT and non-RCT are provided as requested in Section 10.3 (Appendix 3) and Section 10.7 (Appendix 7), respectively. Table 4 shows the data sources interrogated.

Table 4: Data sources for systematic review

Database interrogation	Hand searching	
	Conferences	Other data sources
• MEDLINE® • MEDLINE® In-Process • Embase® • CENTRAL	• European Committee for Treatment and Research in Multiple Sclerosis • American Academy of Neurology • American Neurological Association • European Federation of Neurological Societies	• Clinicaltrials.gov • metaRegister of Controlled Trials • Unpublished data from CSRs held by Biogen Idec

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CSR, Clinical study report; Embase, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for MS, clinical trial design, and pharmacological intervention(s) of interest. The search strategy for RCT evidence is provided in Section 10.2 (Appendix 2), and for non-RCT evidence in Section 10.6 (Appendix 6).

6.2 Study selection

6.2.1 *Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.*

Citations identified were initially assessed based on title and abstract. Each citation was screened by two independent reviewers, and any discrepancies were reconciled by a third independent reviewer; this was repeated at each stage of review. Citations that did not match the eligibility criteria were excluded. Eligibility criteria were then applied to full text citations to yield the final data set for inclusion. The final included data set consisted of RCTs for dimethyl fumarate and those for comparator treatments (in addition to teriflunomide, in order to strengthen the placebo arm of the MTC). The full text of these comparator studies was screened and those suitable for indirect comparison were selected. Eligible studies will be described further in Section 6.7. The final data set for the non-RCT SR consisted of clinical studies for dimethyl fumarate only. Inclusion and exclusion selection criteria are shown in Table 5.

Table 5: Eligibility criteria used in search strategy

	Criteria	Rationale
Inclusion criteria	Population • Age: Adults (≥ 18 years) • Gender: Any • Race: Any • Disease: RRMS (including studies recruiting ≥ 80% RRMS population) • Line of therapy: Any	• The patient population has been restricted to match that stated in the decision problem for dimethyl fumarate in the treatment of MS

	Criteria	Rationale
	Intervention • IFN beta-1a (RCT only) • IFN beta-1b (RCT only) • GA (RCT only) • Dimethyl fumarate (RCT and non-RCT) • Fingolimod (RCT only) • Natalizumab (RCT only) • Teriflunomide[†] (RCT only)	• The review included treatments which are used in clinical practice or are being assessed for treatment of RRMS in clinical trials
	Comparator • Any of the included interventions • Placebo • Best supportive care (BSC)[‡]	• These comparators were selected to potentially enable both direct and indirect comparisons between the interventions of interest
	Dose • Licensed dose studied in at least one arm of interest for placebo/BSC controlled trials • Licensed dose studied in at least two arms of interest for active controlled trials	• Licensed doses of treatments being assessed were selected as the focus of this review was to compare the licensed doses of treatments
	Study design • RCTs with any blinding status	• RCTs are the gold standard of clinical evidence, minimizing the risk of confounding and allowing the comparison of the relative efficacy of interventions. To enhance the quantity of evidence, studies with double blind, single blind and open label design were included
	Language restrictions • English only	• The restriction would not limit results substantially due to data availability in English language
	Publication timeframe[§] RCT • 1960 to October 31, 2012 for literature searches • 2009 to October 31, 2012 for conference searching Non-RCT • 1946 to November 30, 2012 for literature searches • 2009 to November 30, 2012 for conference searching	• Studies which are presented at conferences are usually published in journals within three years
Exclusion criteria	No subgroup analysis • No subgroup analysis for disease of interest • No subgroup analysis for age of interest i.e. adults	• Studies with mixed populations with no subgroup data for the disease and age of interest were not included, since these studies would introduce heterogeneity into the review

Abbreviations: BSC, best supportive care; DMTs, disease modifying therapy; GA, glatiramer acetate; IFN, Interferon; MS, multiple sclerosis; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis.
[†]Included to strengthen the placebo arm of the MTC. [‡]BSC includes (though not restricted to) non-chemotherapy drugs, symptomatic treatment including use of corticosteroids. [§] While these were performed in October/November 2012, the medical department of Biogen Idec have monitored the literature for relevant publications and have not found any in the intervening period.

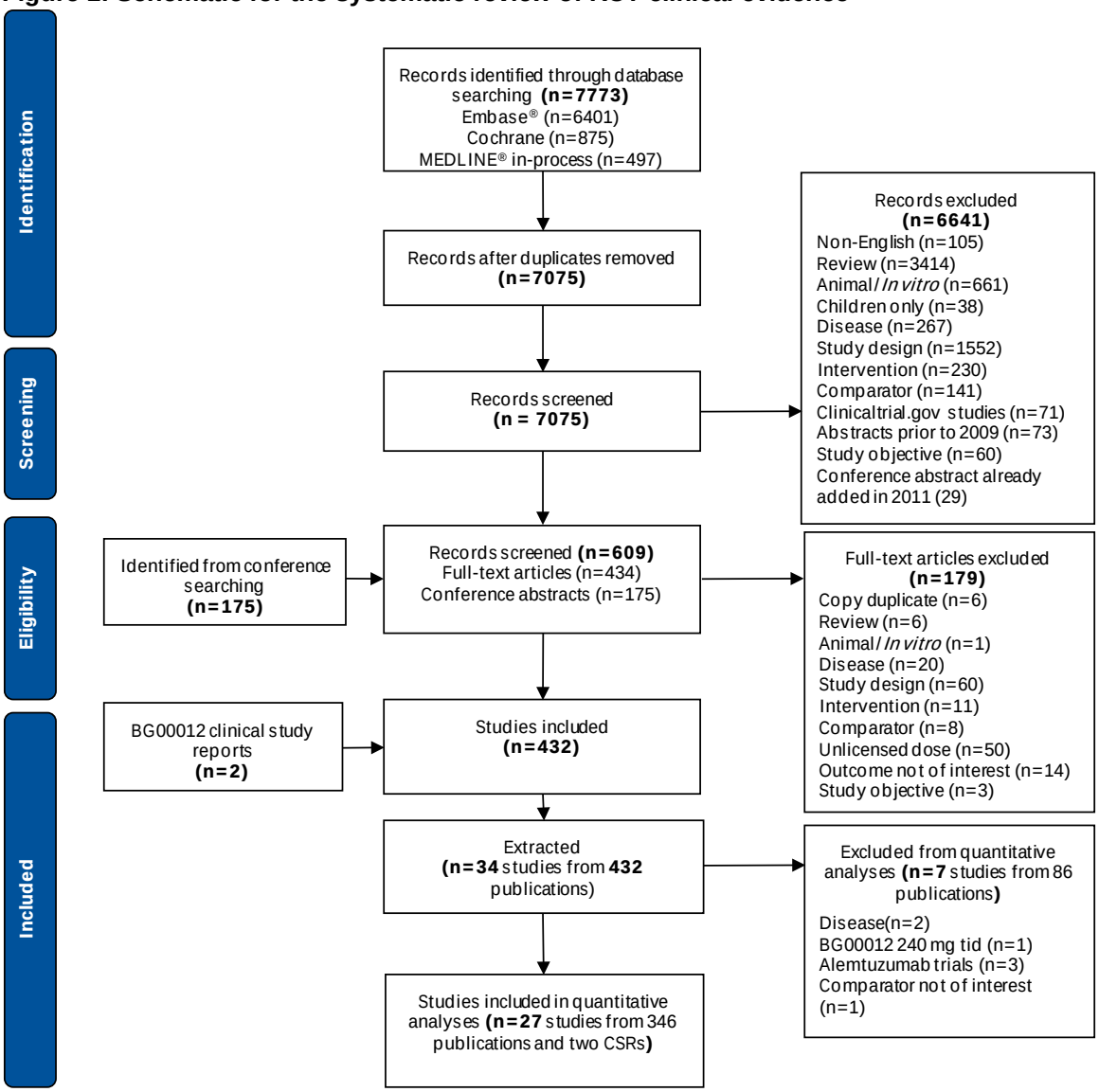
6.2.2 *A flow diagram of included and excluded studies at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses. Such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in Section 6.2.4.*

The RCT SR was performed on October 31st, 2011, with an update performed on October 31st, 2012. Following assessment and exclusion of studies based on title, abstract and full text, 27 studies (reported in 346 publications and two CSRs) were considered to meet the inclusion criteria and were included in the final data set (33, 34, 47-72). Of the 27 included studies:

- Two trials examined the intervention of interest (dimethyl fumarate), reported further in Sections 6.3–6.5
- The remaining 25 studies reported on comparator interventions that are of relevance to the decision problem, or could be used to strengthen the placebo arm of the MTC (teriflunomide). These comparator studies are reported further in Section 6.7.

The RCT SR schematic is shown in Figure 1.

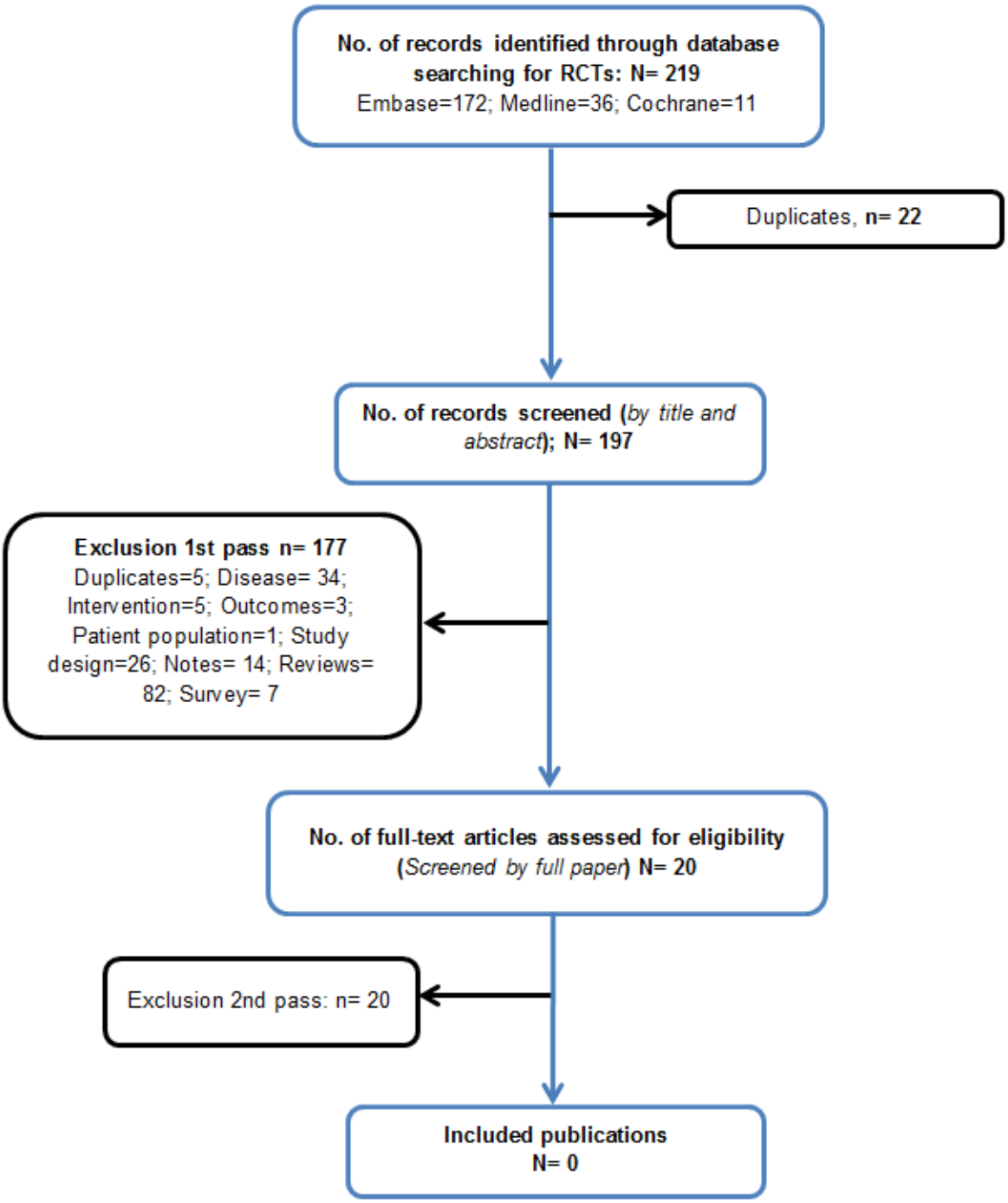
Figure 1: Schematic for the systematic review of RCT clinical evidence



Note: Embase® and MEDLINE® searched through Embase.com. MEDLINE® in-process searched separately.

The non-RCT SR was performed on November 30th, 2012. Following assessment and exclusion of studies based on title, abstract and full text, two records covering two non-RCTs were identified. These are described in Section 6.2.7. The SR schematic for the identification of non-RCT evidence is shown in Figure 2.

Figure 2: Systematic review flow diagram for non-RCTs



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Throughout this submission the evidence presented will be drawn from the DEFINE and CONFIRM trials, primarily using the main publications (and associated appendices) for each (29, 30, 73-76).

MRI and QoL outcomes were not reported in the main publications, and have been sourced from various other publications (Table 6). Other endpoints and analyses have been drawn from the DEFINE and CONFIRM clinical study reports (CSRs) (66, 67). A summary of the published findings from DEFINE and CONFIRM is given in Table 6. As the CSRs offer a greater level of detail than the published evidence, p values have been taken from the CSRs throughout. In certain cases this may result in the presented p values being smaller than the published values; however, this is purely due to rounding.

Table 6: Summary of publications from DEFINE and CONFIRM

Author	Title	Journal/Conference	Summary
Arnold et al 2011 (77)	Efficacy on MRI Endpoints of BG-12, an Oral Therapy, in Relapsing-Remitting Multiple Sclerosis: Data from the Phase 3 DEFINE Trial	ECTRIMS/ACTRIMS 2011	Change from baseline in mean number of T2, T1, and Gd+ lesions at 2 years in DEFINE
Arnold et al 2012 (78)	Effects of BG-12 (Dimethyl Fumarate) on Magnetic Resonance Imaging and Magnetization Transfer Ratio Outcomes in Relapsing–Remitting Multiple Sclerosis: Findings from the Phase 3 DEFINE Study	ECTRIMS 2012	Change from baseline in mean number and volume of T2, T1, and Gd+ lesions at 2 years, and change in brain atrophy and MTR at 2 years in DEFINE
Bar-Or et al 2012 (79)	Clinical Effects of BG-12 (Dimethyl Fumarate) in Subgroups of Patients with Relapsing–Remitting Multiple Sclerosis: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	ECTRIMS 2012	Pooled analysis of ARR, proportion of patients relapsed and disability progression at 2 years in DEFINE and CONFIRM
Bar-Or et al 2012 (80)	Gastrointestinal Tolerability Events in relapsing-Remitting Multiple Sclerosis (RRMS) Patients Treated with Oral BG-12 (Dimethyl Fumarate) in DEFINE and CONFIRM	Latin American Congress of Multiple Sclerosis 2012	Pooled analysis of gastrointestinal events in DEFINE and CONFIRM
Bar-Or et al 2013 (81)	Effect of BG-12 (Dimethyl Fumarate) in Subgroups of Patients with Relapsing–Remitting Multiple Sclerosis: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	AAN 2013	Pooled results in various patient subgroups from DEFINE and CONFIRM
Fox et al 2012 (29, 73, 74)	Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis	New England Journal of Medicine	Main clinical and safety endpoints from DEFINE
Fox et al 2013 (82)	Clinical Efficacy of BG-12 (Dimethyl Fumarate) in Relapsing–Remitting Multiple Sclerosis (RRMS): An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	AAN 2013	Pooled clinical results from DEFINE and CONFIRM
Giovannoni et al 2013 (83)	Relapses Requiring Intravenous Steroid Use and Multiple Sclerosis-related Hospitalizations: An Integrated Analysis of the BG-12 (Dimethyl Fumarate) Phase 3 Studies	AAN 2013	Pooled steroid treated relapse and hospitalisation rates in DEFINE and CONFIRM

Author	Title	Journal/Conference	Summary
Gold et al 2012 (30, 75, 76)	Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis	New England Journal of Medicine	Main clinical and safety endpoints from DEFINE
Gold et al 2013 (84)	BG-12 (Dimethyl Fumarate) and Pregnancy: Preclinical and Clinical Data from the Clinical Development Program	AAN 2013	Details of pregnancies while on dimethyl fumarate
Havrdova et al 2012 (85)	Relapses Requiring Intravenous Steroid Use and MS-related Hospitalizations: Findings from the Phase 3 DEFINE and CONFIRM Studies	ECTRIMS 2012	Analysis of number of relapses requiring IV steroids and MS-related hospitalisations in DEFINE and CONFIRM
Havrdova et al 2013 (86)	BG-12 (Dimethyl Fumarate) Treatment for Relapsing–Remitting Multiple Sclerosis (RRMS) Increases the Proportion of Patients Free of Measured Clinical and Neuroradiologic Disease Activity in the Phase 3 Studies	AAN 2013	Freedom from disease in DEFINE and CONFIRM
Hutchinson et al 2013 (87)	Systematic Literature Review and Mixed Treatment Comparison of BG-12 (Dimethyl Fumarate) and Disease Modifying Therapies for Relapsing–Remitting Multiple Sclerosis	AAN 2013	SR and MTC of treatments for RRMS.
Hutchinson et al 2013 (88)	Clinical Efficacy of BG-12 (Dimethyl Fumarate) for Relapsing–Remitting Multiple Sclerosis (RRMS) According to Prior Therapy: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	AAN 2013	Pooled response to dimethyl fumarate by previous treatment in DEFINE and CONFIRM
Kappos et al 2012 (89)	Effects of BG-12 on Quality of Life in Patients with Relapsing–Remitting Multiple Sclerosis: Findings from the DEFINE Trial	AAN 2012	Results of QoL assessment by SF-36 and Global Impression of Well-being VAS in DEFINE
Kappos et al 2013 (90)	Timecourse of Treatment Effects of BG-12 (Dimethyl Fumarate) for Relapsing–Remitting Multiple Sclerosis	AAN 2013	Pooled response to therapy over time in DEFINE and CONFIRM
Kita et al 2012 (91)	Effects of BG-12 (Dimethyl Fumarate) on Quality of Life in Patients with Relapsing−Remitting Multiple Sclerosis:	ECTRIMS 2012	Results of QoL assessment by SF-36 and Global Impression of Well-being VAS in CONFIRM

Author	Title	Journal/Conference	Summary
	Findings from the CONFIRM Study		
Kita et al 2013 (92)	Effects of BG-12 (Dimethyl Fumarate) on Quality of Life in Patients with Relapsing–Remitting Multiple Sclerosis (RRMS): An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	AAN 2013	Pooled QoL results from DEFINE and CONFIRM
Kita et al 2013 (93)	Clinical and Neuroradiologic Efficacy of BG-12 (Dimethyl Fumarate) in US Patients with Relapsing–Remitting Multiple Sclerosis (RRMS): An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	AAN 2013	Pooled clinical and MRI results from DEFINE and CONFIRM
Meltzer et al 2013 (94)	Gastrointestinal Tolerability Events in Relapsing–Remitting Multiple Sclerosis Patients Treated with BG-12 (Dimethyl Fumarate) in DEFINE and CONFIRM	AAN 2013	Pooled gastrointestinal events in DEFINE and CONFIRM
Miller et al 2012 (95)	Effects of BG-12 (Dimethyl Fumarate) on Magnetic Resonance Imaging Outcomes in Relapsing–Remitting Multiple Sclerosis: An Integrated Analysis of the Phase 3 DEFINE and CONFIRM Studies	ECTRIMS 2012	Pooled analysis of mean number of T2, T1, and Gd+ lesions at 2 years, and change in brain atrophy at 2 years in DEFINE and CONFIRM
Miller et al 2012 (96)	Effects of BG-12 on Magnetic Resonance Imaging Endpoints in Patients with Relapsing-Remitting Multiple Sclerosis: Data from the Phase 3 CONFIRM Study (S11.001)	AAN 2012	Change from baseline in mean number and volume of T2, T1, and Gd+ lesions at 2 years, and change in brain atrophy at 2 years in CONFIRM
Miller et al 2012 (97)	Effect of BG-12 (Dimethyl Fumarate) on Magnetic Resonance Imaging Activity in Subgroups of Patients with Relapsing–Remitting Multiple Sclerosis: Findings from the CONFIRM Study	ECTRIMS 2012	Change from baseline in mean number of T2, T1, and Gd+ lesions at 2 years in patient subgroups in CONFIRM
Phillips et al 2012 (98)	Long-term Safety and Tolerability of Oral BG-12 (Dimethyl Fumarate) in Relapsing–Remitting Multiple Sclerosis: Interim Results from ENDORSE	ECTRIMS 2012	Safety extension results from DEFINE and CONFIRM

Author	Title	Journal/Conference	Summary
Phillips et al 2013 (99)	Safety and Tolerability of BG-12 (Dimethyl Fumarate) in Patients with Relapsing–Remitting Multiple Sclerosis: An Integrated Analysis of Phase 2 and 3 Placebo-controlled Studies	AAN 2013	Pooled safety results from DEFINE, CONFIRM, and Phase II clinical trials
Selmaj et al 2012 (100)	Safety and Tolerability of BG-12 (Dimethyl Fumarate) in Patients with Relapsing–Remitting Multiple Sclerosis: An Integrated Analysis of the Placebo-controlled Studies	ECTRIMS 2012	Pooled analysis of safety outcomes from DEFINE and CONFIRM

Abbreviations: ACTRIMS, American Committee for Treatment and Research in Multiple Sclerosis; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; QoL, quality of life.

6.2.4 *Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form.*

The systematic review of clinical evidence identified two Phase III RCTs of dimethyl fumarate in the population of interest to this submission (Table 7). In addition, one Phase II RCT examined dimethyl fumarate, but did not use the licensed dose. Placebo was the comparator in two studies, with an active reference comparator treatment used in one study.

Table 7: List of relevant RCTs

Trial no. (acronym)	Phase	Intervention	Comparator	Population	Primary study ref.
DEFINE (Study 109MS301)	Phase III	• Dimethyl fumarate 240 mg BID • Dimethyl fumarate 240 mg TID	• Placebo	Patients aged 18–55 years, with diagnosis of RRMS by McDonald criteria, with baseline EDSS score between 0 and 5, with either at least one relapse within 12 months of randomisation and a previous cranial MRI scan showing lesions consistent with multiple sclerosis, or Gd+ lesions on MRI scans done within 6 weeks of randomisation	Gold 2012 (30)
CONFIRM (Study 109MS302)	Phase III	• Dimethyl fumarate 240 mg BID • Dimethyl fumarate 240 mg TID	• Glatiramer acetate (GA) 20 mg OD • Placebo		Fox 2012 (29)
Kappos 2008	Phase II	• Dimethyl fumarate 240 mg TID	• Placebo		Kappos 2008 (56)

Abbreviations: BID, twice daily; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; TID, three times daily

6.2.5 *Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.*

Two pivotal Phase III trials were relevant to this submission, DEFINE and CONFIRM. The intervention of interest, dimethyl fumarate, was compared with placebo in both trials, with GA included as a reference comparator in CONFIRM. It should be noted that the power calculation for CONFIRM was designed to detect a significant difference between dimethyl fumarate and placebo, but not dimethyl fumarate and GA.

6.2.6 *When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.*

The Phase II study by Kappos et al, 2008 (56) has been excluded from further discussion within the clinical data sections as it focuses on dimethyl fumarate 240 mg

TID, which is not the indicated dose for this product according to the Summary of Product Characteristics (SPC) (1).

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in Section 6.8 and key details should be presented in a table.

No non-RCTs were relevant to this submission.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

Two pivotal Phase III trials were relevant to this submission, DEFINE and CONFIRM (66, 67), both of which compared dimethyl fumarate BID and TID with placebo. CONFIRM also included glatiramer acetate as a reference arm, and whilst the study was not powered to detect a statistical difference between the treatments, the results provide a useful benchmark to current therapy. The methodologies of the DEFINE and CONFIRM studies are summarised in Table 8.

Table 8: Comparative summary of methodology of the RCTs

Trial no. (acronym)	DEFINE	CONFIRM
Study objective	***Primary:*** To determine the effectiveness of dimethyl fumarate in reducing the proportion of relapsing patients at 2 years, compared with placebo. ***Secondary:*** To evaluate the effect on ARR, progression of disability on the EDSS, and MRI lesion number (in a subset of patients) at 2 years. ***Tertiary:*** Safety, tolerability, PRO, and sub-clinical endpoints	***Primary:*** To determine the effectiveness of dimethyl fumarate in reducing ARR at 2 years, compared with placebo. ***Secondary:*** To evaluate the effect on the proportion of relapsing patients, progression of disability on the EDSS, and MRI lesion number (in a subset of patients) at 2 years. ***Tertiary:*** Safety, tolerability, PRO, and sub-clinical endpoints
Location	Conducted at 198 sites in 28 countries across Central and Northern America, Asia, Eastern and Western Europe, the Middle East, and Australasia. http://clinicaltrials.gov/ct2/show/NCT00	Conducted at 200 sites in 28 countries across Central and Northern America, Asia, Eastern and Western Europe, the Middle East, and Australasia http://clinicaltrials.gov/ct2/show/NCT00

Trial no. (acronym)	DEFINE	CONFIRM
	420212 29 patients at 7 centres in the UK were treated.	451451 There were no UK centres included.
Design	A Phase III, randomised, multicentre, international, placebo-controlled, three-arm dose-comparison study in 1,237 patients with RRMS.	A Phase III, randomised, multicentre, international, placebo-controlled and active reference four-armed comparison study in 1,430 patients with RRMS.
Duration of study	The study began on 14th March 2007, with each patient treated for a total of 96 weeks. The final patient completed treatment on 20th February 2011.	The study began on 28th July 2007, with each patient treated for a total of 96 weeks. The final patient completed treatment on 24th August 2011.
Method of randomisation	Patients were randomised in a 1:1:1 ratio to receive either dimethyl fumarate BID, dimethyl fumarate TID, or placebo, stratified by site. Randomisation was performed by centralised IVRS.	Patients were randomised in a 1:1:1:1 ratio to receive either dimethyl fumarate BID, dimethyl fumarate TID, GA, or placebo, stratified by site. Randomisation was performed by centralised IVRS.
Method of blinding (care provider, patient and outcome assessor)	All study management and site personnel, patients, and investigators directly involved in the study were blinded to patient treatment. Separate study personnel were designated to treat patients and conduct efficacy assessments.	All study management and site personnel, patients, and investigators directly involved in the study were blinded to patient treatment in dimethyl fumarate and placebo groups. Study personnel and patients in the GA group were unblinded. Examining neurologists and technicians were blinded to all 4 groups.
Intervention(s) (n =) and comparator(s) (n =)	**Dimethyl fumarate 240 mg BID (n=410)** Patients received one 120 mg dimethyl fumarate capsule twice daily (morning and night) and one placebo capsule (midday) during the first week. Patients were escalated to two 120 mg dimethyl fumarate capsules twice daily and two placebo capsules OD after the first week. **Dimethyl fumarate 240 mg TID (n=416)** Patients received one 120 mg dimethyl fumarate capsule three times daily (morning, midday, and night) during the first week. Patients were escalated to two 120 mg dimethyl fumarate capsules TID after the first week. **Placebo (n=408)** Capsules matching dimethyl fumarate in size, shape, colour, and taste were used. Patients received one placebo capsule three times daily (morning, midday, and night) during the first week. Patients were escalated to two placebo capsules TID after the first	**Dimethyl fumarate 240 mg BID (n=359)** As for DEFINE. **Dimethyl fumarate 240 mg TID (n=345)** As for DEFINE **Glatiramer acetate (n=350)** Patients received 20 mg SC injections OD, open label. **Placebo (n=363)** As for DEFINE **All patients** As for DEFINE

Trial no. (acronym)	DEFINE	CONFIRM
	week. **All patients** The point of randomisation was designated Week 0/Day 1. Patients were to take study medication with food. Temporary modification of the treatment schedule due to flushing or abnormal laboratory tests was permitted. Patients were to reduce their dose to one capsule TID, for 1 month, after which they were to resume their allocated treatment. Patients still unable to tolerate the study treatment were to discontinue; prematurely discontinuing patients remained in the study, and continued on a modified schedule of tests and assessments with their treatment allocation still blinded. Patients were not to take study medication for <4 hours prior to study assessment visits, due to the potential for unblinding of investigators as a result of flushing, a known side-effect of dimethyl fumarate.	
Permitted and disallowed concomitant medications	**Permitted medications:** • Non-systemic steroids (e.g. topical, inhaled) • Symptomatic therapies, such as treatments for spasticity, depression, or fatigue • IV methylprednisolone in the event of a relapse **Disallowed therapies:** • Previous treatment with fumaderm or dimethyl fumarate • Previous treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, or any therapeutic monoclonal antibody, with the exception of natalizumab • Previous treatment within 1 year of randomisation with mitoxantrone or cyclophosphamide • Previous treatment within 6 months of randomisation with cyclosporine, azathioprine, methotrexate, natalizumab , mycophenolate mofetil, IV immunoglobulin, plasmapheresis or cytapheresis • Previous treatment within 3 months of randomisation with SC or oral GA, IFNα, or IFNβ • Previous treatment within 50 days of randomisation with steroids or 4-aminopyridine • Previous treatment within 6 months of randomisation with another investigational drug or approved therapy for investigational use	
Dis-continuation of study therapy	Patients withdrew from the study for the following reasons: • Death • Pregnancy	

Trial no. (acronym)	DEFINE	CONFIRM
	• Inability to tolerate study medication • Receipt of disallowed concomitant medications • Poor compliance • Unacceptable toxicity • Patient choice to withdraw from treatment (follow-up permitted by patient) • Withdrawal of patient consent (cessation of follow-up)	
Assessments	All patients were constantly monitored for relapses, 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. Hospitalisations and relapses requiring IV steroids were also constantly monitored. The following assessments were performed at baseline, and thereafter at: *Weeks 1–96:* Vital signs *Weeks 1–12, then every 12 weeks:* Haematology *Weeks 1–24, then every 12 weeks:* Lipid profile *Every 12 weeks:* EDSS, MSFC, VAS (global well-being), visual acuity (using low-contrast Sloan charts) *Weeks 24, 48, and 96:* SF-36 and EQ-5D A subset of patients (***DEFINE***: dimethyl fumarate BID n=176, dimethyl fumarate TID n=184, placebo n=180; ***CONFIRM:*** dimethyl fumarate BID n=169, dimethyl fumarate TID n=170, placebo n=167) were included in the assessment of MRI outcomes at baseline and Weeks 24, 48 and 96. The assessments performed were on T2 hyperintense lesions, Gd+ lesions, T1 hypointense lesions, brain atrophy, and MTR.	
Primary outcomes	**Proportion of patients with ≥ 1 relapse at 2 years:** 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.	**ARR:** 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.
Secondary/ tertiary outcomes	• ARR • Disability progression, as measured by the EDSS and MSFC • PROs (VAS [global well-being], SF-36, and EQ-5D) • MRI outcomes, including number/volume of brain lesions, brain atrophy, and MTR • Visual acuity	• Disability progression, as measured by the EDSS and MSFC • PROs (VAS, SF-36, and EQ-5D) • MRI outcomes, including number/volume of brain lesions, brain atrophy, and MTR • Visual acuity
Duration of follow-up	Patients were treated for 96 weeks, with a follow-up study visit at 100 weeks for patients who completed treatment, but did not enter the extension study.	

Abbreviations: ARR, annualised relapse rate; BID, twice daily; EQ-5D, European quality of life-5 dimensions; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhancing; Ig, immunoglobulin; IV, intravenous; IVRS, interactive voice response; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; MTR, magnetization transfer ratio; OD, once daily; PRO, patient reported outcome; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SF-36, short-form 36; TID, three times daily; VAS, visual analogue scale.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. Highlight any differences between the trials.

The inclusion and exclusion criteria for DEFINE and CONFIRM are summarised in Table 9.

Table 9: Eligibility criteria of DEFINE and CONFIRM

	DEFINE and CONFIRM
Inclusion criteria (73, 75)	• 18–55 years old • Confirmed diagnosis of RRMS according to McDonald Criteria 1 to 4 • Baseline EDSS score of 0.0–5.0 inclusive • ≥ 1 relapse in the 12 months prior to randomisation, with a prior brain MRI demonstrating lesions consistent with MS or evidence of Gd+ lesions ≤ 6 weeks prior to randomisation • Willing to practice effective contraception
Exclusion criteria	• PPMS, SPMS or progressive relapsing MS • Inability to perform any of the MSFC tests • Inability to perform visual function tests • History of malignancy, with the exception of completely excised basal cell carcinoma • History of severe allergic or anaphylactic reactions or known drug hypersensitivity • History of abnormal laboratory results • History of clinically significant major disease • HIV infection • History of drug/alcohol abuse within 2 years of randomisation • MS relapse within 50 days of randomisation and/or not stabilised from previous relapse • Hepatitis C antibody positive • Hepatitis B surface antigen positive • Abnormal blood or urine tests at screening • Previous treatment with fumaderm or dimethyl fumarate • Previous treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, or any therapeutic monoclonal antibody, with the exception of natalizumab • Previous treatment within 1 year of randomisation with mitoxantrone or cyclophosphamide • Previous treatment within 6 months of randomisation with cyclosporine, azathioprine, methotrexate, natalizumab , mycophenolate mofetil, IV immunoglobulin, plasmapheresis or cytapheresis • Previous treatment within 3 months of randomisation with SC or oral GA, IFNα, or IFNβ • Previous treatment within 50 days of randomisation with steroids or 4-aminopyridine • Previous treatment within 6 months of randomisation with another investigational drug or approved therapy for investigational use

Abbreviations: EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhancing; HIV, human immunodeficiency virus; IFN, interferon; IV, intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Patient demographics and characteristics at baseline are summarised in Table 10 and Table 11 for the overall population and MRI cohort, respectively. Baseline MRI characteristics for the MRI cohort are provided in Table 12. There were no significant differences between the treatment groups in DEFINE or CONFIRM. As MS is more prevalent in women than men, the majority of patients in both studies were female (DEFINE=74%, CONFIRM=70%). The mean age of patients was 38.5 years old in DEFINE, and 37.3 in CONFIRM, with the majority of patients of white ethnic origin in both studies (DEFINE=79%, CONFIRM=84%).

Table 10: Characteristics of participants in the overall populations of DEFINE and CONFIRM across randomised groups *(Academic in confidence information removed)*

Baseline characteristics		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410) n (%)	Dimethyl fumarate TID (N=416) n (%)	Placebo (N=408) n (%)	Dimethyl fumarate BID (N=359) n (%)	Dimethyl fumarate TID (N=345) n (%)	GA (N=350) n (%)	Placebo (N=363) n (%)
Age, years	18–29	86 (21)	68 (16)	77 (18)	78 (21)	74 (22)	85 (24)	88 (24)
	30–39	138 (34)	146 (35)	129 (32)	130 (36)	119 (34)	130 (37)	125 (34)
	40–55	186 (45)	200 (48)	200 (49)	151 (42)	152 (44)	135 (39)	149 (41)
	>55	0	2 (<1)	2 (<1)	0	0	0	1 (<1)
Sex	Male	114 (28)	110 (26)	102 (25)	114 (32)	95 (28)	103 (29)	112 (31)
	Female	296 (72)	306 (74)	306 (75)	245 (68)	250 (72)	247 (71)	251 (69)
Previous MS treatment	IFNβ-1a	114 (28)	111 (27)	106 (26)	66 (18)	70 (20)	76 (22)	80 (22)
	IFNβ-1b	57 (14)	60 (14)	55 (13)	42 (12)	39 (11)	33 (9)	43 (12)
	GA	52 (13)	60 (14)	75 (18)	1 (<1)	3 (<1)	1 (<1)	1 (<1)
	Nat	8 (2)	18 (4)	8 (2)	2 (<1)	6 (2)	2 (<1)	6 (2)
Race	White	321 (78)	330 (79)	318 (78)	304 (85)	292 (85)	290 (83)	305 (84)
	Asian	38 (9)	36 (9)	42 (10)	28 (8)	26 (8)	25 (7)	28 (8)
	Unknown	21 (5)	20 (5)	22 (5)	11 (3)	10 (3)	11 (3)	11 (3)
	Black	8 (2)	10 (2)	8 (2)	2 (<1)	5 (1)	11 (3)	9 (2)
Region[†]	1							
	2							
	3							
McDonald	1 (a)	336 (82)	326 (78)	338 (83)	291 (81)	284 (82)	294 (84)	309 (85)

Baseline characteristics		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410) n (%)	Dimethyl fumarate TID (N=416) n (%)	Placebo (N=408) n (%)	Dimethyl fumarate BID (N=359) n (%)	Dimethyl fumarate TID (N=345) n (%)	GA (N=350) n (%)	Placebo (N=363) n (%)
criteria[‡]	2 (b)	52 (13)	62 (15)	54 (13)	38 (11)	40 (12)	32 (9)	37 (10)
	3 (c)	16 (4)	21 (5)	9 (2)	22 (6)	17 (5)	19 (5)	12 (3)
	4 (d)	6 (1)	7 (2)	7 (2)	8 (2)	4 (1)	5 (1)	5 (1)
Baseline EDSS score	≤ 2.0	212 (52)	224 (54)	202 (50)	161 (45)	159 (46)	156 (45)	160 (44)
	>2.0	197 (48)	192 (46)	206 (50)	198 (55)	186 (54)	194 (55)	203 (56)
No. of relapses in previous 3 years	0							
	1							
	2							
	3							
	≥ 4							

Abbreviations: BID, twice daily; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; MS, multiple sclerosis; Nat, natalizumab; TID, three times daily.
[†]Region 1: USA and Puerto Rico; Region 2: Western Europe, Australia, Canada, New Zealand, Israel, and South Africa; Region 3: Eastern Europe, India, Guatemala, and Mexico.
[‡]McDonald criteria: (a) ≥ 2 relapses with ≥ 2 objective lesions; (b) ≥ 2 relapses, with 1 objective lesion with dissemination in space confirmed by MRI or ≥ 2 MRI lesions consistent with MS, or further clinical attack involving a different site; (c) 1 relapse, ≥ 2 objective lesions with dissemination in time confirmed by MRI or second clinical attack; (d) 1 (mono-symptomatic) relapse, with 1 objective lesion with dissemination in space confirmed by MRI, or positive CSF and ≥ 2 MRI lesions consistent with MS, with dissemination in time confirmed by MRI or second clinical attack.

Table 11: Characteristics of participants in the MRI cohort in DEFINE and CONFIRM across randomised groups *(Academic in confidence information removed)*

Baseline characteristics		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=169) n (%)	Dimethyl fumarate TID (N=170) n (%)	Placebo (N=180) n (%)	Dimethyl fumarate BID (N=169) n (%)	Dimethyl fumarate TID (N=170) n (%)	GA (N=175) n (%)	Placebo (N=167) n (%)
Age, years								
Sex								
Previous MS treatment								
Race								
Region[†]								
McDonald								

Baseline characteristics		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=169) n (%)	Dimethyl fumarate TID (N=170) n (%)	Placebo (N=180) n (%)	Dimethyl fumarate BID (N=169) n (%)	Dimethyl fumarate TID (N=170) n (%)	GA (N=175) n (%)	Placebo (N=167) n (%)
criteria[‡]								
Baseline EDSS score								
No. of relapses in previous 3 years								

Abbreviations: BID, twice daily; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; MS, multiple sclerosis; Nat, natalizumab; TID, three times daily.
[†]Region 1: USA and Puerto Rico; Region 2: Western Europe, Australia, Canada, New Zealand, Israel, and South Africa; Region 3: Eastern Europe, India, Guatemala, and Mexico.
[‡]McDonald criteria: (a) ≥ 2 relapses with ≥ 2 objective lesions; (b) ≥ 2 relapses, with 1 objective lesion with dissemination in space confirmed by MRI or ≥ 2 MRI lesions consistent with MS, or further clinical attack involving a different site; (c) 1 relapse, ≥ 2 objective lesions with dissemination in time confirmed by MRI or second clinical attack; (d) 1 (mono-symptomatic) relapse, with 1 objective lesion with dissemination in space confirmed by MRI, or positive CSF and ≥ 2 MRI lesions consistent with MS, with dissemination in time confirmed by MRI or second clinical attack.

Table 12: Baseline MRI characteristics of the MRI cohort of patients in DEFINE and CONFIRM *(Academic in confidence information removed)*

Baseline MRI characteristics		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=176)	Dimethyl fumarate TID (N=184)	Placebo (N=180)	Dimethyl fumarate BID (N=169)	Dimethyl fumarate TID (N=170)	GA (N=175)	Placebo (N=167)
Number of Gd+ lesions, n (%)								
Volume of Gd+ lesions (mm^3), n (%)								
Number of T2 lesions, n (%)								
Volume of T2 lesions (mm^3), n (%)								
Number of T1								

Baseline MRI characteristics		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=176)	Dimethyl fumarate TID (N=184)	Placebo (N=180)	Dimethyl fumarate BID (N=169)	Dimethyl fumarate TID (N=170)	GA (N=175)	Placebo (N=167)
lesions, n (%)								
Volume of T1 lesions (mm^3), n (%)								
Normalised whole brain volume (cm^3)								
MTR of whole brain								
MTR of normal appearing brain tissue								

Abbreviations: BID, twice daily; GA, glatiramer acetate; Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; MTR, magnetisation transfer ratio; SD, standard deviation; TID, three times daily.

Table 13: Patient baseline characteristics by region in DEFINE and CONFIRM *(Academic in confidence information removed)*

Characteristic		DEFINE			CONFIRM		
		Region 1 (n=201)	Region 2 (n=519)	Region 3 (n=514)	Region 1 (n=268)	Region 2 (n=212)	Region 3 (n=937)
Age	Mean±SD						
Sex (%)	Male Female						
Race (%)	White Black Asian Other Unknown						
Height (cm)	Mean±SD						
Weight (kg)	Mean±SD						
BMI (kg/m^2)	Mean±SD						
Baseline EDSS score	Mean						
Prior MS treatment (%)	Yes No						
No. relapses in past 3 months	Mean						
Time since 1st MS symptoms	Years						

Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation.

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

The primary and secondary endpoints evaluated in the DEFINE and CONFIRM studies are consistent with other studies of MS therapies and EMEA recommendations for studies in the disease (101). The primary, secondary, and tertiary outcomes for each trial are given in Table 14.

Table 14: Outcomes used in DEFINE and CONFIRM and their relevance to clinical practice

Outcome	Relevance to clinical practice
Clinical outcomes	
Proportion of relapsing patients: 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 3 members of an independent committee consisting of eight blinded neurologists with expertise in MS. The proportion of patients who had experienced a relapse was compared after 2 years.	Relapses, or attacks, are defined as an episode of neurological disturbance typical of MS. Relapses form part of the widely used revised McDonald diagnostic criteria for MS (102), which are used by NICE (22). Relapses contribute to impairment and disease progression (103), and an increased relapse frequency leads to faster disease progression (104, 105).
ARR at 2 years: ARR was defined as the mean number of relapses experienced by a patient in 1 year.	
Proportion of patients relapsed at 1 year	
ARR at 1 year	
Disability progression (EDSS): The EDSS was used to measure disability progression, defined as a ≥ 1.0-point increase in EDSS score from a baseline score ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase in score from a baseline of 0 that was sustained for 12 weeks. The EDSS is based on ambulation and scores determined for seven functional systems; visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, and cerebral. Scores range from 0.0 (normal exam) to 10.0 (death due to MS).	Physical and mental disability accumulates in patients with RRMS as they experience relapses and an increasing lesion burden (104, 105). Disability is therefore a quantifiable physical manifestation of disease progression (104, 105).
Disability progression (MSFC): The MSFC consists of three components measuring changes in ambulation, cognition, and upper extremity function and dexterity, measured by the T25FW test, PASAT-3 test, and 9-HPT, respectively. It is less heavily weighted towards ambulation than the EDSS, and may therefore be more sensitive to small changes in disability. Subjects completed three practice tests prior to randomisation in order to minimise any learning effect.	
Number of relapses requiring IV steroid therapy	More severe relapses may require IV steroid therapy; reducing the frequency of these will therefore indicate benefit of treatment to the patient.
MS-related hospitalisations: The number of MS-related hospitalisations was determined using the coded hospitalisation preferred term, as defined by the Medical Dictionary for Regulatory Activities.	MS patients may require hospitalisation as a result of relapses or MS-related disability. Reducing the frequency of such hospitalisations will therefore indicate benefit of treatment to the patient.
MRI outcomes	
Number/volume of T2, T1 Gd+ lesions: Lesion number was assessed using MRI imaging in a subset of patients.	Brain and CNS lesions on MRI are one of the main

Outcome	Relevance to clinical practice
Brain MRI images were obtained at the patients' institution, and evaluated by a central laboratory at NeuroRx Research, Montreal, Canada (DEFINE), or the University of Central London Institute of Neurology (CONFIRM). T2 and T1 lesions were defined as lesions detected by T2- and T1-weighted MRI-sequences, respectively, while Gd+ lesions were defined as lesions detected using Gadolinium as a contrast enhancing agent.	identifying characteristics of MS, and are consequently a useful marker for treatment efficacy (104, 105).
Brain atrophy: Brain atrophy over 2 years was measured by the percentage change in normalised brain volume and brain parenchymal fraction, using the Structural Image Evaluation, using Normalisation, of Atrophy method (106).	Brain atrophy has been shown to occur in patients with MS (107). Slowing brain atrophy is therefore likely to be indicative of efficacy.
MTR at 1 and 2 years: MTR imaging scans reflect the exchange of magnetisation between freely mobile protons and those associated with macromolecules such as myelin or axonal membranes.	MTR has been shown to correlate to changes in the myelin content of white matter, with MTR decreases indicating acute demyelination and MTR increases indicating remyelination (108).
PROs	
Quality of life was assessed using the: **VAS**, which assesses the patients' global impression of well-being on study treatment on a linear scale, with 0 as 'poor' and 100 as the 'excellent'. **SF-36**, a widely used generic instrument for measuring QoL (where higher scores indicate a higher QoL), with eight multiple-item scales and two summary scores, the physical component score (PCS) and mental component score (MCS) (109). **EQ-5D**, a 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 20cm scale from 0 to 100 where 0 represents 'worst imaginable health state' and 100 represents 'best imaginable health state'.	QoL has been shown to decrease as MS progresses (110); preventing or reversing this decline is therefore a useful indication of efficacy. The EQ-5D is the QoL measure preferred by NICE (111), while the SF-36 and VAS are accepted by NICE as alternatives to the EQ-5D (112).

Abbreviations: 9-HPT, 9-hole peg test; ARR, annualised relapse rate; CNS, central nervous system; EDSS, Expanded Disability Status Scale; EQ-5D, European quality of life 5 dimensions; Gd+, gadolinium enhancing; IV, intravenous; MCS, mental component score; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; MRI, magnetic resonance imaging; MTR, magnetisation transfer ratio; NICE, National Institute of Health and Care Excellence; PASAT-3, paced auditory serial addition test 3; PCS, physical component score; QoL, quality of life; SF-36, short form 36; T25FW, timed 25-foot walk test; VAS, visual analogue scale.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

Patient datasets analysed (DEFINE and CONFIRM)

ITT population

All patients who were randomised and received ≥ 1 dose of study treatment. The ITT population was the primary population for analysis of efficacy outcomes.

Per-protocol population

Patients in the ITT population without any major protocol violations, defined as:

- No confirmed diagnosis of RRMS according to the McDonald criteria
- Baseline EDSS not between 0.0–5.0, inclusive
- No relapses within 12 months prior to randomisation
- Poor study compliance (<70%)
- Enrolment at any of the three sites closed due to issues with good clinical practice compliance (DEFINE only).
- Prior treatment with GA (CONFIRM only)

MRI cohort

Patients in the ITT population with any MRI data.

Safety population

All patients who received ≥ 1 dose of study treatment and were >50% compliant.

Statistical analyses: DEFINE and CONFIRM

The statistical analyses for DEFINE and CONFIRM are summarised in Table 15.

Table 15: Summary of statistical analyses in RCTs

	DEFINE	CONFIRM
Hypothesis objective	The primary hypothesis was that treatment would result in a reduction in the proportion of patients who relapsed at 2 years, based on data from a prior MS clinical trial comparing an active drug with a placebo (62).	The primary hypothesis was that treatment would result in a reduction in the number of relapses at 2 years, based on data from the Phase II clinical trial of dimethyl fumarate (67).
Sample size, power calculation	The sample size was calculated based on a 90% power to detect a 30% reduction in the proportion of patients who relapsed at 2 years in each of the dimethyl fumarate groups, compared with placebo (based on the Chi-square test). A dropout rate of 23% over the 2 years was assumed, with a 5% type I error rate used to determine the sample size, which was determined to be 337 subjects per group.	The sample size was calculated based on an 84% power to detect a 25% reduction in ARR at 2 years in each of the dimethyl fumarate groups, compared with placebo. A dropout rate of 23% over the 2 years was assumed, giving a sample size of 308 subjects per group. This study was not powered to detect a treatment difference between either dose of dimethyl fumarate and GA.
Population used in primary analysis	ITT	ITT

	DEFINE	CONFIRM
Type I error control: Primary endpoint	Statistical testing was based on a sequential procedure to control for the overall type I error; if the first comparison (dimethyl fumarate TID vs placebo) was statistically significant (p<0.05), the second comparison would be performed. If the first comparison was not significant, then the second comparison would not be considered statistically significant.	
Type I error control: Secondary endpoints	A closed testing procedure was used, as for the primary endpoint. Endpoints were tested in the order: 1) Number of new T2 lesions 2) Number of Gd+ lesions 3) ARR 4) Progression of disability If an endpoint was not found to be significant for dimethyl fumarate TID vs placebo, then all lower ranked endpoints for that dose would also be considered non-significant.	A closed testing procedure was used, as for the primary endpoint. Endpoints were tested in the order: 1) Number of new T2 lesions 2) Number of T1 lesions 3) Proportion of subjects relapsed 4) Progression of disability If an endpoint was not found to be significant for dimethyl fumarate dose vs placebo, then all lower ranked endpoints for that dose would also be considered non-significant.
Type I error control: Tertiary endpoints	No closed testing procedures were performed.	
Statistical analysis: Primary outcome	A Cox proportional hazards model was used, based on estimates from the Kaplan-Meier curve for the time to first relapse.	A negative binomial regression model was used, adjusted for baseline EDSS score (≤ 2.0 vs >2.0), baseline age (<40 vs ≥ 40 years), region†, and number of relapses in the year prior to study entry.
Statistical analysis: Secondary outcomes	**Number of new T2 lesions (MRI population)**: Negative binomial regression model, adjusted for treatment group, region† and baseline lesion volume.	
	Number of Gd+ lesions (MRI population): Ordinal logistic regression, adjusted for treatment, region†, and baseline number.	**Number of T1 lesions (MRI population):** Negative binomial regression model, adjusted for treatment group, region† and baseline lesion volume.
	ARR (ITT population): Negative binomial regression model, adjusted for baseline EDSS score (≤ 2.0 vs >2.0), baseline age (<40 vs ≥ 40 years), region†, and number of relapses in the year prior to study entry.	**Proportion of subjects relapsed (ITT population):** Cox proportional hazards model, based on estimates from the Kaplan-Meier curve for the time to first relapse.
	Progression of disability (ITT population): Cox proportional hazards model, adjusted for baseline EDSS value as a continuous variable, region†, and age (<40 vs ≥ 40 years).	
Statistical analysis: Tertiary outcomes (Clinical, ITT population)	**Proportion of subjects relapsed at 1 year:** Cox proportional hazards, adjusted for treatment group, number of relapses in year prior to study entry, baseline age (<40 vs ≥ 40 years), baseline EDSS (≤ 2.0 vs >2.0), and region†.	
	ARR at 1 year: As for secondary ARR outcome.	
	Number of relapses requiring IV steroids: Negative binomial regression, adjusted for treatment and region†.	
	MS-related hospitalisations: Negative binomial regression, adjusted for treatment and region†.	
	MSFC: ANCOVA, adjusted for treatment, region, and baseline MSFC score.	
	Progression of cognitive deficit: Cox proportional hazards, adjusted for treatment, region†, and baseline PASAT-3 score.	
	Visual function: ANCOVA, adjusted for treatment, region†, and baseline score.	
Statistical analysis: Tertiary outcomes (MRI, MRI population)	**Number of new T1/T2 lesions:** Negative binomial regression model, adjusted for treatment, region† and baseline lesion volume.	
	Volume of T2/T1/Gd+ lesions: ANCOVA, adjusted for treatment, region†, and baseline volume.	
	Number of Gd+ lesions: Ordinal logistic regression, adjusted for treatment, region†, and baseline number.	
	Brain atrophy: ANCOVA, adjusted for treatment, region†, and week 24 brain volume.	

	DEFINE	CONFIRM
	MTR: ANCOVA, adjusted for treatment, region†, and baseline MTR value.	
	Conversion of Gd+ lesions to T1: Logistic regression, adjusted for treatment and baseline number.	
Statistical analysis: Secondary outcomes (PROs, ITT population)	ANCOVA, adjusted for treatment, region†, and baseline score.	
Data management, patient withdrawals	For the primary analysis of MRI, MSFC, visual function, and PRO endpoints, post-baseline data that were missing for any reason (including withdrawal or switching to an alternative MS medication) were imputed using the patient's observed post-baseline data.	

†Region 1: USA and Puerto Rico; Region 2: Western Europe, Australia, Canada, New Zealand, Israel, and South Africa; Region 3: Eastern Europe, India, Guatemala, and Mexico.
Abbreviations: ANCOVA, analysis of covariance; ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; INEC, independent neurology examining committee; ITT, intention-to-treat; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; MTR, magnetisation transfer ratio; PASAT-3, paced audio serial addition test; TID, three times daily.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-specified subgroup analyses were performed for the primary and secondary endpoints. The subgroups are listed below:

- Baseline EDSS (EDSS ≤ 2.0 vs EDSS>2.0)
- Age at baseline (<40 vs ≥ 40 years)*
- Gender*
- Region (Region 1: USA and Puerto Rico; Region 2: Western Europe, Australia, Canada, New Zealand, Israel, and South Africa; Region 3: Eastern Europe, India, Guatemala, and Mexico)
- Baseline weight*
- Baseline number of relapses (≤ 1 and ≥ 2) in the year prior to study entry
- Baseline McDonald criteria (1 vs 2, 3, and 4)
- Prior MS treatment (yes vs no)
- MRI cohort (yes vs no)
- Baseline Gd+ lesions (absent or present, MRI cohort only)*
- Baseline T2 lesion volume (above or below median, MRI cohort only)

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

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

CONSORT flow charts showing the numbers of patients who were eligible to enter the relevant RCTs, and who were randomised and allocated to each treatment are presented in Figure 3 and Figure 4.

Figure 3: Participant flow: DEFINE

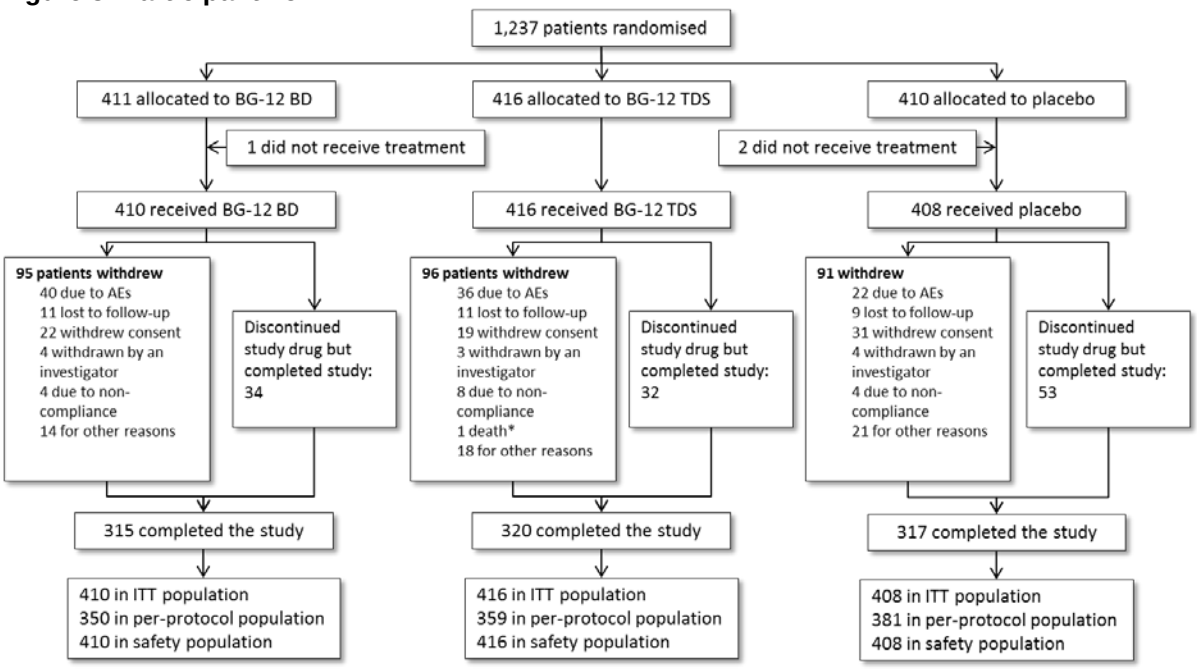
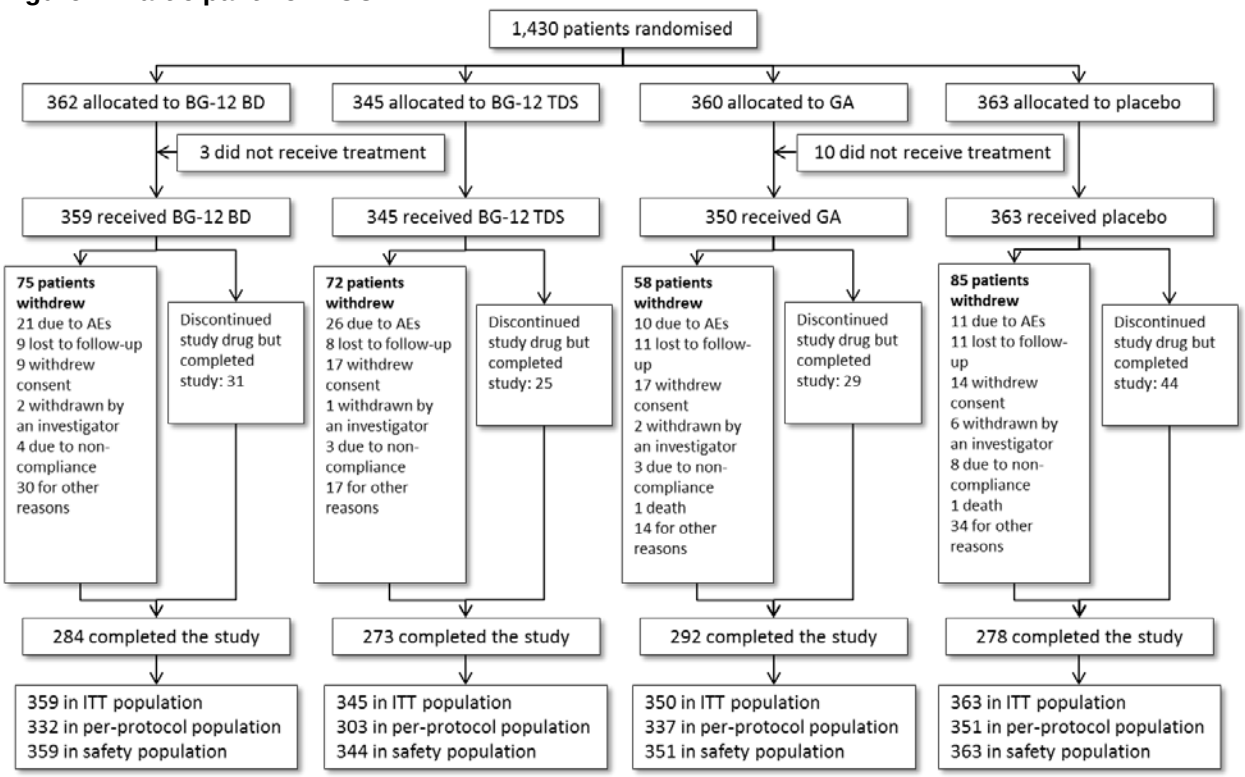


Figure 4: Participant flow: CONFIRM



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, appendix 3 for a suggested format.

A complete quality assessment for each RCT is provided in Section 10.3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.

Critical appraisals of the relevant RCTs are presented in Table 16. A complete quality assessment for each RCT is provided in Section 10.3.

Table 16: Quality assessment results for RCTs

Study question	DEFINE	CONFIRM
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- ***The unit of measurement.***
- ***The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio in an equivalent statistic. Both absolute and relative data should be presented.***
- ***A 95% confidence interval.***

- ***Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.***
- ***When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.***
- ***Other relevant data that may assist in the interpretation of the results may be included, such as adherence to medication and/or study protocol.***
- ***Discuss and justify definitions of any clinically important differences.***
- ***Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.***

DEFINE and CONFIRM included both BID and TID dosing for dimethyl fumarate; however, the licensed dose of dimethyl fumarate is BID. **The results for dimethyl fumarate TID will therefore be presented in this section, but not discussed in detail.**

DEFINE

The DEFINE Study achieved its primary efficacy outcome and has been published in the New England Journal of Medicine (30). The results for the relevant dimethyl fumarate BID dose are summarised below:

- Significant 49% reduction in the proportion of patients relapsing at 2 years, compared with placebo (HR 0.51, 95% CI: 0.40, 0.66)
- Significant 53% reduction in ARR at 2 years, compared with placebo (RR 0.47, 95% CI: 0.37, 0.61)
- At 2 years, there was a significant 38% reduction in the risk of confirmed EDSS disability progression sustained for 3 months, compared with placebo (HR 0.62, 95% CI: 0.44, 0.87)
- Patients had significantly fewer T2, T1, and Gd+ lesions, compared to those treated with placebo, with reductions of 85% (mean ratio 0.15, 95% CI: 0.10, 0.23), 72% (mean ratio 0.28, 95% CI: 0.20, 0.39), and 90% (odds ratio 0.10, 95% CI 0.05, 0.22), respectively
- Quality of life was significantly improved as measured by:
    - Change in VAS from baseline (p=0.003)
    - Change in EQ-5D VAS score from baseline (p=0.0008)
    - Aspects of the SF-36 were also significantly improved, in particular physical functioning (p<0.001), role-physical (p<0.001), general health (p<0.01), vitality (p<0.05), social functioning (p<0.01), role-emotional (p≤0.01), and PCS (p=0.0003)

Subgroup analysis demonstrated generally consistent results across a range of patient characteristics, including previous treatment history

CONFIRM

It should be noted that CONFIRM was not statistically powered to detect a difference between dimethyl fumarate and GA. Results for GA are therefore for comparison only and were generally consistent with the results of previous studies of GA in RRMS, providing a

useful benchmark to current therapy.

The CONFIRM Study achieved its primary efficacy outcome and has been published in the New England Journal of Medicine (29). The results for dimethyl fumarate BID are summarised below:

- Significant 44% reduction in ARR at 2 years, compared with placebo (RR 0.56, 95% CI 0.42–0.74)
    - GA reduction vs placebo: 29% (RR 0.71, 95% CI 0.55–0.93)
- Significant 34% reduction in proportion of patients relapsing at 2 years, compared with placebo (HR 0.66, 95% CI 0.51–0.86)
    - GA reduction vs placebo: 29% (HR 0.71, 95% CI 0.55–0.92)
- At 2 years, there was a non-significant 21% reduction in the risk of confirmed EDSS disability progression sustained for 3 months, compared with placebo (HR 0.79, 95% CI 0.52–1.19; p=0.2536)
    - GA reduction vs placebo: 7% (HR 0.93, 95% CI 0.63–1.37; p=0.7036)
- Patients had significantly fewer T2, T1, and Gd+ lesions, compared to those treated with placebo, with reductions of 71% (mean ratio 0.29, 95% CI 0.21–0.41), 57% (mean ratio 0.43, 95% CI 0.30–0.61), and 74% (odds ratio 0.26, 95% CI 0.15–0.46), respectively
    - GA reductions vs placebo: 54% (mean ratio 0.46, 95% CI 0.33–0.63), 41% (mean ratio 0.42–0.82), and 61% (mean ratio 0.39, 95% CI 0.24–0.65), respectively
- Quality of life was significantly improved as measured by:
    - Change in VAS from baseline (p=0.0003)
    - Physical functioning (p=0.0250), role-physical (p=0.0348), general health (p=0.0243), and PCS (p=0.0217) aspects of the SF-36

Subgroup analysis demonstrated generally consistent results across a range of patient characteristics, including previous treatment history.

6.5.4 Results: DEFINE and CONFIRM

Primary Efficacy Results: DEFINE

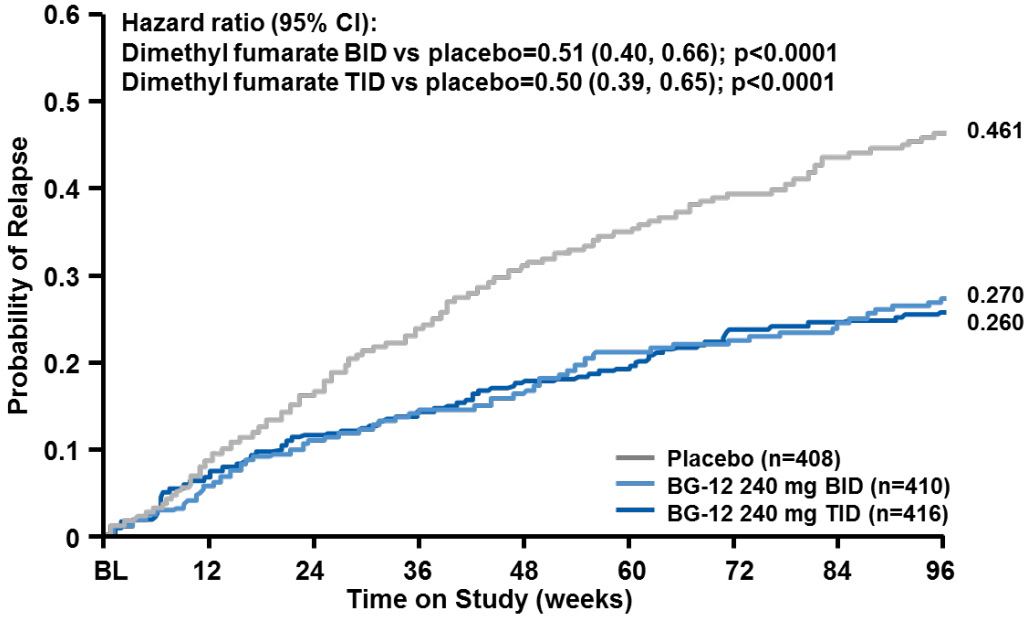
After 2 years of treatment 98 patients receiving dimethyl fumarate BID, and 95 patients receiving dimethyl fumarate TID had experienced an independent neurology examining committee (INEC) confirmed relapse (Table 14), compared to 171 patients in the placebo group. The Kaplan-Meier estimate of the proportion of patients relapsed at 2 years was 27.0% in the dimethyl fumarate BID group, and 26.0% in the dimethyl fumarate TID group compared to 46.0% in the placebo group (Table 17, Figure 5).

Table 17: Primary efficacy outcome results: DEFINE

Primary outcome: DEFINE		Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)
Proportion of patients relapsing at 2 years[†]	Estimated proportion of patients	0.27	0.26	0.46
	Hazard ratio[‡] (95% CI)	0.51 (0.40, 0.66)	0.50 (0.39, 0.65)	-
	p value[‡]	<0.0001	<0.0001	-
	% reduction vs placebo	49%	50%	-

[†]Based on the Kaplan-Meier method; [‡]versus placebo.
Abbreviations: BID, twice daily; CI, confidence interval; TID, three times daily.

Figure 5: Kaplan-Meier estimate of the proportion of patients relapsed at 2 years (DEFINE)



Number of patients at risk

	BL	12	24	36	48	60	72	84	96
Placebo	408	356	321	282	243	224	205	190	115
240 mg BID	410	353	324	303	286	267	255	243	154
240 mg TID	416	346	322	301	286	270	251	244	166

Abbreviations: BID, twice daily; CI, confidence interval; TID, three times daily.

Eight sensitivity analyses of the primary endpoint were performed:

- Three used logistic regression, varying the assumptions around patients with an unknown relapse status
    1. Subjects in the ITT population who withdrew from the study or discontinued study treatment/switched to an alternative MS medication for reasons indicative of an MS relapse or lack of efficacy were assumed to have relapsed.
    2. As above, using only ITT patients who completed the study.
    3. All patients in the ITT population with an unknown relapse status were assumed to have relapsed.
- Five used the Cox proportional hazards model

1. An analysis using site-assessed objective relapses, as defined by the protocol-defined relapse criteria, instead of INEC confirmed relapses.
2. An analysis including data after switching to an alternative MS medication.
3. An analysis using all relapses reported on the unscheduled relapse case report form
4. An analysis using the per-protocol population.
5. An analysis using the ITT population, excluding 23 patients enrolled at the three sites with GCP violations.

Figure 6: Sensitivity analyses of the primary efficacy outcome: DEFINE *(Academic in confidence information removed)*

Abbreviations: BID, twice daily; CI, confidence interval; TID, three times daily.

Conclusion

All of the sensitivity analyses performed (Figure 6) supported the result of the primary endpoint analysis, with significantly fewer patients experiencing a relapse in all dimethyl fumarate groups vs placebo.

Primary Efficacy Results: CONFIRM

The total number of INEC-confirmed relapses over 2 years was 124, 106, 163, and 212, for dimethyl fumarate BID, dimethyl fumarate TID, GA and placebo, respectively. After adjustment for baseline EDSS score, age, region, and number of relapses in the previous 2 years, the ARR was

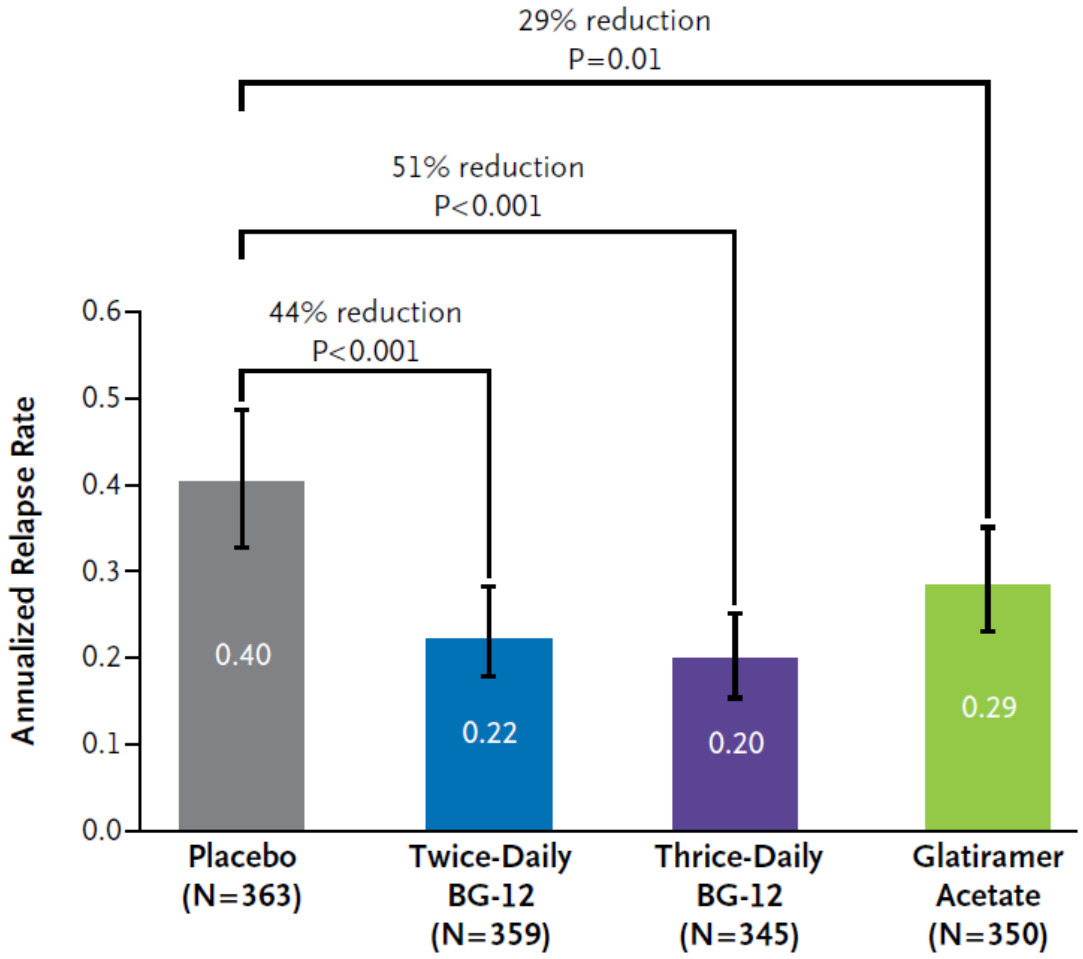
calculated to be 0.22 for dimethyl fumarate BID, 0.20 for dimethyl fumarate TID, and 0.29 for GA, compared with 0.40 for placebo (Table 18 and Figure 7). This corresponded to a 44% reduction in ARR for dimethyl fumarate BID (rate ratio 0.56, 95% CI 0.42–0.74; p<0.0001), compared with placebo.

Table 18: Primary efficacy outcome results: CONFIRM

Primary outcome: CONFIRM		Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=345)	GA (N=350)	Placebo (N=363)
ARR at 2 years	ARR (95% CI)	0.22 (0.18, 0.28)	0.20 (0.16, 0.25)	0.29 (0.23, 0.35)	0.40 (0.33, 0.49)
	Rate ratio[†] (95% CI)	0.56 (0.42, 0.74)	0.495 (0.37, 0.66)	0.71 (0.55, 0.93)	-
	p value[‡]	<0.0001	<0.0001	0.0128	-
	% reduction vs placebo	44%	50.5%	29%	-

[†]Ratio of active comparator to placebo; [‡]versus placebo.
Abbreviations: BID, twice daily; CI, confidence interval; GA, glatiramer acetate; TID, three times daily.

Figure 7: Primary efficacy outcome results: CONFIRM



Four sensitivity analyses of the primary endpoint were performed:

1. An analysis using site-assessed objective relapses, as defined by the protocol-defined relapse criteria, instead of INEC confirmed relapses.
2. An analysis including data after patients switched to an alternative MS medication.
3. An analysis using all relapses reported on the unscheduled relapse case report form
4. An analysis using the per-protocol population.

Figure 8: Sensitivity analyses of the primary efficacy endpoint: CONFIRM *(Academic in confidence information removed)*

Conclusion

All of the sensitivity analyses performed (Figure 8) supported the result of the primary endpoint analysis, with significantly fewer patients experiencing a relapse in all dimethyl fumarate group vs placebo.

Secondary Efficacy Results (DEFINE and CONFIRM)

Proportion of patients relapsed (CONFIRM only)

Analysis of the proportion of patients relapsed at 2 years demonstrated that dimethyl fumarate BID significantly reduced the number of patients experiencing relapses, compared with placebo (Table 19). The relative risk reduction for dimethyl fumarate BID was 34% (HR 0.66, 95% CI 0.51–0.86; p=0.0020), compared with placebo.

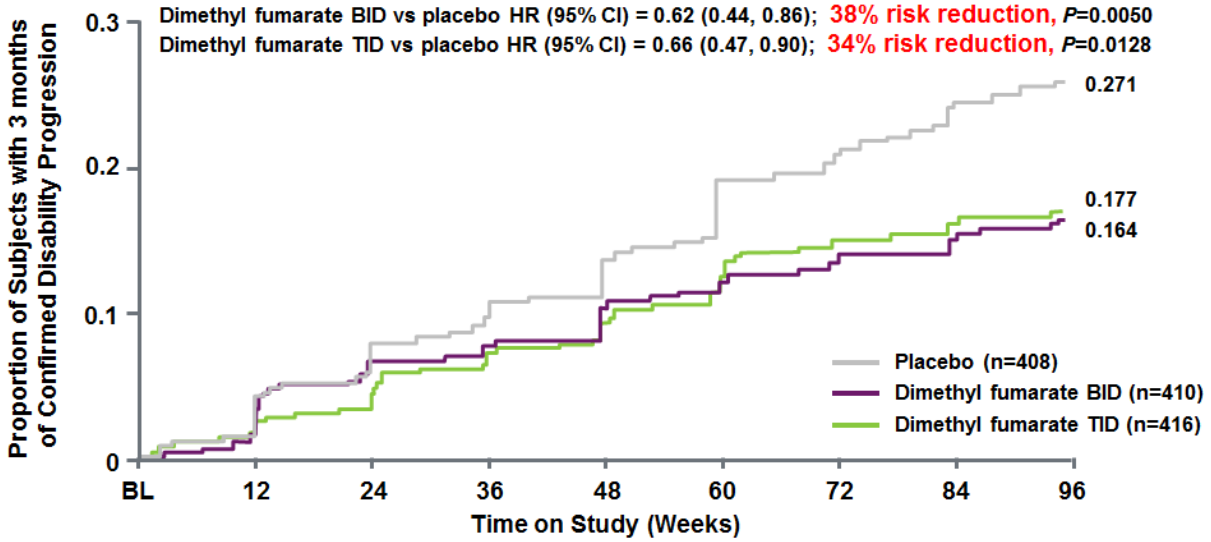
ARR (DEFINE only)

The analysis of the secondary efficacy outcome of ARR at 2 years demonstrated that dimethyl fumarate BID significantly reduced the ARR, by 53% (rate ratio 0.47, 95% CI 0.37–0.61; p<0.0001), compared with placebo (Table 19).

EDSS disability progression (DEFINE and CONFIRM)

In DEFINE, the risk of confirmed EDSS disability progression sustained for 3 months at 2 years was significantly reduced with dimethyl fumarate BID, by 38% compared with placebo (HR 0.62, 95% CI: 0.44, 0.87) (Table 19 and Figure 9).

Figure 9: Time to 3-month confirmed disability progression (DEFINE)

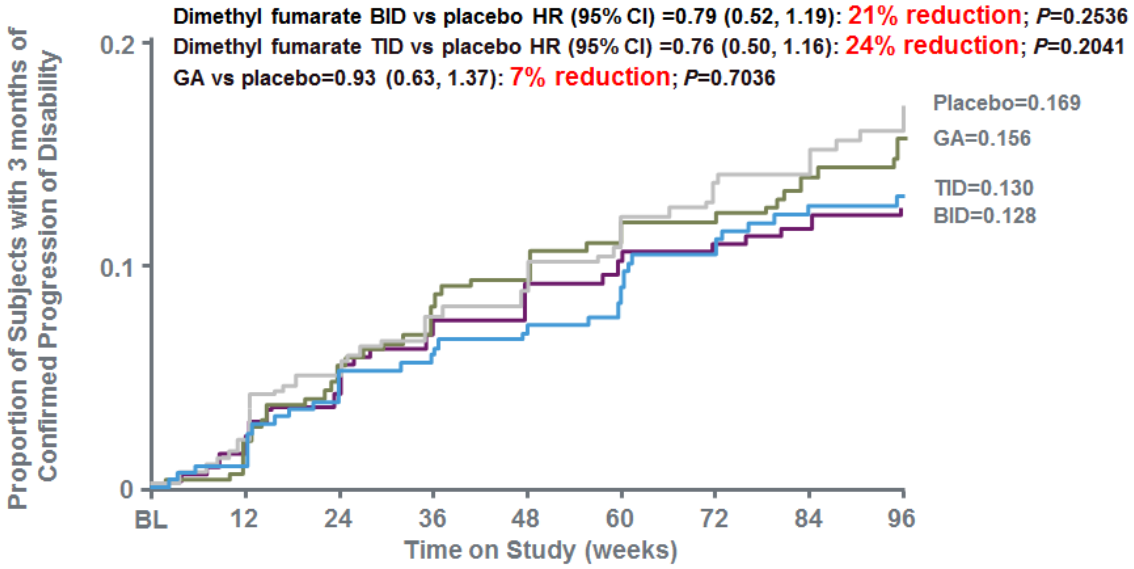


Abbreviations: BID, twice daily; CI, confidence interval; HR, hazard ratio; TID, three times daily.

In CONFIRM, dimethyl fumarate BID showed a reduction of 21% versus placebo in the time to 3-month confirmed disability progression that, although it did not reach statistical significance (HR 0.79, 95% CI 0.52–1.19; p=0.2536) (Table 19 and Figure 10), is consistent with the results from DEFINE. Disability progression was the last secondary end-point per ranked order in both studies and neither study was powered to detect a statistically significant difference. The proportion of patients in the placebo group with confirmed 12-week progression was much lower in the CONFIRM study (16.9%) compared with the DEFINE study (27.1%). However, patients with tentative progression who withdrew or switched to an alternative medication had their data censored, and were therefore not included in the disability progression data. An additional sensitivity analysis in which these patients were assumed to have progressed was therefore performed (dimethyl fumarate BID, n=6; dimethyl fumarate TID, n=7; placebo, n=15). In this analysis, the estimated proportion of patients with progression was 14.8% in the dimethyl fumarate

BID group, 14.4% in the dimethyl fumarate TID group, and 21.1% in the placebo group. The hazard ratios for disability progression at 2 years were 0.71 (95% CI, 0.49-1.0) for the dimethyl fumarate BID group and 0.70 (95% CI, 0.48-1.02) in the dimethyl fumarate TID group, representing reductions over placebo of 29% (p=0.0769) and 30% (p=0.0659), respectively. These results suggest that the primary analysis of 12-week confirmed progression may have been affected by a higher proportion of patients in the placebo group who had tentative progression but were censored after they withdrew from the study or switched to alternative MS medications before 12-week progression could be confirmed.

Figure 10: Time to 3-month confirmed disability progression (CONFIRM)



Abbreviations: BID, twice daily; CI, confidence interval; GA, glatiramer acetate; HR, hazard ratio; TID, three times daily.

MRI (DEFINE and CONFIRM)

In DEFINE, number of lesions was significantly reduced on T2- and Gd+ weighted MRI at 2 years with dimethyl fumarate BID, by 85% (mean ratio 0.15, 95% CI 0.10–0.23; p<0.0001) and 90% (mean ratio 0.10, 95% CI 0.05–0.22; p<0.0001), respectively, compared with placebo (Table 20).

In CONFIRM, analysis of the mean number of lesions on T2- and T1-weighted MRI at 2 years demonstrated that dimethyl fumarate reduced the lesion burden, by 71% (mean ratio 0.29, 95% CI 0.21–0.41; p<0.00010) and 57% (mean ratio 0.43, 95% CI 0.30–0.61; p<0.0001), respectively, compared with placebo (Table 20).

Table 19: Secondary clinical outcome results: DEFINE and CONFIRM

Secondary clinical outcomes		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=345)	GA (N=350)	Placebo (N=363)
Proportion of patients relapsed	Estimated proportion of patients	Primary outcome			0.291	0.241	0.321	0.410
	Hazard ratio[†] (95% CI)				0.66 (0.51, 0.86)	0.55 (0.42, 0.73)	0.71 (0.55, 0.92)	-
	p value[†]				0.0020	<0.0001	0.0097	-
	% reduction vs placebo				34%	45%	29%	-
ARR	ARR (95% CI)	0.17 (0.14, 0.21)	0.19 (0.15, 0.23)	0.36 (0.30, 0.44)	Primary outcome			
	Rate ratio[‡] (95% CI)	0.47 (0.37, 0.61)	0.52 (0.40, 0.67)	-				
	p value[†]	<0.0001	<0.0001	-				
	% reduction vs placebo	53%	48%	-				
EDSS disability progression[§]	Proportion progressed at 2 years (%)	16	18	27	13	13	16	17
	Hazard ratio[†] (95% CI)	0.62 (0.44, 0.87)	0.66 (0.48, 0.92)	-	0.79 (0.52, 1.19)	0.76 (0.50, 1.16)	0.93 (0.63, 1.37)	-
	p value[†]	0.0050	0.0128	-	0.2536	0.2041	0.7036	-
	% reduction vs placebo	38%	34%	-	21%	24%	7%	

All outcomes are at 2 years, unless otherwise stated. Grey highlighting indicates a statistically significant result vs placebo [†]Versus placebo; [‡]ratio of active comparator to placebo; [§]≥ 1.0-point increase in EDSS score from a baseline score ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase in score from a baseline of 0 that was sustained for 12 weeks.
Abbreviations: ARR, annualised relapse rate; BID, twice daily; CI, confidence interval; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhancing; SD, standard deviation; TID, three times daily.

Table 20: Secondary MRI outcome results: DEFINE and CONFIRM

Secondary MRI outcomes		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=176)	Dimethyl fumarate TID (N=184)	Placebo (N=180)	Dimethyl fumarate BID (N=169)	Dimethyl fumarate TID (N=170)	GA (N=175)	Placebo (N=167)
No. T2 lesions	Mean number (95% CI)	2.6 (2.0, 3.5)	4.4 (3.2, 5.9)	17.0 (12.9, 22.4)	5.1 (3.9, 6.6)	4.7 (3.6, 6.2)	8.0 (6.3, 10.2)	17.0 (13.5, 22.4)
	Mean ratio† (95% CI)	0.15 (0.10, 0.23)	0.26 (0.17, 0.38)	-	0.29 (0.21, 0.41)	0.27 (0.20, 0.38)	0.46 (0.33, 0.63)	-
	p value†	<0.0001	<0.0001	-	<0.0001	<0.0001	<0.0001	-
	% reduction vs placebo	85%	74%	-	71%	73%	54%	-
No. T1 lesions	Mean number±SD	Tertiary outcome			3.0 (2.3, 4.0)	2.4 (1.8, 3.2)	4.1 (3.2, 5.3)	7.0 (5.3, 9.2)
	Mean ratio† (95% CI)				0.43 (0.30, 0.61)	0.35 (0.24, 0.49)	0.59 (0.42, 0.82)	-
	p value†				<0.0001	<0.0001	0.0021	-
	% reduction vs placebo				57%	65%	41%	-
No. Gd+ lesions	Mean number±SD	0.1±0.6	0.5±1.7	1.8±4.2	Tertiary outcome			
	Odds ratio† (95% CI)	0.10 (0.05, 0.22)	0.27 (0.15, 0.46)	-				
	p value†	<0.0001	<0.0001	-				
	% reduction vs placebo	90%	73%	-				

All outcomes are at 2 years, unless otherwise stated. Grey highlighting indicates a statistically significant result vs placebo. †Versus placebo.
Abbreviations: BID, twice daily; CI, confidence interval; GA, glatiramer acetate; SD, standard deviation; TID, three times daily.

Tertiary outcomes: DEFINE and CONFIRM

Clinical outcome results

In DEFINE statistically significant results in favour of dimethyl fumarate BID, compared with placebo, were observed for:

- proportion of patients relapsed at 1 year (HR 0.49, 95% CI 0.36–0.67; p<0.0001)
- ARR at 1 year (rate ratio 0.50, 95% CI 0.37–0.68; p<0.0001)
- MSFC score (change in mean composite score from baseline 0.09±0.48, compared with -0.07±0.84; p=0.0006)
- Number of relapses requiring IV steroids outcomes (rate ratio 0.48, 95% CI 0.36–0.63).

In CONFIRM statistically significant results in favour of dimethyl fumarate BID, compared with placebo, were observed for:

- Proportion of patients relapsed at 1 year (HR 0.63, 95% CI 0.47–0.86; p=0.0030)
- ARR at 1 year (rate ratio 0.57, 95% CI 0.42–0.77; p=0.0002)
- Number of relapses requiring IV steroids (rate ratio 0.56, 95% CI 0.42–0.76; p=0.0002)

Of particular note are the proportion of patients relapsed and ARR at 1 year, which demonstrate that the efficacy of dimethyl fumarate is evident even in the early stages of treatment. Relapses requiring steroid treatment and hospitalisations for MS are also of interest, as these may be considered a surrogate for relapse severity. Relapses requiring steroid treatment demonstrated that dimethyl fumarate reduces relapse severity in both trials; while the reduction in hospitalisations did not reach significance, this outcome was numerically in favour of dimethyl fumarate BID. No significant difference between dimethyl fumarate and placebo was found for any other tertiary clinical outcome (Table 21).

MRI outcome results

In DEFINE and CONFIRM, statistically significant results in favour of dimethyl fumarate BID were found for the majority of the tertiary MRI outcomes (Table 22). Percentage brain atrophy change at 2 years significantly favoured dimethyl fumarate BID in DEFINE, although this result was not significant in the CONFIRM trial. Of particular note are the significant reductions in the number of T2 (mean ratio 0.16, 95% CI 0.11–0.24; p<0.0001 and 0.33, 95% CI 0.24–0.46; p<0.0001, respectively) and Gd+ (mean ratio 0.08, 95% CI 0.04–0.17; p<0.0001 and 0.13, 95% CI 0.07–0.23; p<0.0001, respectively) lesions at 1 year, compared with placebo, which demonstrate that the efficacy of dimethyl fumarate is evident even at the early stages of treatment.

PRO results

In DEFINE significant results in favour of dimethyl fumarate BID, compared with placebo, were observed for (Table 23):

- Change in global well-being VAS from baseline (mean change from baseline 0.4±20.0 vs -4.0±22.3, p=0.0031)
- SF-36 PCS (physical component score) (and the majority of sub-scales) of the SF-36 (mean change from baseline 0.5±0.71 vs -1.4±7.2, p=0.0003)
- Mean EQ-5D VAS change (mean change from baseline -0.3±15.7 s -4.2±17.8, p=0.0008)

In CONFIRM significant results in favour of dimethyl fumarate BID, compared with placebo, were observed for (Table 23):

- Change in global well-being VAS from baseline (mean change from baseline 0.3±22.0 vs -3.9±21.2, p=0.0003)
- SF-36 physical functioning (mean change from baseline 0.77±18.92 vs -2.15±18.95, p=0.0250)
- SF-36 role-physical (mean change from baseline 3.15±39.29 vs -2.24±36.68, p=0.0348)
- SF-36 general health (mean change from baseline 1.67±17.63 vs -0.58±15.76, p=0.0243)
- SF-36 PCS (mean change from baseline 0.49±7.85 vs -0.71±7.43, p=0.0217)

Table 21: Tertiary clinical outcome results: DEFINE and CONFIRM *(Academic in confidence information removed)*

Tertiary outcomes (clinical)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=345)	GA (N=350)	Placebo (N=363)
Proportion of patients relapsed at 1 year	Percentage of patients	17	18	31	20.6	19.1	23.9	31.8
	Hazard ratio† (95% CI)	0.49 (0.36, 0.67)	0.54 (0.40, 0.73)	-	0.63 (0.47, 0.86)	0.58 (0.42, 0.79)	0.71 (0.53, 0.95)	-
	p value†	<0.0001	<0.0001	-	0.0030	0.0006	0.0217	-
ARR at 1 year	ARR (95% CI)	0.18 (0.14, 0.24)	0.21 (0.16, 0.27)	0.37 (0.30, 0.45)	0.26 (0.20, 0.34)	0.25 (0.19, 0.32)	0.34 (0.27, 0.43)	0.46 (0.38, 0.57)
	Rate ratio‡ (95% CI)	0.50 (0.37, 0.68)	0.56 (0.42, 0.76)	-	0.57 (0.42, 0.77)	0.54 (0.40, 0.74)	0.73 (0.56, 0.97)	-
	p value†	<0.0001	0.0002	-	0.0002	<0.0001	0.0298	-
No. relapses requiring IV steroids	ARR requiring IV steroids (95% CI)	0.15 (0.12, 0.19)	0.15 (0.12, 0.19)	0.31 (0.25, 0.38)	0.19 (0.15, 0.25)	0.18 (0.14, 0.23)	0.26 (0.20, 0.32)	0.34 (0.28, 0.42)
	Rate ratio‡ (95% CI)	0.48 (0.36, 0.63)	0.49 (0.37, 0.64)	-	0.56 (0.42, 0.76)	0.51 (0.38, 0.70)	0.74 (0.56, 0.99)	-
	p value†	<0.0001	<0.0001	-	0.0002	<0.0001	0.0404	-
MS-related hospital-isations	Annualised rate (95% CI)	0.036 (0.021, 0.064)	0.030 (0.017, 0.055)	0.056 (0.032, 0.096)	0.038 (0.023, 0.061)	0.028 (0.016, 0.047)	0.032 (0.019, 0.052)	0.055 (0.036, 0.086)
	Rate ratio‡ (95% CI)	0.65 (0.41, 1.04)	0.55 (0.34, 0.88)	-	0.68 (0.42, 1.09)	0.50 (0.30, 0.85)	0.57 (0.35, 0.94)	-
	p value†	0.0708	0.0125	-	0.1092	0.0098	0.0282	-
MSFC score (change from	T25FW, mean±SD	-0.05±1.13	-0.15±1.32	-0.33±2.11	-0.13±0.82	-0.12±1.50	-0.07±1.02	-0.24±1.35
	p value†	0.1180	0.6901	-	0.1983	0.0380	0.0070	-

Tertiary outcomes (clinical)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=345)	GA (N=350)	Placebo (N=363)
baseline)	9-HPT, mean±SD	0.04±0.66	0.09±0.56	-0.03±0.69	0.05±0.56	0.03±0.55	0.06±0.61	0.04±0.61
	p value[†]	0.0031	0.0010	-	0.5357	0.7258	0.6262	-
	PASAT-3, mean±SD	0.22±0.58	0.24±0.66	0.15±0.69	0.13±0.65	0.15±0.57	0.16±0.67	0.09±0.58
	p value[†]	0.0041	0.0114	-	0.1096	0.2368	0.2498	-
	Composite[§], mean±SD	0.09±0.48	0.06±0.58	-0.07±0.84	0.02±0.46	0.02±0.61	0.05±0.49	-0.03±0.56
	p value[†]	0.0006	0.0004	-	0.0576	0.1986	0.0512	-
Progression of cognitive deficit[¶]	Proportion with progression (%)							
	Hazard ratio[†] (95% CI)							
	p value[†]							
Visual function[††] (change from baseline)	100% contrast, mean ±SD	0.7±6.6	-0.2±5.1	0.0±5.8	-0.3±6.2	-0.2±6.2	0.1±5.5	-0.5±5.5
	p value[†]	0.1461	0.9621	-	0.5858	0.6147	0.1606	-
	2.5% contrast, mean±SD	0.3±8.6	-0.2±8.0	-0.4±8.6	0.1±8.5	-0.3±8.7	0.0±8.1	-0.9±9.4
	p value[†]	0.1831	0.5689	-	0.0620	0.4685	0.1041	-
	1.25% contrast, mean±SD	-0.9±9.1	-1.4±8.9	-1.0±10.0	-0.4±10.1	-1.5±9.8	-0.9±10.5	-1.7±10.4
	p value[†]	0.5240	0.7350	-	0.0526	0.7877	0.3097	-

All outcomes are at 2 years, unless otherwise stated. Grey highlighting indicates a statistically significant result vs placebo. [†]Versus placebo; [‡]Ratio of active comparator to placebo; [§]Composite of T25FW, 9-HPT, and PASAT-3 scores; [¶]a 0.5 SD decrease from baseline on the PASAT-3, confirmed for 12 weeks; [††]as measured on Low-Contrast Sloan Letter Charts. Abbreviations: 9-HPT, 9-hole peg test; ARR, annualised relapse rate; BID, twice daily; CI, confidence interval; GA, glatiramer acetate; IV, intravenous; MSFC, multiple sclerosis functional composite; PASAT-3, paced audio serial addition test 3; SD, standard deviation; T25FW, timed 25-foot walk test; TID, three times daily.

Table 22: Tertiary MRI outcome results: DEFINE and CONFIRM *(Academic in confidence information removed)*

Tertiary outcomes (MRI)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=176)	Dimethyl fumarate TID (N=184)	Placebo (N=180)	Dimethyl fumarate BID (N=169)	Dimethyl fumarate TID (N=170)	GA (N=175)	Placebo (N=167)
No. T1 lesions	Mean number±SD	2.0±4.1	2.5±4.8	5.7±8.3	Secondary outcome			
	Mean ratio† (95% CI)	0.28 (0.20, 0.39)	0.37 (0.26, 0.52)	-				
	p value†	<0.0001	<0.0001	-				
Vol. T2 lesions at 1 and 2 years (mm^3)	Mean change from baseline to 1 year, mean±SD							
	p value†							
	Mean change from baseline to 2 years, mean±SD							
	p value†							
Vol. T1 lesions at 1 and 2 years (mm^3)	Mean change from baseline to 1 year, mean±SD							
	p value†							
	Mean change from baseline to 2 years, mean±SD							
	p value†							
Vol. Gd+ lesions at 1 and 2 years (mm^3)	Mean change from baseline to 1 year, mean±SD							
	p value†							
	Mean change from							

Tertiary outcomes (MRI)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=176)	Dimethyl fumarate TID (N=184)	Placebo (N=180)	Dimethyl fumarate BID (N=169)	Dimethyl fumarate TID (N=170)	GA (N=175)	Placebo (N=167)
	baseline to 2 years, mean±SD							
	p value†							
No. new T2 lesions at 1 year	Mean number±SD	2.0±4.8	3.0±7.4	10.1±18.3	3.1	2.8	4.6	9.5
	Mean ratio† (95% CI)	0.16 (0.11, 0.24)	0.25 (0.17, 0.37)	-	0.33 (0.24, 0.46)	0.30 (0.21, 0.42)	0.48 (0.35, 0.67)	-
	p value†	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001	-
No. Gd+ lesions at 1 year	Mean number±SD	0.1±0.7	0.4±2.8	1.4±3.1	0.4±1.6	0.4±1.1	0.7±1.9	2.2±5.6
	Odds ratio† (95% CI)	0.08 (0.04, 0.17)	0.13 (0.07, 0.25)	-	0.13 (0.07, 0.23)	0.23 (0.13, 0.39)	0.37 (0.23, 0.59)	-
	p value†	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001	-
	Mean number at 1 year±SD	Secondary outcome			0.5±1.67	0.4±1.18	0.7±1.75	2.0±5.59
	Odds ratio† (95% CI)				0.26 (0.15, 0.46)	0.35 (0.20, 0.59)	0.39 (0.24, 0.65)	-
	p value†				<0.0001	<0.0001	0.0003	-
Brain atrophy (change in brain volume from 4 months)	Mean number at 2 years±SD	-0.23±0.51	-0.26±0.51	-0.25+0.52	-0.41±0.73	0.23±0.63	-0.28±0.70	-0.19±0.80
	Odds ratio† (95% CI)	0.6065	0.8982	-	0.0857	0.4636	0.1190	-
	Percentage change at 2 years	-0.60+0.96	-0.72±0.90	-0.78±1.01	-0.89±1.72	-0.64±1.43	-0.65±1.41	-0.80±1.40
	p value†	0.0214	0.2478	-	0.8306	0.5621	0.7063	-
Brain MTR	Percentage change at 2 years (whole	0.13±1.47	0.10±1.42	-0.39±1.26	-0.85±4.91	-0.67±5.26	-0.02±5.87	0.39±5.17

Tertiary outcomes (MRI)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=176)	Dimethyl fumarate TID (N=184)	Placebo (N=180)	Dimethyl fumarate BID (N=169)	Dimethyl fumarate TID (N=170)	GA (N=175)	Placebo (N=167)
	brain)							
	p value†	0.0027	0.0051	-	0.0640	0.1078	0.4708	-
	Percentage change at 2 years (NABT)	0.19±1.44	0.12±1.42	-0.39±1.26	NA			
	p value†	0.0006	0.0029	-				
Conversion of Gd+ lesions to T1 lesions at 2 years	Total number converted/total Gd+ lesions							
	Odds ratio† (95% CI)							
	p value†							

All outcomes are at 2 years, unless otherwise stated. Grey highlighting indicates a statistically significant result vs placebo. †Versus placebo, ‡ratio of active comparator to placebo, §≥ 1.0-point increase in EDSS score from a baseline score ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase in score from a baseline of 0 that was sustained for 12 weeks.
Abbreviations: BID, twice daily; CI, confidence interval; GA, glatiramer acetate; Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; MTR, magnetisation transfer ratio; NABT, normal appearing b rain tissue; SD, standard deviation; TID, three times daily.

Table 23: Tertiary PRO results: DEFINE and CONFIRM

Tertiary outcomes (PROs)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=345)	GA (N=350)	Placebo (N=363)
Change in Global well-being VAS from baseline	Mean±SD	0.4±20.0	-0.8±19.8	-4.0±22.3	0.3±22.0	-0.3±20.6	2.1±22.3	-3.9±21.2
	p value†	0.0031	<0.0001	-	0.0003	0.0025	<0.0001	-
Change in SF-36 from baseline	Physical functioning, mean±SD	0.4±17.3	0.5±16.9	-3.7±17.3	0.77±18.92	1.71±18.28	0.27±16.47	-2.15±18.95
	p value†	0.0011	0.0002	-	0.0250	0.0022	0.0236	-
	Role-physical, mean±SD	2.8±37.9	5.3±37.2	-6.3±37.2	3.15+39.29	0.98±40.03	0.31±37.04	-2.24±36.68
	p value†	0.0001	<0.0001	-	0.0348	0.1525	0.4332	-
	Bodily pain, mean±SD	0.0+20.8	0.4±20.2	-1.9±20.2	0.15±23.29	1.57±21.10	2.30±21.80	-1.28±21.76
	p value†	0.1997	0.0270	-	0.1930	0.1222	0.0133	-
	General health, mean±SD	1.7±14.8	1.6±15.7	-1.6±15.8	1.67±17.63	-0.60±17.15	1.86±15.85	-0.58±15.76
	p value†	0.0006	0.0014	-	0.0243	0.7770	0.0317	-
	Vitality, mean±SD	1.2±17.1	2.4±16.6	-1.7±15.8	2.01±19.20	-1.02±18.03	1.07±17.54	0.36±17.65
	p value†	0.0376	0.0002	-	0.0788	0.2562	0.3934	-
	Social functioning, mean±SD	0.3±22.3	2.8±20.7	-4.0±19.7	0.57±21.45	0.36±22.22	-0.05±22.72	-0.58±23.01
	p value†	0.0055	<0.0001	-	0.1792	0.4913	0.5951	-
	Role-emotional, mean±SD	-1.0±37.7	1.6±37.6	-5.9±37.4	-0.96±38.42	1.90±41.03	1.42±42.05	-3.34±40.49
	p value†	0.0080	0.0005	-	0.3270	0.0426	0.0539	-

Tertiary outcomes (PROs)		DEFINE			CONFIRM			
		Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=345)	GA (N=350)	Placebo (N=363)
	Mental health, mean±SD	1.2±17.1	1.8±15.6	-1.0±15.5	1.65±16.35	0.58±16.58	0.31±16.81	0.59±17.76
	p value†	0.1016	0.0110	-	0.1057	0.8034	0.8654	-
	MCS, mean±SD	0.2±10.1	1.1±9.3	-1.1±8.9	0.45±9.80	0.11±9.72	0.20±10.29	-0.07±10.17
	p value†	0.0651	0.0017	-	0.1671	0.6868	0.6487	-
	PCS, mean±SD	0.5±7.1	0.5±7.1	-1.4±7.2	0.49±7.85	0.33±7.57	0.42±7.58	-0.71±7.43
	p value†	0.0003	<0.0001	-	0.0217	0.0519	0.0259	-
Change in EQ-5D from baseline	Mean EQ-5D change±SD	0.00±0.20	0.02±0.19	-0.01±0.20	0.01±0.21	0.00±0.19	0.00±0.20	0.00±0.20
	p value†	0.0910	0.0053	-	0.1454	0.6057	0.7835	-
	Mean EQ-5D VAS change±SD	-0.3±15.7	0.1±16.7	-4.2±17.8	-1.64±17.94	-0.82±17.30	1.04±19.26	-2.39±17.86
	p value†	0.0008	0.0002	-	0.1783	0.1272	0.0031	-

All outcomes are at 2 years, unless otherwise stated. Grey highlighting indicates a statistically significant result vs placebo. †Versus placebo.
Abbreviations: BID, twice daily; EQ-5D, European Quality of Life 5 Dimensions; GA, glatiramer acetate; MCS, mental component score; PCS, physical component score; PRO, patient reported outcome; SD, standard deviation; SF-36, short-form 36; VAS, visual analogue scale.

Pre-specified subgroup analyses (ITT)

The results of the pre-specified subgroup analyses for DEFINE are generally consistent with the results for the overall population. Of particular note is that the results were consistent for both treatment naïve (proportion relapsed: HR 0.37, 95% CI 0.24–0.57; ARR: rate ratio 0.33, 95% CI 0.21–0.52; EDSS progression: HR 0.38, 95% CI 0.22–0.65) and treatment experienced patients (proportion relapsed: HR 0.65, 95% CI 0.48–0.89; ARR: rate ratio 0.61, 95% CI 0.45–0.84; EDSS progression: HR 0.83, 95% CI 0.54–1.29), although the reduction in disability progression was not found to be significant for the previously treated subgroup (Table 24).

Table 24: Pre-specified subgroup analysis results – DEFINE *(Academic in confidence information removed)*

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
Relapses in year prior to study entry	**≤1**	**Dimethyl fumarate BID**	289	0.24	0.52 (0.38, 0.71)	289	0.15 (0.11,0.20)	0.48 (0.35,0.67)	288	0.15	0.59 (0.39, 0.89)
		Dimethyl fumarate TID	303	0.22	0.51 (0.37, 0.70)	303	0.17 (0.13,0.22)	0.54 (0.39,0.74)	303	0.17	0.66 (0.45, 0.98)
		Placebo	292	0.42	-	292	0.31 (0.25,0.39)	-	292	0.27	-
	≥2	**Dimethyl fumarate BID**	121	0.34	0.51 (0.34, 0.77)	121	0.24 (0.17,0.34)	0.45 (0.30,0.67)	121	0.18	0.67 (0.38, 1.20)
		Dimethyl fumarate TID	113	0.36	0.49 (0.32, 0.74)	113	0.26 (0.18,0.37)	0.48 (0.32,0.72)	113	0.21	0.71 (0.40, 1.28)
		Placebo	116	0.57	-	116	0.53 (0.39,0.72)	-	116	0.28	-
McDonald criteria	**1**	**Dimethyl fumarate**	336	0.29	0.53 (0.40, 0.69)	336	0.18 (0.14, 0.23)	0.48 (0.36, 0.62)	335	0.17	0.63 (0.44, 0.91)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression §		
			n	Proportion of patients	Hazard ratio† (95% CI)	n	ARR (95% CI)	Rate ratio‡ (95% CI)	n	Proportion progressed at 2 years	Hazard ratio† (95% CI)
		BID									
		Dimethyl fumarate TID	326	0.29	0.55 (0.42, 0.72)	326	0.20 (0.16, 0.25)	0.53 (0.41, 0.69)	326	0.17	0.63 (0.44, 0.91)
		Placebo	338	0.47	-	338	0.38 (0.31, 0.45)	-	338	0.27	-
	2,3 or 4	**Dimethyl fumarate BID**	74	0.19	0.45 (0.23, 0.87)	74	0.14 (0.07, 0.25)	0.46 (0.21, 1.02)	74	0.15	0.51 (0.22, 1.14)
		Dimethyl fumarate TID	90	0.16	0.37 (0.18, 0.72)	90	0.15 (0.09, 0.28)	0.52 (0.24, 1.11)	90	0.21	0.72 (0.34, 1.49)
		Placebo	70	0.40	-	70	0.30 (0.17, 0.53)	-	70	0.26	-
Prior MS treatment	**No**	**Dimethyl fumarate BID**	187	0.17	0.37 (0.24, 0.57)	187	0.09 (0.05, 0.15)	0.33 (0.21, 0.52)	187	0.12	0.38 (0.22, 0.65)
		Dimethyl fumarate TID	186	0.21	0.44 (0.29, 0.66)	186	0.10 (0.06, 0.18)	0.39 (0.25, 0.60)	186	0.14	0.46 (0.28, 0.77)
		Placebo	181	0.42	-	181	0.26 (0.15, 0.44)	-	181	0.28	-
	Yes	**Dimethyl fumarate BID**	223	0.36	0.65 (0.48, 0.89)	223	0.23 (0.18, 0.29)	0.61 (0.45, 0.84)	222	0.20	0.83 (0.54, 1.29)
		Dimethyl fumarate TID	230	0.31	0.55 (0.40, 0.76)	230	0.24 (0.18, 0.30)	0.63 (0.47, 0.86)	230	0.21	0.86 (0.56, 1.32)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression §		
			n	Proportion of patients	Hazard ratio† (95% CI)	n	ARR (95% CI)	Rate ratio‡ (95% CI)	n	Proportion progressed at 2 years	Hazard ratio† (95% CI)
		Placebo	227	0.50	-	227	0.37 (0.30, 0.46)	-	227	0.26	-
Baseline EDSS	**≤2.0**	**Dimethyl fumarate BID**	212	0.19	0.35 (0.24, 0.51)	212	0.10 (0.07, 0.14)	0.29 (0.20, 0.44)	212	0.15	0.52 (0.32, 0.82)
		Dimethyl fumarate TID	224	0.19	0.34 (0.23, 0.50)	224	0.11 (0.08, 0.16)	0.33 (0.22, 0.49)	224	0.15	0.50 (0.31, 0.81)
		Placebo	202	0.46	-	202	0.34 (0.26, 0.45)	-	202	0.29	-
	>2.0	**Dimethyl fumarate BID**	197	0.36	0.71 (0.51, 0.99)	197	0.27 (0.20, 0.35)	0.70 (0.50, 0.98)	197	0.18	0.73 (0.45, 1.17)
		Dimethyl fumarate TID	192	0.34	0.68 (0.49, 0.95)	192	0.28 (0.22, 0.37)	0.74 (0.53, 1.04)	192	0.21	0.85 (0.54, 1.33)
		Placebo	206	0.47	-	206	0.38 (0.30, 0.49)	-	206	0.25	-
Baseline T2 lesion volume	**≤median**	**Dimethyl fumarate BID**	87	0.28	0.50 (0.29, 0.84)	87	0.17 (0.11, 0.27)	0.53 (0.31, 0.88)	87	0.24	1.07 (0.55, 2.08)
		Dimethyl fumarate TID	87	0.35	0.67 (0.41, 1.09)	87	0.29 (0.20, 0.43)	0.89 (0.56, 1.42)	87	0.18	0.82 (0.40, 1.68)
		Placebo	96	0.50	-	96	0.33 (0.23, 0.46)	-	96	0.23	-
	>median	**Dimethyl fumarate**	89	0.23	0.33 (0.19, 0.57)	89	0.18 (0.11, 0.27)	0.37 (0.23, 0.62)	89	0.18	0.58 (0.30, 1.12)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression §		
			n	Proportion of patients	Hazard ratio† (95% CI)	n	ARR (95% CI)	Rate ratio‡ (95% CI)	n	Proportion progressed at 2 years	Hazard ratio† (95% CI)
		BID									
		Dimethyl fumarate TID	97	0.31	0.46 (0.28, 0.75)	97	0.21 (0.15, 0.32)	0.46 (0.29, 0.72)	97	0.23	0.68 (0.37, 1.26)
		Placebo	84	0.59	-	84	0.47 (0.34, 0.66)	-	84	0.33	-
MRI cohort	**Yes**	**Dimethyl fumarate BID**	176	0.25	0.41 (0.28, 0.59)	176	0.17 (0.13, 0.24)	0.43 (0.30, 0.62)	176	0.21	0.80 (0.51, 1.27)
		Dimethyl fumarate TID	184	0.33	0.56 (0.40, 0.79)	184	0.25 (0.19, 0.33)	0.63 (0.46, 0.88)	184	0.21	0.76 (0.48, 1.21)
		Placebo	180	0.54	-	180	0.40 (0.31, 0.51)	-	180	0.28	-
	No	**Dimethyl fumarate BID**	234	0.28	0.63 (0.45, 0.89)	234	0.17 (0.13, 0.23)	0.53 (0.37, 0.76)	233	0.13	0.48 (0.29, 0.78)
		Dimethyl fumarate TID	232	0.21	0.45 (0.31, 0.65)	232	0.14 (0.10, 0.19)	0.42 (0.29, 0.62)	232	0.15	0.57 (0.36, 0.90)
		Placebo	228	0.39	-	228	0.32 (0.25, 0.42)	-	228	0.27	-
Region	**1**	**Dimethyl fumarate BID**									
		Dimethyl fumarate TID									

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		Placebo									
	2	Dimethyl fumarate BID									
		Dimethyl fumarate TID									
		Placebo									
	3	Dimethyl fumarate BID									
		Dimethyl fumarate TID									
		Placebo									

Grey highlighting indicates a statistically significant result vs placebo. [†]Versus placebo, [‡]ratio of active comparator to placebo, [§]≥ 1.0-point increase in EDSS score from a baseline score ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase in score from a baseline of 0 that was sustained for 12 weeks.
Abbreviations: ARR, annualised relapse rate; BID, twice daily; CI, confidence interval; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis

The results of the pre-specified subgroup analyses for CONFIRM were generally consistent with those for the overall population. Of particular note is that the results were generally consistent for both treatment naïve (proportion relapsed: HR 0.73, 95% CI 0.51–1.05; ARR: rate ratio 0.64, 95% CI 0.44–0.95; EDSS progression: HR 0.56, 95% CI 0.30–1.03) and treatment experienced patients (proportion relapsed: HR 0.57, 95% CI 0.38–0.84; ARR: rate ratio 0.47, 95% CI 0.31–0.69; EDSS progression: HR 1.07, 95% CI 0.60–1.89), although the reduction in proportion of patients relapsed was not found to be significant for the treatment naive subgroup (Table 25).

Table 25: Pre-specified subgroup analysis results - CONFIRM *(Academic in confidence information removed)*

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression §		
			n	Proportion of patients	Hazard ratio† (95% CI)	n	ARR (95% CI)	Rate ratio‡ (95% CI)	n	Proportion progressed at 2 years	Hazard ratio† (95% CI)
Relapses in year prior to study entry	**≤1**	**Dimethyl fumarate BID**	252	0.26	0.61 (0.44, 0.85)	252	0.19 (0.14, 0.25)	0.52 (0.36, 0.73)	252	0.13	0.89 (0.54, 1.49)
		Dimethyl fumarate TID	224	0.18	0.41 (0.28, 0.61)	224	0.14 (0.10, 0.19)	0.37 (0.25, 0.55)	224	0.12	0.77 (0.45, 1.33)
		GA	237	0.28	0.67 (0.49, 0.93)	237	0.24 (0.18, 0.32)	0.67 (0.48, 0.94)	237	0.18	1.29 (0.80, 2.06)
		Placebo	254	0.38	-	254	0.36 (0.28, 0.47)	-	254	0.15	-
	≥2	**Dimethyl fumarate BID**	107	0.37	0.69 (0.45, 1.08)	107	0.33 (0.23, 0.47)	0.66 (0.42, 1.04)	107	0.13	0.62 (0.30, 1.27)
		Dimethyl fumarate TID	120	0.36	0.73 (0.48, 1.11)	120	0.35 (0.25, 0.50)	0.72 (0.47, 1.11)	120	0.16	0.73 (0.38, 1.43)
		GA	113	0.40	0.74 (0.49, 1.12)	113	0.39 (0.29, 0.54)	0.80 (0.53, 1.22)	113	0.10	0.44 (0.20, 0.94)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		Placebo	108	0.48	-	108	0.49 (0.36, 0.68)	-	108	0.22	-
McDonald criteria	**1**	**Dimethyl fumarate BID**	291	0.30	0.65 (0.49, 0.87)	291	0.23 (0.18, 0.30)	0.55 (0.40, 0.75)	291	0.13	0.73 (0.47, 1.15)
		Dimethyl fumarate TID	284	0.25	0.58 (0.43, 0.78)	284	0.22 (0.17, 0.29)	0.52 (0.38, 0.71)	284	0.13	0.72 (0.46, 1.14)
		GA	294	0.34	0.76 (0.58, 0.99)	294	0.30 (0.24, 0.38)	0.72 (0.54, 0.96)	294	0.17	0.97 (0.65, 1.47)
		Placebo	309	0.41	-	309	0.42 (0.34, 0.52)	-	309	0.18	-
	2,3 or 4	**Dimethyl fumarate BID**	68	0.27	0.69 (0.36, 1.34)	68	0.21 (0.12, 0.36)	0.63 (0.32, 1.27)	68	0.11	1.07 (0.34, 3.36)
		Dimethyl fumarate TID	61	0.20	0.44 (0.21, 0.92)	61	0.14 (0.07, 0.25)	0.41 (0.19, 0.88)	61	0.14	1.24 (0.39, 3.93)
		GA	56	0.21	0.54 (0.26, 1.15)	56	0.23 (0.13, 0.40)	0.68 (0.33, 1.39)	56	0.06	0.45 (0.11, 1.93)
		Placebo	54	0.39	-	54	0.33 (0.20, 0.56)	-	54	0.12	-
Prior MS treatment	**No**	**Dimethyl fumarate BID**	211	0.27	0.73 (0.51, 1.05)	211	0.20 (0.15, 0.28)	0.64 (0.44, 0.95)	211	0.08	0.56 (0.30, 1.03)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		Dimethyl fumarate TID	207	0.22	0.59 (0.40, 0.86)	207	0.17 (0.12, 0.24)	0.54 (0.36, 0.81)	207	0.14	0.85 (0.49, 1.46)
		GA	211	0.30	0.78 (0.55, 1.09)	211	0.24 (0.18, 0.33)	0.78 (0.54, 1.12)	211	0.14	0.88 (0.52, 1.49)
		Placebo	216	0.37	-	216	0.31 (0.23, 0.42)	-	216	0.16	-
	Yes	**Dimethyl fumarate BID**	148	0.32	0.57 (0.38, 0.84)	148	0.24 (0.17, 0.33)	0.47 (0.31, 0.69)	148	0.19	1.07 (0.60, 1.89)
		Dimethyl fumarate TID	138	0.28	0.52 (0.35, 0.79)	138	0.23 (0.16, 0.32)	0.45 (0.30, 0.68)	138	0.12	0.63 (0.32, 1.22)
		GA	139	0.35	0.67 (0.45, 0.98)	139	0.33 (0.25, 0.44)	0.65 (0.44, 0.94)	139	0.19	1.02 (0.57, 1.83)
		Placebo	147	0.47	-	147	0.51 (0.39, 0.66)	-	147	0.19	-
Baseline EDSS	**≤2.0**	**Dimethyl fumarate BID**	161	0.24	0.60 (0.40, 0.92)	161	0.18 (0.13, 0.27)	0.48 (0.30, 0.78)	161	0.12	0.78 (0.42, 1.45)
		Dimethyl fumarate TID	159	0.16	0.39 (0.24, 0.63)	159	0.13 (0.08, 0.20)	0.34 (0.20, 0.56)	159	0.13	0.77 (0.41, 1.42)
		GA	156	0.26	0.63 (0.42, 0.95)	156	0.24 (0.17, 0.33)	0.62 (0.39, 0.97)	156	0.16	0.94 (0.52, 1.68)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		Placebo	160	0.37	-	160	0.38 (0.27, 0.53)	-	160	0.17	-
	>2.0	**Dimethyl fumarate BID**	198	0.33	0.68 (0.49, 0.95)	198	0.28 (0.21, 0.37)	0.63 (0.45, 0.89)	198	0.13	0.74 (0.43, 1.29)
		Dimethyl fumarate TID	186	0.31	0.66 (0.47, 0.93)	186	0.28 (0.21, 0.37)	0.63 (0.44, 0.89)	186	0.13	0.72 (0.41, 1.28)
		GA	194	0.37	0.75 (0.54, 1.04)	194	0.35 (0.27, 0.45)	0.79 (0.57, 1.08)	194	0.16	0.88 (0.52, 1.49)
		Placebo	203	0.44	-	203	0.44 (0.35, 0.57)	-	203	0.16	-
Baseline T2 lesion volume	**≤median**	**Dimethyl fumarate BID**	83	0.27	0.64 (0.36, 1.16)	83	0.20 (0.12, 0.34)	0.50 (0.25, 0.99)	83	0.07	0.75 (0.25, 2.24)
		Dimethyl fumarate TID	93	0.24	0.64 (0.36, 1.14)	93	0.26 (0.16, 0.42)	0.63 (0.33, 1.22)	93	0.10	1.01 (0.36, 2.79)
		GA	87	0.25	0.58 (0.32, 1.04)	87	0.30 (0.19, 0.47)	0.74 (0.39, 1.38)	87	0.18	1.66 (0.67, 4.13)
		Placebo	77	0.37	-	77	0.41 (0.26, 0.65)	-	77	0.11	-
	>median	**Dimethyl fumarate BID**	86	0.33	0.51 (0.31, 0.83)	86	0.27 (0.17, 0.42)	0.50 (0.30, 0.82)	86	0.17	0.80 (0.37, 1.70)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		Dimethyl fumarate TID	76	0.34	0.60 (0.36, 0.99)	76	0.30 (0.19, 0.47)	0.56 (0.33, 0.92)	76	0.23	1.09 (0.53, 2.24)
		GA	87	0.39	0.65 (0.41, 1.03)	87	0.39 (0.26, 0.58)	0.72 (0.46, 1.14)	87	0.18	0.81 (0.39, 1.69)
		Placebo	90	0.51	-	90	0.54 (0.37, 0.79)	-	90	0.21	-
MRI cohort	**Yes**	**Dimethyl fumarate BID**	169	0.30	0.57 (0.39, 0.82)	169	0.24 (0.17, 0.33)	0.50 (0.33, 0.75)	169	0.12	0.79 (0.42, 1.46)
		Dimethyl fumarate TID	170	0.28	0.59 (0.40, 0.85)	170	0.27 (0.20, 0.37)	0.56 (0.38, 0.84)	170	0.16	1.02 (0.57, 1.83)
		GA	175	0.32	0.60 (0.42, 0.86)	175	0.35 (0.26, 0.46)	0.73 (0.50, 1.06)	175	0.18	1.13 (0.64, 1.97)
		Placebo	167	0.45	-	167	0.48 (0.36, 0.64)	-	167	0.16	-
	No	**Dimethyl fumarate BID**	190	0.28	0.72 (0.50, 1.05)	190	0.22 (0.16, 0.29)	0.62 (0.43, 0.91)	190	0.14	0.78 (0.45, 1.36)
		Dimethyl fumarate TID	175	0.20	0.49 (0.32, 0.75)	175	0.14 (0.10, 0.20)	0.40 (0.26, 0.62)	175	0.10	0.58 (0.31, 1.07)
		GA	175	0.33	0.80 (0.56, 1.15)	175	0.23 (0.17, 0.32)	0.67 (0.46, 0.98)	175	0.13	0.75 (0.42, 1.32)

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		Placebo	196	0.38	-	196	0.35 (0.26, 0.45)	-	196	0.17	-
Region	**1**	**Dimethyl fumarate BID**									
		Dimethyl fumarate TID									
		GA									
		Placebo									
	2	**Dimethyl fumarate BID**									
		Dimethyl fumarate TID									
		GA									
		Placebo									
	3	**Dimethyl fumarate BID**									
		Dimethyl fumarate TID									

Subgroup		Treatment	Proportion of patients relapsed			ARR			EDSS disability progression [§]		
			n	Proportion of patients	Hazard ratio[†] (95% CI)	n	ARR (95% CI)	Rate ratio[‡] (95% CI)	n	Proportion progressed at 2 years	Hazard ratio[†] (95% CI)
		GA									
		Placebo									

Grey highlighting indicates a statistically significant result vs placebo. [†]Versus placebo, [‡]ratio of active comparator to placebo, [§]≥ 1.0-point increase in EDSS score from a baseline score ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase in score from a baseline of 0 that was sustained for 12 weeks.
Abbreviations: ARR, annualised relapse rate; BID, twice daily; CI, confidence interval; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis.

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Freedom from disease activity

An additional post-hoc analysis of freedom from disease activity was performed for DEFINE and CONFIRM (86). In DEFINE, compared with placebo, patients receiving dimethyl fumarate BID were significantly more likely to be:

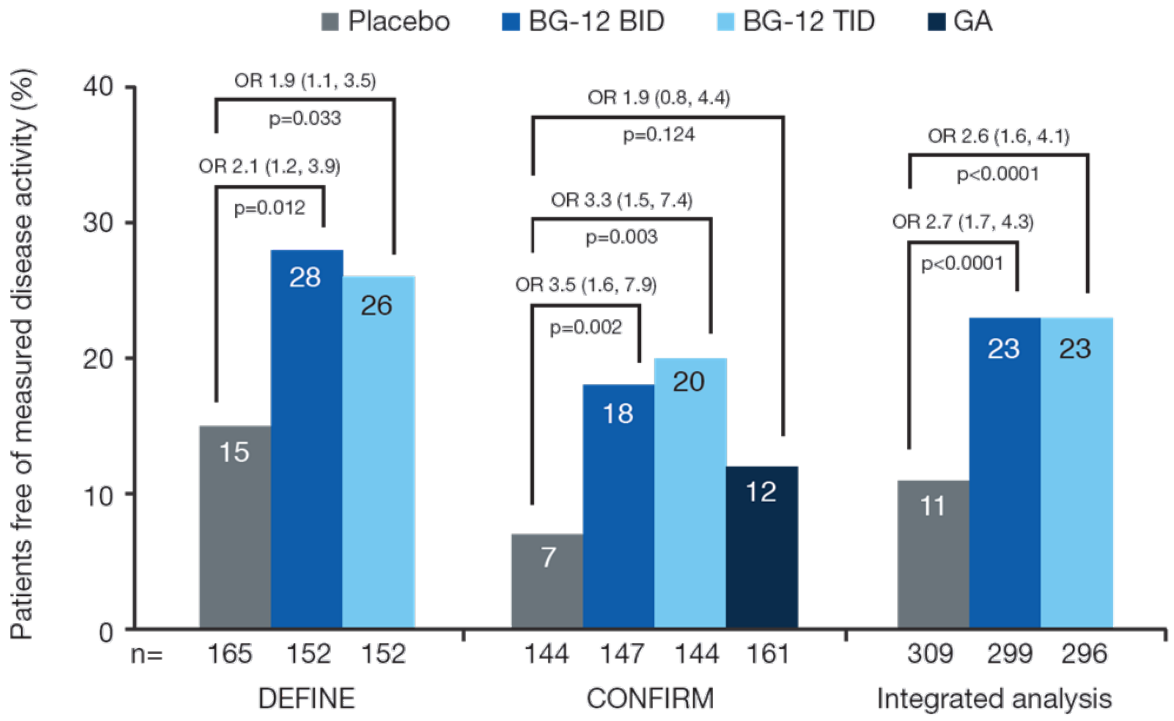
- Free from relapses (odds ratio (OR) 2.4, 95% CI 1.8–3.3; p<0.0001)
- Free from EDSS progression (OR 1.7, 95% CI 1.2–2.5; p=0.004)
- Free from new/newly enlarging T2 lesions (OR 2.4, 95% CI 1.5–3.8; p=0.0004)
- Free from Gd+ lesions (OR 9.4, 95% CI 5.1–17.1; p<0.0001)
- Free from overall clinical disease activity (relapses and EDSS progression, OR 2.4, 95% CI 1.8–3.2; p<0.0001)
- Free from overall MRI activity (T2 and Gd+ lesions, OR 2.1, 95% CI 1.3–3.5; p=0.004)
- Free from combined clinical and MRI disease activity (OR 2.1, 95% CI 1.2–3.9; p=0.012) (Figure 11)

In CONFIRM, compared with placebo, patients receiving dimethyl fumarate BID were significantly more likely to be:

- Free from relapses (odds ratio (OR) 1.8, 95% CI 1.3–2.5; p=0.0004)
- Free from new/newly enlarging T2 lesions (OR 2.8, 95% CI 1.5–5.3; p=0.002)
- Free from Gd+ lesions (OR 4.8, 95% CI 2.8–8.1; p<0.0001)
- Free from overall clinical disease activity (relapses and EDSS progression, OR 1.6, 95% CI 1.2–2.3; p=0.001)
- Free from overall MRI activity (T2 and Gd+ lesions, OR 3.0, 95% CI 1.5–5.9; p=0.002)
- Free from combined clinical and radiological disease activity (OR 3.5, 95% CI 1.6–7.9; p=0.002) (Figure 11)

EDSS progression (OR 1.3, 95% CI 0.9–2.1; p=0.211) numerically favoured dimethyl fumarate BID in CONFIRM, although the OR did not reach significance. A combined analysis of DEFINE and CONFIRM also demonstrated that, compared with placebo, patients receiving dimethyl fumarate BID were significantly more likely to be free from combined clinical and radiological disease activity (OR 2.7, 95% CI 1.7–4.3; p<0.0001) (Figure 11).

Figure 11: Freedom from combined clinical and radiological disease activity in DEFINE and CONFIRM



Source: Havrdova et al, 2013 (86).
Abbreviations: BID, twice daily; GA, glatiramer acetate; OR, odds ratio; TID, three times daily.

6.6 *Meta-analysis*

Summary

- Dimethyl fumarate was significantly better than placebo for all efficacy outcomes in the meta-analysis of DEFINE and CONFIRM
- Dimethyl fumarate was significantly better than GA for ARR and rate of relapses requiring steroids in the direct comparison from CONFIRM
- Significantly more GI events and flushing/skin reactions occurred with dimethyl fumarate than with placebo or GA
- Significantly more withdrawals due to AEs occurred with dimethyl fumarate than with placebo or GA; however, there was no difference in the number of withdrawals due to any cause

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- ***Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.***
- ***Statistically combine (pool) the results for the both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).***

- ***Provide an adequate description of the methods of statistical combination and justify their choice.***
- ***Undertake sensitivity analysis when appropriate.***
- ***Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).***

Methodology

A comparison of the various efficacy, safety, and tolerability outcomes among the included interventions was conducted by pooling data from DEFINE and CONFIRM using standard meta-analytic techniques.

The minimum requirements for a meta-analysis to be conducted for a particular combination of outcome, treatment comparison, and study grouping were as follows:

- For ARR and annualized steroid-treated relapse rate, the total number of event and person years
- For dichotomous and ordinal outcomes, except for the safety outcomes, the number of patients in which the outcome was observed and the size of the ITT population
- For safety outcomes, the number of patients in which the outcome was observed and the size of the treated population (if data were not reported for the treated population then ITT population was used)
- For continuous outcomes, the mean and a measure of variance for that outcome and the number of patients in which those statistics were calculated (size of the evaluable population)

Meta-analyses were performed in STATA® statistical software using the *metan* meta-analysis command. The reported outputs were:

- Both fixed- and random-effects model results
- Risk ratio (RR) for dichotomous outcomes, with their 95% CI
- Weighted mean difference (WMD) for continuous outcomes, with their 95% CI
- Associated p values
- I^2, indicator of observed heterogeneity
- Forest plots for all outcomes

Effect size from the fixed-effects model were estimated with the Mantel-Haenszel (M-H) method, while effect sizes from the random-effects model were estimated with the DerSimonian & Laird (D-L) approach (113). For continuous outcomes, fixed-effect was reported via inverse variance method. The key assumption underlying a fixed-effects model is that the effect sizes measurable in each pooled study are identical. The key assumption underlying a random-effects model is that the effect sizes measurable in each pooled study are different, but exchangeable.

The results of the meta-analyses were displayed using ‘forest plot’ diagrams, which display the results from each study on a separate row and present the pooled results in the bottom row. The graphical representation displays the treatment effect from each trial as a filled diamond (♦), with CIs marked as a line extending on either side of the diamond (-♦-). The percentage weight of individual studies was also presented within the plot under relevant headings (dichotomous data: M-H Weight for fixed-effect and D-L Weight for random-effect; continuous data: I-V Weight for fixed-effect and D-L Weight for random-effect). The overall

pooled estimate is denoted as a diamond, where the widest part in the centre is the point estimate and the horizontal width is the CI.

Efficacy outcomes

The results of the meta-analysis of DEFINE and CONFIRM are given in Table 26, with Forest plots for each outcome given in Figure 12–Figure 20. Dimethyl fumarate was found to be significantly better than placebo for all outcomes, and for ARR and ARR requiring steroids when compared with GA.

Figure 12: Forest plot depicting the meta-analysis results for ARR with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio <1 indicates better efficacy of intervention.
Abbreviations: ARR, annualized relapse rate; BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; I-V, Inverse Variance, indicates fixed effect model.

Figure 13: Forest plot depicting the meta-analysis results for annualized steroid-treated relapse rate with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio <1 indicates better efficacy of intervention.
Abbreviations: ARR, annualized relapse rate; BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; I-V, Inverse Variance, indicates fixed effect model; M-H, Mantel–Haenszel, indicates fixed effect model.

Figure 14: Forest plot depicting the meta-analysis results for proportion of patients with relapse at 12 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio <1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; RR, Risk Ratio.

Figure 15: Forest plot depicting the meta-analysis results for proportion of patients with relapse at 24 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio <1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; RR, Risk Ratio.

Figure 16: Forest plot depicting the meta-analysis results for patients remaining relapse free at 12 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio >1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; RR, Risk Ratio.

Figure 17: Forest plot depicting the meta-analysis results for patients remaining relapse free at 24 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio >1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; RR, Risk Ratio.

Figure 18: Forest plot depicting the meta-analysis results for change in EDSS score from baseline at 24 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

WMD >1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; EDSS, Expanded Disability Status Scale; I-V, Inverse Variance, indicates fixed effect model; M-H, Mantel–Haenszel, indicates fixed effect model; WMD, Weighted Mean Difference.

Figure 19: Forest plot depicting the meta-analysis results for disability progression sustained for 3 months at 24 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio >1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; RR, Risk Ratio.

Figure 20: Forest plot depicting the meta-analysis results for disability progression sustained for 6 months at 24 months with dimethyl fumarate BID compared to placebo *(Academic in confidence information removed)*

Risk ratio >1 indicates better efficacy of intervention.
Abbreviations: BID, twice daily; CI, confidence interval; D+L, DerSimonian and Laird, indicates random effect model; M-H, Mantel–Haenszel, indicates fixed effect model; RR, Risk Ratio.

Table 26: Meta-analysis results for the efficacy outcomes from DEFINE and CONFIRM *(Academic in confidence information removed)*

Outcome	Intervention	Comparator	Number of studies	N	Effect size measure	Fixed effect		Random effect		I^2
						Effect size (95% CI)	p value	Effect size (95% CI)	p value	
ARR	Dimethyl fumarate BID	Placebo								
		GA OD								
ARR-steroids	Dimethyl fumarate BID	Placebo								
		GA OD								
Proportion of patients with relapse at 24 months	Dimethyl fumarate BID	Placebo								
		GA OD								
Proportion of patients with relapse at 12 months	Dimethyl fumarate BID	Placebo								
		GA OD								
Patients remaining relapse free at 24 months	Dimethyl fumarate BID	Placebo								
		GA OD								
Patients remaining relapse free at 12 months	Dimethyl fumarate BID	Placebo								
		GA OD								
Change in EDSS at 24 months	Dimethyl fumarate BID	Placebo								
		GA OD								
Confirmed disability progression sustained for 3 months at 24 months	Dimethyl fumarate BID	Placebo								
		GA OD								
Confirmed disability progression sustained for 6 months at 24 months	Dimethyl fumarate BID	Placebo								
		GA OD								

Grey highlighting indicates a statistically significant result.
Abbreviations: ARR, annualised relapse rate; BID, twice daily; CI, confidence interval; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; $I^{2:}$ Heterogeneity; NA, not applicable; OD, once daily; RR, risk ratio; WMD, weighted mean difference.

Safety outcomes

The results of the meta-analysis for the safety outcomes are summarised in Table 27.

Table 27: Meta-analysis results for the safety outcomes from DEFINE and CONFIRM *(Academic in confidence information removed)*

Outcome	Intervention	Comparator	Number of studies	N	Fixed effect		Random effect		I^2
					RR (95% CI)	p value	RR (95% CI)	p value	
Abdominal pain	Dimethyl fumarate BID	Placebo							
		GA OD							
Upper abdominal pain	Dimethyl fumarate BID	Placebo							
		GA OD							
ALT increased	Dimethyl fumarate BID	Placebo							
		GA OD							
Any AEs	Dimethyl fumarate BID	Placebo							
		GA OD							
Any GI disorder	Dimethyl fumarate BID	Placebo							
		GA OD							
Any serious AEs	Dimethyl fumarate BID	Placebo							
		GA OD							
Arthralgia	Dimethyl fumarate BID	Placebo							
		GA OD							
Atrioventricular conduction block (first degree)	Dimethyl fumarate BID	Placebo							
		GA OD							
Back pain	Dimethyl fumarate BID	Placebo							
		GA OD							
Bradycardia	Dimethyl fumarate BID	Placebo							
		GA OD							
Chest pain	Dimethyl fumarate BID	Placebo							
		GA OD							
Cough	Dimethyl fumarate BID	Placebo							

Outcome	Intervention	Comparator	Number of studies	N	Fixed effect		Random effect		I^2
					RR (95% CI)	p value	RR (95% CI)	p value	
		GA OD							
Depression		Placebo							
	Dimethyl fumarate BID	GA OD							
Diarrhoea		Placebo							
	Dimethyl fumarate BID	GA OD							
Fatigue		Placebo							
	Dimethyl fumarate BID	GA OD							
Flu-like symptoms		Placebo							
	Dimethyl fumarate BID	GA OD							
Flushing		Placebo							
	Dimethyl fumarate BID	GA OD							
Gastroenteritis		Placebo							
	Dimethyl fumarate BID	GA OD							
Headache		Placebo							
	Dimethyl fumarate BID	GA OD							
Influenza		Placebo							
	Dimethyl fumarate BID	GA OD							
Leukopenia		Placebo							
	Dimethyl fumarate BID	GA OD							
Lower respiratory tract infections		Placebo							
	Dimethyl fumarate BID	GA OD							
Nausea		Placebo							
	Dimethyl fumarate BID	GA OD							
Pain in extremity		Placebo							
	Dimethyl fumarate BID	GA OD							
Pruritus		Placebo							
	Dimethyl fumarate BID	GA OD							

Outcome	Intervention	Comparator	Number of studies	N	Fixed effect		Random effect		I^2
					RR (95% CI)	p value	RR (95% CI)	p value	
Rash	Dimethyl fumarate BID	Placebo							
		GA OD							
Urinary tract infection	Dimethyl fumarate BID	Placebo							
		GA OD							

Grey highlighting indicates a statistically significant result. Risk ratios <1 indicate better safety of the intervention
Abbreviations: AE, adverse events; ALT, alanine transaminase; BID, twice daily; CI, confidence interval; GA, glatiramer acetate; GI, gastro-intestinal; I^2: Heterogeneity; NA, not applicable; OD, once daily; RR, risk ratio.

Tolerability outcomes

The results of the meta-analysis of tolerability outcomes are presented in Table 28.

Table 28: Meta-analysis of tolerability outcomes from DEFINE and CONFIRM *(Academic in confidence information removed)*

Outcome	Intervention	Comparator	Number of studies	N	Fixed effect		Random effect		I^2
					RR (95% CI)	p value	RR (95% CI)	p value	
Discontinuation due to adverse events	Dimethyl fumarate BID	Placebo							
		GA OD							
Discontinuation due to any cause	Dimethyl fumarate BID	Placebo							
		GA OD							
Discontinuation due to death	Dimethyl fumarate BID	Placebo							
		GA OD							

Grey highlighting indicates a statistically significant result. Risk ratios <1 indicate better safety of the intervention
Abbreviations: BID, twice daily; CI, confidence interval; GA, glatiramer acetate; I^2: Heterogeneity; NA, not applicable; OD, once daily; RR, risk ratio.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

N/A

6.6.3 If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

The study by Kappos et al (56) was excluded from the meta-analysis as it did not include the licensed dose of dimethyl fumarate (Table 7).

6.7 Indirect and mixed treatment comparisons

Summary of results

- **A mixed treatment comparison found that dimethyl fumarate was:**
  - Significantly better than placebo for ARR, proportion of patients relapsed at 24 months, proportion of patients relapse free at 24 months, and confirmed disability progression sustained for 3 months
  - Significantly better than all IFNs (Avonex®, Rebif®, and Betaferon®/Extavia®), and GA (Copaxone®), and both doses of teriflunomide (Aubagio®) for ARR
  - Significantly better than all IFNs (Avonex®, Rebif®, and Betaferon®/Extavia®), GA (Copaxone®) and teriflunomide 7 mg (Aubagio®) for proportion of patients relapsed at 24 months
  - Significantly better than IM IFNβ-1a 30 µg (Avonex®) for annualised steroid treated relapse rate and patients remaining relapse free at 24 months
  - Significantly better than SC IFNβ-1a 22 µg TIW (Rebif® 22 µg) for annualised steroid treated relapse rate
  - Difference in proportion of patients relapse free at 24 months is statistically significant in favour of natalizumab (Tysabri®) and fingolimod (Gilenya®)
  - Difference in change in EDSS score at 24 months is statistically significant and in favour of SC IFNβ-1b 250 µg EOD (Betaferon®/Extavia®)
  - Differences in ARR and annualised steroid treated relapse rate were statistically significant and in favour of natalizumab (Tysabri®)

No other significant differences were found between dimethyl fumarate and the comparators for any other outcomes.

In line with the scope issued by NICE, a de novo mixed treatment comparison was performed to assess the relative efficacy of dimethyl fumarate against the other relevant treatments for RRMS, including IFN, GA, natalizumab, and fingolimod. Data for dimethyl fumarate were derived from the DEFINE and CONFIRM RCTs, and a common placebo comparator was used to compare the available therapies. Although not defined as a relevant comparator in the scope, data from teriflunomide trials were included to strengthen the placebo arm. The NICE scope deemed several subgroups as relevant (inadequate response to therapy, intolerant to therapy, highly active RRMS, rapidly evolving severe RRMS); however, these subgroups have not been specifically examined in the majority of trials. There is therefore a lack of data for the comparators, and it was not possible to perform analyses in these subgroups. However, the overall populations in these trials include patients in these subgroups and are therefore indicative of efficacy in these groups.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 10.4, appendix 4.

Please see Section 6.1 for the methods used to identify trials for use in the mixed treatment comparison of dimethyl fumarate with other treatments for RRMS.

6.7.2 Please follow the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Study selection

Eligibility criteria and a flow diagram of included and excluded studies can be found in Section 6.2.

Summary of methodology of relevant RCTs

The included trials are summarised in Table 29, with the baseline characteristics of the patient population in Table 30.

Table 29: Summary of methodology of relevant RCTs

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
AFFIRM	Polman, 2006 (62)	Randomised, multicentre, international, double-blind, placebo-controlled Phase III study Cross-over was not permitted	99 sites across Europe, North America, Australia, and New Zealand	• IV natalizumab 300 mg OM (627) • Placebo (315)	24 months	• Aged 18–50 years • RRMS • EDSS score 0 to 5.0 • MRI showing lesions consistent with multiple sclerosis with ≥ 1 medically documented relapse within the 12 months before study initiation • No IFNβ or GA therapy within 6 months of randomisation
BECOME	Cadavid, 2009 (49)	Phase IV trial	2 sites in the USA	• SC GA 20 mg OD (39) • SC IFNβ-1b 250 µg EOD (36)	24 months	• Aged 18–55 years • EDSS score 0–5.5 • RRMS with ≥ 1 clinical and/or MRI attacks during the 6 previous months OR • CIS characteristic of CNS demyelination (optic neuritis or transverse myelitis or brainstem attack) confirmed on examination with onset within the 6 previous months plus evidence of dissemination in time and space
BEYOND	O'Connor, 2009 (61)	Prospective, randomised, multicentre, international, double-blind, Phase III trial Cross-over was not permitted	198 sites in 26 countries worldwide	• SC GA 20 mg OD (448) • SC IFNβ-1b 250 µg EOD (897) • SC IFNβ-1b 500 µg EOD (899)	At least 2 years of follow-up (maximum of 3.5 years)	• Aged 18–55 years • Treatment-naive • RRMS with ≥ 1 relapse in the year before entry into the study • Treatment-naive • EDSS score 0–5
NA	Bornstein, 1987 (47)	Prospective randomised trial. Cross-over was not permitted	Single centre in the US	• SC GA 20 mg OD (25) • Placebo (25)	24 months	• Aged 20–35 years • MS with ≥ 2 exacerbations in the two years before admission • Kurtzke Disability Status Scale ≤ 6

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
BRAVO	Vollmer, 2011 (72)	Prospective, randomised, multicentre, international, double blind[†], Phase III trial Cross-over was not permitted	153 sites in 18 countries worldwide	• IM IFNβ-1a 30 µg OW (447) • Placebo (450) • Laquinimod (n=434)	24 months	• RRMS with EDSS 0–5.5 • ≥1 relapse in prior 12 months, or 2 relapses in prior 24 months, or 1 relapse in past 12–24 months with 1 Gd+ lesion in the year prior to screening
NA	Calabrese, 2011 (50)	Prospective, randomised, single-centre, Phase IV trial Cross-over was not permitted	Single centre in Italy	• SC GA 20 mg OD (48) • IM IFNβ-1a 30 µg OW (47) • SC IFNβ-1a 44 µg TIW (46)	24 months	• Aged 18–55 years • RRMS • EDSS score ≤ 5.0
CONFIRM	CSR 109MS302, 2011 (29)	Randomised, multicentre, international, double-blind (dimethyl fumarate and placebo arms), placebo-controlled, Phase III trial Cross-over was not permitted	200 sites across 28 countries worldwide	• Oral dimethyl fumarate 240 mg BID (362) • Oral dimethyl fumarate 240 mg TID (345) • SC GA 20 mg OD (360) • Placebo (363)	24 months	• Aged 18–55 years • RRMS • EDSS score 0–5.0 • ≥ 1 relapse in the 12 months prior to randomisation with a brain MRI demonstrating lesions consistent with MS or evidence of Gd+ lesions of the brain on an MRI performed within the six months prior to randomisation • No IFNβ or GA treatment within 3 months of randomisation
Copolymer 1 Multiple Sclerosis trial	Johnson, 1995 (34)	Randomised, multicentre, international, double-blind, placebo-controlled Phase III trial Cross-over was not permitted	11 sites across the US	• SC GA 20 mg OD (125) • Placebo (126)	24 months	• Aged 18–45 years • Ambulatory patients • EDSS score 0–5.0 • MS with ≥ 2 relapses in the 2 years prior to entry and onset of the first relapse ≥ 1 year before randomisation, with a period of neurologic stability and freedom from corticosteroid therapy for ≥ 30 days prior to entry

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
DEFINE	CSR 109MS301, 2011 (30)	Randomised, multicentre, international, double-blind, placebo-controlled, Phase III trial Cross-over was not permitted	198 sites across 28 countries worldwide	• Oral dimethyl fumarate BID (411) • Oral dimethyl fumarate TID (416) • Placebo (410)	24 months	• Aged 18–55 years • RRMS • EDSS score 0–5.0 • ≥ 1 relapse within the 12 months prior to randomisation, with a prior brain MRI demonstrating lesions consistent with MS, or evidence of Gd+ lesions on an brain MRI performed within the six weeks prior to randomisation • No IFNβ or GA treatment within 3 months of randomisation
NA	Etemadifar, 2006 (55)	Randomised, singe-centre, single-blind (physicians assessing outcomes) trial Cross-over was not permitted	Single centre in Iran	• IM IFNβ-1a 30 µg OW (30) • SC IFNβ-1a 44 µg TIW (30) • SC IFNβ-1b 250 µg EOD (30)	24 months	• Aged 15–50 years • EDSS score 0–5.0 • Relapsing MS with ≥ 2 relapses within the 2-year period to treatment initiation
European/ Canadian glatiramer acetate trial	Comi, 2001 (48)	Randomised, multicentre, international, double-blind, placebo-controlled trial Cross-over was not permitted	29 sites across Europe and Canada	• SC GA 20 mg OD (119) • Placebo (120)	9 months	• Adult patients • RRMS for ≥ 1 year • EDSS score 0–5 • ≥ 1 documented relapse in previous two years and ≥ 1 Gd+ lesion on their screening brain MRI • GA naïve

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
EVIDENCE	Schwid, 2007 (63)	Randomised, multicentre, international, single-blind (physicians assessing outcomes) trial Cross-over was permitted after 48 weeks of initial treatment	56 sites in 10 countries	• IM IFNβ-1a 30 µg OW (338) • SC IFNβ-1a 44 µg TIW (339)	1-2 years Median duration of treatment was 62 weeks in the comparative phase and 34 weeks in the crossover phase	• Aged 18–55 years • RRMS • IFN-naïve • EDSS scores 0–5.5 • ≥ 2 exacerbations in the previous 2 years • IFNβ naïve
FREEDOMS	Kappos, 2010 (58)	Randomised, multicentre, international, double-blind, placebo-controlled Phase III trial Cross-over was not permitted	138 sites in 22 countries	• Oral fingolimod 1.25 mg OD (429) • Oral fingolimod 0.5 mg OD (425) • Placebo (418)	24 months	• Aged 18–55 years • EDSS score 0–5.5 • RRMS with ≥ 1 relapses in the previous year and ≥ 2 relapses in the previous two years • No IFNβ or GA therapy for ≥ 3 months before randomisation
FREEDOMS II	Calabresi 2012 (68)	Randomised, multicentre, international, double-blind, placebo controlled Phase III trial Cross-over was not permitted	Mainly USA (no additional information provided in poster)	• Oral fingolimod 0.5 mg OD (358) • Oral fingolimod 1.25 mg OD (370) • Placebo (355)	2 years	• Aged 18–55 years • EDSS score 0–5.5 • RRMS with ≥ 1 relapses in the previous year and ≥ 2 relapses in the previous two years • IFNβ or GA therapy stopped 3 or more months before randomization and natalizumab at least 6 months prior to randomization

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
IFNβ MS trial	Sibley, 1995 (64)	Phase III trial	11 sites (countries not stated)	• SC IFNβ-1b 250 µg EOD (124) • Placebo (123)	Up to a median of 48 months on study treatment	• Aged 18–50 years • MS ≥ 1 year • EDSS 0–5.5 • ≥ 2 acute exacerbations in the previous 2 years, with clinical stability for ≥ 30 days before entry •
IMPROVE	DeStefano, 2010 (52)	Randomised, multicentre, double-blind (prior to cross-over, rater blinded post-cross-over), placebo controlled Phase III trial After 4 months of treatment, all patients received IFNβ-1a 44 µg for a further 6 months	Multicentre (countries not stated)	• SC IFNβ-1a 44 µg TIW (120) • Placebo (60)	10 months	• Aged 18–60 years • RRMS for ≥ 12 months • EDSS score 0–5.5 • ≥ 1 clinical event and Gd+ lesion within six months prior to randomisation
INCOMIN	Durelli, 2002 (53)	Prospective, randomised, multicentre, single-blind (physicians performing assessments) trial Cross-over was not permitted	15 sites in Italy	• IM IFNβ-1a 30 µg OW (92) • SC IFNβ-1b 250 µg OW (96)	24 months	• Aged 18–50 years • RRMS • EDSS score 1–3.5 • ≥ 2 clinically documented relapses during the preceding two years and no relapse for ≥ 30 days prior to study entry • No prior treatment with IFNβ

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
NA	Kappos, 2011 (57)	Randomised, multicentre, international, double-blind, placebo controlled Phase II trial. Cross-over was not permitted.	79 sites across 20 countries	• IM IFNβ-1a 30 µg OW (54) • IV ocrelizumab 600 mg (55) • IV ocrelizumab 2000 mg (55) • Placebo (54)	12 months	• Aged 18–55 years • RRMS • EDSS 1–6.0 • ≥ 2 relapses within 3 years of screening, ≥ 1 of which occurred in the previous year OR • ≥ 6 T2 lesions in the year before screening • No GA or IFN within previous 12 weeks
NA	Knobler, 1993 (59)	Randomised, multicentre, double-blind, dose-ranging, placebo-controlled trial	3 sites in the US	• SC IFNβ-1b TIW, either 0.8 mU (6), 4 mU (6), 8 mU (6), or 16 mU (6) • Placebo (7)	36 months	• Aged 18–50 years • RRMS ≥ 1 year, ≤ 15 years • EDSS score of 0.0-5.5 • ≥ 2 exacerbations in the 2 years prior to entry into the study
MSCRG	Jacobs, 1996 (33)	Randomised, multicentre, double-blind, placebo controlled Phase III trial Cross-over was not permitted	4 sites across the US	• IM IFNβ-1a 30 µg OW (158) • Placebo (143)	26 months	• Aged 18–55 years • Relapsing MS for ≥ 1 year • EDSS score 1.0–3.5 • ≥ 2 exacerbations in the previous 3 years and no exacerbations for ≥ 2 months at study entry • IFNβ naïve
NA	O'Connor, 2006 (69)	Randomised, multicentre, double-blind, placebo controlled Phase II trial Cross-over was not permitted	10 sites in Canada and 6 sites in France	• Oral teriflunomide 7 mg OD • Oral teriflunomide 14 mg OD • Placebo	9 months	• Age 18–65 years • EDSS score ≤6 • ≥2 documented relapses in previous 3 years • ≥1 clinical relapse in the preceding year

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
PRISMS	Ebers, 1998 (54)	Randomised, multicentre, international, double-blind, placebo controlled Phase III trial Cross-over was not permitted	22 sites across 9 countries	• SC IFNβ-1a 22 µg TIW (189) • SC IFNβ-1a 44 µg TIW (184) • Placebo (187)	24 months	• Adult patients • RRMS for ≥ 1 year • EDSS scores of 0–5.0 • ≥ 2 relapses in the preceding 2 years • IFNβ naïve
REGARD	Mikol, 2008 (60)	Randomised, multicentre, international, open-label Phase IV trial Cross-over was not permitted	81 sites across 14 countries	• SC GA 20 mg OD (378) • SC IFNβ-1a 44 µg TIW (386)	24 months	• Aged 18–60 years • RRMS • EDSS score 0–5.5 • ≥ 1 attack in the preceding 12 months, with clinical stability or neurological improvement during the 4 weeks before randomisation • IFNβ and GA naive
NA	Saida, 2012 (71)	Randomised, Phase II trial Cross-over was permitted after 6 months (re-randomisation)	Japan (unknown number of sites)	• Oral fingolimod 0.5 mg OD • Oral fingolimod 1.25 mg OD • Placebo • 167 patients randomised	6 months, followed by re-randomisation and a further 6 months	• Relapsing MS, age 18–60 years • ≥1 relapse in previous year or 2 or more relapses in previous 2 years or ≥1 Gd+ lesions within 30 days of study commencement
TEMSO	O'Connor, 2011 (70)	Randomised, multicentre, international, double-blind, placebo controlled Phase III trial Cross-over was not permitted	Sites across 21 countries worldwide	• Oral teriflunomide 7 mg OD (365) • Oral teriflunomide 14 mg OD (358) • Placebo (363)	2 years	• Relapsing MS, aged 18–55 years • EDSS score ≤5.5 • ≥2 relapses in previous 2 years or 1 relapse in year prior to randomisation • No relapses in 60 days prior to randomisation

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
TRANSFORMS	Cohen, 2010 (51)	Randomised, multicentre, international, double-blind, double dummy, placebo controlled Phase III trial Cross-over was not permitted	172 sites across 18 countries	• Oral fingolimod 1.25 mg OD (426) • Oral fingolimod 0.5 mg OD (431) • IM IFNβ-1a 30 µg OW (435)	12 months	• Aged 18–55 years • RRMS • EDSS score 0–5.5 • ≥ 1 relapse during the previous year or ≥ 2 two relapses during the previous 2 years
NA	Wroe, 2005 (65)	Randomised, multicentre, international, double-blind, placebo controlled Phase IV trial	Nine sites in Germany and the UK	• SC IFNβ-1b 250 µg EOD (65) • Placebo (33)	24 months	• Aged 18–55 years • RRMS for ≥ 1 year • EDSS score 0–5.5 • ≥ 2 relapses within the preceding 24 months and no relapse, or neurological deterioration related to relapse, for ≥ 30 days prior to entry • IFNβ naïve

Abbreviations: ACTH, adrenocorticotrophic hormone; BID, twice daily; EDSS, Expanded Disability Status Scale; EOD, every other day; GA, glatiramer acetate; Gd+, gadolinium enhancing; IFNβ, interferon β; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; mU, million units; NA, not applicable; OD, once daily; OW, once weekly; RRMS, relapsing remitting multiple sclerosis; SC, subcutaneous; TID, three times daily; TIW, three times a week.

Table 30: Summary of baseline characteristics of patients in trials included in the MTC

Study name	Treatment	N	Mean age (years)	Mean disease duration (years)[‡]	Percent female	Relapses in 1 year prior to baseline	Relapses in 2 years prior to baseline	Mean EDSS at baseline
AFFIRM (62)	Natalizumab, 300 mg, every 4 weeks	627	35.6	5[†]	72	1.53	-	2.3
	Placebo	315	36.7	6[†]	67	1.5	-	2.3
BECOME (49)	GA, 20 mg OD	39	36	1.2[†]	64	-	-	2[†]

Study name	Treatment	N	Mean age (years)	Mean disease duration (years)[‡]	Percent female	Relapses in 1 year prior to baseline	Relapses in 2 years prior to baseline	Mean EDSS at baseline
	IFNβ-1b, 250 µg EOD	36	36	0.9[†]	75	-	-	2[†]
BEYOND (61)	GA, 20 mg OD	448	35.2	5.1	68	1.6	-	2.28
	IFNβ-1b, 250 µg EOD	897	35.8	5.3	70	1.6	-	2.35
BRAVO (72)	IFNβ-1a 30 µg OW	447	-	-	-	-	-	-
	Placebo	450	-	-	-	-	-	-
Bornstein 1987 (47)	GA, 20 mg OD	25	30	4.9	56	-	3.8	2.9
	Placebo	25	31	6.1	60	-	3.9	3.2
Calabrese 2011 (50)	GA, 20 mg OD	48	38.9	5.5	72.9	-	-	2.1
	IFNβ-1a, 30 µg, OW	47	34.8	5.3	68	-	-	1.9
	IFNβ-1a, 44 µg, TIW	46	35.9	5.7	69.5	-	-	1.9
CONFIRM (67)	Dimethyl fumarate, 240 mg BID	359	37.8	4.9	68	1.3	-	2.56
	Dimethyl fumarate, 240 mg TID	345	37.8	4.6	72	1.4	-	2.52
	GA, 20 mg OD	350	36.7	4.4	71	1.4	-	2.57
	Placebo	363	36.9	4.8	69	1.4	-	2.59
Copolymer 1 Multiple Sclerosis trial (34)	GA, 20 mg OD	125	34.58	7.25	70.4	-	2.91	2.82
	Placebo	126	34.33	6.64	76.2	-	2.93	2.42
DEFINE (66)	Dimethyl fumarate, 240 mg BID	410	38.1	5.6	72	1.3	-	2.4
	Dimethyl fumarate, 240 mg TID	416	38.8	5.1	74	1.3	-	2.36
	Placebo	408	38.5	5.8	75	1.3	-	2.48
Etemadifar 2006 (55)	IFNβ-1a, 30 µg, OW	30	28.1	2.9	80	2	-	1.9
	IFNβ-1a, 44 µg, TIW	30	27.4	3	76.7	2.4	-	2.1

Study name	Treatment	N	Mean age (years)	Mean disease duration (years)[‡]	Percent female	Relapses in 1 year prior to baseline	Relapses in 2 years prior to baseline	Mean EDSS at baseline
	IFNβ-1b, 250 µg EOD	30	29.9	3.7	70	2.2	-	1.9
European and Canadian glatiramer trial (48)	GA, 20 mg OD	119	34.1	7.9	76.99	-	2.8	2.3
	Placebo	120	34	8.3	72.81	-	2.5	2.4
EVIDENCE (63)	IFNβ-1a, 30 µg, OW	338	37.4	6.7	74.6	-	2.6	2.3
	IFNβ-1a, 44 µg, TIW	339	38.3	6.5	74.9		2.6	2.3
FREEDOMS (58)	Fingolimod, 0.5 mg OD	425	36.6	8	69.6	1.5	2.1	2.3
	Placebo	418	37.2	8.1	71.3	1.4	2.2	2.5
FREEDOMS II (68)	Fingolimod 0.5 mg od	358	40.6	10.4	76.8	1.4	2.2	2.4
	Placebo	355	40.1	10.6	81.1	1.5	2.2	2.4
IFNB MS (64)	IFNβ-1b, 250 µg EOD	124	35.2	4.7	69.35	-	3.4	3
	Placebo	123	36	3.9	71.54	-	3.6	2.8
IMPROVE (52)	IFN beta-1a, 44 µg, TIW	120	-	-	-	-	-	-
	Placebo	60	-	-	-	-	-	-
INCOMIN (53)	IFNβ-1a, 30 µg, OW	92	34.9	6.7	62	-	-	1.96
	IFNβ-1b, 250 µg EOD	96	38.8	5.9	69	-	-	1.97
Kappos 2011 (57)	IFNβ-1a, 30 µg, once weekly	54	-	-	-	-	-	-
	Placebo	54	-	-	-	-	-	-
Knobler 1993 (59)	IFNβ-1b, 250 µg EOD	6	35.4	4.2	33.33	-	4	2.7
	Placebo	7	34.5	7	71.43	-	2.3	3.1
MSCRG (33)	IFNβ-1a, 30 µg, OW	158	36.7	6.6	75	-	-	2.4
	Placebo	143	36.9	6.4	72	-	-	2.3

Study name	Treatment	N	Mean age (years)	Mean disease duration (years)[‡]	Percent female	Relapses in 1 year prior to baseline	Relapses in 2 years prior to baseline	Mean EDSS at baseline
O`Connor 2006 (69)	Teriflunomide 7 mg OD	61	40.1	10.3	75.41	1[†]		2.5[†]
	Teriflunomide 14 mg OD	57	40.1	8.5	78.95	1[†]		2[†]
	Placebo	61	39.2	8.6	67.21	1[†]		2.5[†]
PRISMS (54)	IFNβ-1a, 22 µg, TIW	189	34.8[†]	5.4[†]	67	-	3	2.5
	IFNβ-1a, 44 µg, TIW	184	35.6[†]	6.4[†]	66	-	3	2.5
	Placebo	187	34.6[†]	4.3[†]	75	-	3	2.4
REGARD (60)	GA, 20 mg OD	378	36.8	-	72	-	-	2.33
	IFNβ-1a, 44 µg, TIW	386	36.7	3.7[†]	69	1[†]	-	2.35
Saida 2012 (71)	Fingolimod 0.5 mg od	57	35	8.2	70.2	1.4	2.2	2.3
	Placebo	57	35	8.2	68.4	1.7	2.8	2.1
TEMSO trial (70)	Teriflunomide 7 mg OD	366	37.4	8.8	69.7	1.4	2.3	2.68
	Teriflunomide 14 mg OD	359	37.8	8.7	71	1.3	2.2	2.67
	Placebo	363	38.4	8.6	75.8	1.4	2.2	2.68
TRANSFORMS (51)	Fingolimod, 0.5 mg OD	431	36.7	7.5	65.4	1.5	2.3	2.24
	IFNβ-1a, 30 µg, OW	435	36	7.4	67.8	1.5	2.3	2.19
Wroe 2005 (65)	IFNβ-1b, 250 µg EOD	65	35	-	73.85	-	2.66	2.92
	Placebo	33	38	-	72.73	-	2.47	3.09

[†] Median value, [‡] Disease duration was defined inconsistently across the trials; in some cases as time from diagnosis, and in others as time from first relapse.
Abbreviations: EDSS, Expanded Disability Status Scale; EOD, every other day; GA, glatiramer acetate; IFN, Interferon; NA, not applicable; OD, Once Daily; TID, three times

Critical appraisal of relevant RCTs

A critical appraisal of the relevant trials was carried out according to the criteria set out below (Table 31):

- Randomization: Was randomization carried out appropriately?
- Baseline characteristics: Were the groups similar at the outset of the study in terms of prognostic factors?
- Blinding: Were the care providers, participants and outcome assessors blind to treatment allocation?
- Withdrawal/discontinuation: Were there any unexpected imbalances in drop-outs between groups?
- Outcome selection, reporting, and other sources of bias: Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Statistical analysis: Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

A detailed quality assessment of the trials used in the MTC is provided in Appendix 5 (Section 10.5).

Table 31: Summary of quality assessment of trials included in the MTC

Study name	Randomisation	Baseline characteristics	Blinding	Withdrawal/ dis-continuation	Outcome selection, reporting, and other sources of bias	Statistical analysis
AFFIRM trial	LR	LR	LR	LR	LR	LR
BECOME trial	NR	LR	LR	LR	LR	LR
BEYOND trial	LR	LR	LR	LR	LR	LR
Bornstein 1987	NR	LR	LR	NR	NR	LR
BRAVO trial*	NR	NR	LR	NR	NR	NR
Calabrese 2011	LR	NR	NR	LR	NR	HR
CONFIRM trial*	LR	LR	LR	LR	LR	LR
Copolymer 1 Multiple Sclerosis trial	NR	LR	LR	LR	NR	LR
DEFINE trial	LR	LR	LR	LR	LR	LR
Etemadifar 2006	NR	LR	LR	LR	NR	LR
European and Canadian glatiramer trial	LR	LR	LR	LR	NR	LR
EVIDENCE trial	LR	LR	LR	LR	NR	LR
FREEDOMS II trial	NR	LR	NR	NR	LR	NR
FREEDOMS trial	NR	LR	LR	LR	LR	LR
IFNB MS trial	NR	LR	LR	LR	NR	LR
IMPROVE	NR	LR	NR	NR	LR	LR

Study name	Randomisation	Baseline characteristics	Blinding	Withdrawal/ dis-continuation	Outcome selection, reporting, and other sources of bias	Statistical analysis
trial						
INCOMIN trial	LR	LR	NR	LR	NR	LR
Kappos 2010*	LR	LR	LR	LR	LR	LR
Knobler 1993	NR	LR	NR	LR	NR	LR
MSCRG trial	LR	LR	LR	NR	NR	LR
O`Connor 2006	NR	LR	LR	LR	NR	LR
PRISMS trial	LR	LR	LR	LR	NR	LR
REGARD trial	LR	LR	LR	LR	LR	LR
Saida 2012	LR	LR	LR	LR	LR	LR
TEMSO trial	NR	LR	LR	LR	LR	LR
TRANSFORMS trial	LR	LR	LR	LR	LR	LR
Wroe 2005	NR	LR	NR	LR	NR	LR

*Bias assessment was performed on the basis of overall study design (double-blind), however, active comparator was open label and rater masked in three of the trials (BRAVO trial; Kappos 2010; CONFIRM trial); HR: High Risk; LR: Low Risk; NR: Not Reported.

Summary of results of relevant RCTs

A summary of the data used to perform the indirect comparison is provided in Section 6.7.4.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison.

A summary of trials used to conduct the indirect comparison is provided in Section 6.7.2, Table 29.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

A summary of the data used from each trial for the analysis is given in Table 32.

Table 32: Summary of data from RCTs used in the indirect comparison

Study name	Treatment (n)	Mean ARR †	Mean ARR-ST†	Patients with relapse at 12 months, n (%)	Patients with relapse at 24 months, n (%)	Proportion relapse-free at 12 months, n (%)	Proportion relapse-free at 24 months, n (%)	EDSS score change at 24 months (mean±SD)	CDPS3M at 24 months, n (%)	CDPS6M at 24 months, n (%)	Any AE, n (%)	Any SAE, n (%)	All withdrawals, n (%)	Withdrawal due to AEs, n (%)	Withdrawals due to death, n (%)
AFFIRM (62)	Natalizumab 300 mg OM (627)	0.22	0.13	126 (20.1)	173 (27.6)	501 (79.9)	454 (72.4)	0.04 (0.86)	107 (17.1)	-	596 (95.1)	119 (19.0)	52 (8.3)	15 (2.4)	2 (0.3)
	Placebo (315)	0.64	0.43	126 (40.0)	169 (53.7)	189 (60.0)	146 (46.3)	0.41 (1.09)	91 (28.9)	-	300 (96.2)	75 (24.0)	34 (10.8)	6 (1.9)	0 (0.0)
BECOME (49)	GA 20 mg OD	0.33	-	11 (28.2)	11 (28.2)	28 (71.8)	28 (71.8)	-	-	6 (15.4)	-	-	4 (10.3)	-	-
	IFNβ-1b 250 µg QAD	0.37	-	10 (27.8)	17 (47.2)	26 (72.2)	19 (52.8)	-	-	4 (11.1)	-	-	7 (19.4)	-	-
BEYOND (61)	GA 20 mg OD (448)	0.34	-	-	186 (41.5)	-	262 (58.5)	-	92 (20.5)	-	-	-	71 (15.8)	8 (1.8)	1 (0.2)
	IFNβ-1b 250 µg QAD (897)	0.36	-	-	377 (42.0)	-	520 (58.0)	-	244 (27.2)	-	-	-	113 (12.6)	13 (1.4)	0 (0.0)
Bornstein 1987 (47)	GA 20 mg OD (25)	0.34	-	-	11 (44.0)	-	14 (56.0)	-	5 (20.0)	-	-	-	-	-	-
	Placebo (25)	1.38	-	-	17 (68.0)	-	6 (24.0)	-	11 (44.0)	-	-	-	-	-	-
Calabrese 2011 (50)	GA 20 mg OD (48)	0.50	-	-	-	-	-	0.30 (0.50)	-	-	-	-	7 (12.7)	-	-
	IFNβ-1a 30 µg OW (47)	0.50	-	-	-	-	-	0.20 (0.40)	-	-	-	-	8 (14.5)	-	-
	IFNβ-1a 44 µg TIW (46)	0.40	-	-	-	-	-	0.20 (0.50)	-	-	-	-	9 (16.4)	-	-

Study name	Treatment (n)	Mean ARR †	Mean ARR-ST†	Patients with relapse at 12 months, n (%)	Patients with relapse at 24 months, n (%)	Proportion relapse-free at 12 months, n (%)	Proportion relapse-free at 24 months, n (%)	EDSS score change at 24 months (mean±SD)	CDPS3M at 24 months, n (%)	CDPS6M at 24 months, n (%)	Any AE, n (%)	Any SAE, n (%)	All withdrawals, n (%)	Withdrawal due to AEs, n (%)	Withdrawals due to death, n (%)
CONFIRM (67)	Dimethyl fumarate 240 mg BID (359)	0.22	0.20	68 (18.8)	93 (25.7)	291 (80.4)	266 (73.5)	-0.11 (0.79)	40 (11.0)	24 (6.6)	338 (94.2)	61 (17.0)	78 (21.5)	21 (5.8)	0 (0.0)
	GA 20 mg OD (350)	0.29	0.26	79 (21.9)	104 (28.9)	271 (75.3)	246 (68.3)	-0.01 (0.86)	48 (13.3)	34 (9.4)	304 (86.6)	60 (17.1)	68 (18.9)	10 (2.8)	1 (0.3)
	Placebo (363)	0.38	0.34	111 (30.6)	140 (38.6)	252 (69.4)	223 (61.4)	0.02 (0.89)	52 (14.3)	39 (10.7)	333 (91.7)	79 (21.8)	85 (23.4)	11 (3.0)	1 (0.3)
Copolymer 1 Multiple Sclerosis trial (34)	GA 20 mg OD (125)	0.59	-	-	83 (66.4)	-	42 (33.6)	-0.05 (1.13)	27 (21.6)	-	-	-	28 (22.4)	5 (4.0)	-
	Placebo (126)	0.84	-	-	92 (73.0)	-	34 (27.0)	0.21 (0.99)	31 (24.6)	-	-	-	29 (23.0)	1 (0.8)	-
DEFINE (66)	Dimethyl fumarate BID (410)	0.20	0.18	62 (15.1)	98 (23.8)	348 (84.7)	312 (75.9)	-0.06 (0.77)	57 (13.9)	44 (10.7)	395 (96.3)	74 (18.0)	96 (23.4)	40 (9.7)	0 (0.0)
	Placebo (408)	0.40	0.35	119 (29.0)	171 (41.7)	289 (70.5)	237 (57.8)	0.06 (0.95)	89 (21.7)	57 (13.9)	387 (94.9)	86 (21.1)	93 (22.7)	22 (5.4)	0 (0.0)
Etemadifar 2006 (55)	IFNβ-1a 30 µg OW (30)	0.95	-	-	24 (80.0)	-	6 (20.0)	-0.10 (0.98)	-	-	-	-	-	-	-
	IFNβ-1a 44 µg TIW (30)	1.10	-	-	13 (43.3)	-	17 (56.7)	-0.30 (0.66)	-	-	-	-	-	-	-
	IFNβ-1b 250 µg QAD (30)	1.08	-	-	17 (56.7)	-	13 (43.3)	-0.70 (0.56)	-	-	-	-	-	-	-
European and Canadian glatiramer (48)	GA 20 mg OD (119)	0.81	0.72	-	-	-	-	-	-	-	-	10 (8.4)	7 (5.9)	3 (2.5)	-
	Placebo (120)	1.21	1.12	-	-	-	-	-	-	-	-	6 (5.0)	7 (5.8)	2 (1.7)	-
EVIDENCE (63)	IFNβ-1a 30 µg OW (338)	0.64	0.28	161 (47.6)	-	177 (52.4)	-	-	-	-	-	-	32 (9.5)	18 (5.3)	0 (0.0)
	IFNβ-1a 44 µg TIW (339)	0.54	0.19	130 (38.3)	-	209 (61.7)	-	-	-	-	-	-	40 (11.8)	19 (5.6)	1 (0.3)

Study name	Treatment (n)	Mean ARR †	Mean ARR-ST†	Patients with relapse at 12 months, n (%)	Patients with relapse at 24 months, n (%)	Proportion relapse-free at 12 months, n (%)	Proportion relapse-free at 24 months, n (%)	EDSS score change at 24 months (mean±SD)	CDPS3M at 24 months, n (%)	CDPS6M at 24 months, n (%)	Any AE, n (%)	Any SAE, n (%)	All withdrawals, n (%)	Withdrawal due to AEs, n (%)	Withdrawals due to death, n (%)
FREEDOMS (58)	Fingolimod 0.5 mg OD (425)	0.21	0.17	-	126 (29.6)	-	299 (70.4)	0.00 (0.88)	75 (17.6)	53 (12.5)	401 (94.4)	43 (10.1)	56 (13.2)	23 (5.4)	0 (0.0)
	Placebo (418)	0.47	0.38	-	227 (54.3)	-	191 (45.7)	0.13 (0.94)	101 (24.2)	79 (18.9)	387 (92.6)	56 (13.4)	86 (20.6)	20 (4.8)	2 (0.5)
FREEDOMS II (68)	Fingolimod 0.5 mg OD (358)	0.21	0.12	-	131 (36.6)	-	227 (63.4)	-	91 (25.4)	49 (13.7)	350 (97.8)	53 (14.8)	80 (18.8)	35 (9.8)	-
	Placebo (355)	0.40	0.30	-	246 (69.3)	-	109 (30.7)	-	103 (29.0))	63 (17.7)	343 (96.6)	45 (12.7)	115 (27.5)	27 (7.6)	-
IFNB MS trial (64)	IFNβ-1b 250 µg QAD (124)	0.84	-	-	79 (63.7)	-	36 (29.0)	-	-	-	-	-	-	-	-
	Placebo (123)	1.27	-	-	94 (76.4)	-	18 (14.6)	-	-	-	-	-	-	-	-
IMPROVE (52)	IFNβ-1a 44 µg TIW (120)	0.48	-	-	-	-	-	-	-	-	86 (71.7)	-	8 (6.7)	-	-
	Placebo (60)	1.10	-	-	-	-	-	-	-	-	18 (30.0)	-	3 (5.0)	-	-
INCOMIN (53)	IFNβ-1a 30 µg OW (92)	0.70	0.50	-	59 (64.1)	-	33 (35.9)	0.54 (0.70)	-	28 (30.4)	-	-	19 (20.7)	1 (1.1)	-
	IFNβ-1b 250 µg OW (96)	0.50	0.38	-	47 (49.0)	-	49 (51.0)	0.13 (0.66)	-	13 (13.5)	-	-	11 (11.5)	5 (5.2)	-
Kappos 2010 (58)	IFNβ-1a 30 µg OW (55)	0.36	-	-	-	-	-	-	-	-	30 (55.6)	2 (3.6)	-	-	-
	Placebo (55)	0.64	-	-	-	-	-	-	-	-	38 (70.4)	1 (1.8)	-	-	-
Knobler 1993 (59)	IFNβ-1b 250 µg QAD (6)	0.87	-	-	-	-	-	-	-	-	-	-	1 (16.7)	-	-

Study name	Treatment (n)	Mean ARR †	Mean ARR-ST†	Patients with relapse at 12 months, n (%)	Patients with relapse at 24 months, n (%)	Proportion relapse-free at 12 months, n (%)	Proportion relapse-free at 24 months, n (%)	EDSS score change at 24 months (mean±SD)	CDPS3M at 24 months, n (%)	CDPS6M at 24 months, n (%)	Any AE, n (%)	Any SAE, n (%)	All withdrawals, n (%)	Withdrawal due to AEs, n (%)	Withdrawals due to death, n (%)
	Placebo (7)	1.79	-	-	-	-	-	-	-	-	-	-	1 (14.3)	-	-
MSCRG trial (33)	IFNβ-1a 30 µg OW (158)	0.61	-	-	53 (33.5)	-	32 (20.3)	0.25 (1.28)	-	35 (22.2)	-	-	-	7 (4.4)	-
	Placebo (143)	0.90	-	-	64 (44.8)	-	23 (16.1)	0.74 (1.49)	-	50 (35.0)	-	-	-	2 (1.4)	-
O'Connor 2006 (69)	Teriflunomide 7 mg OD (366)	0.58	-	-	-	-	-	-	-	-	-	5 (8.2)	3 (4.9)	3 (4.9)	-
	Teriflunomide 14 mg OD (359)	0.55	-	-	-	-	-	-	-	-	-	7 (12.3)	12 (21.1)	8 (14.0)	-
	Placebo (363)	0.81	-	-	-	-	-	-	-	-	-	7 (11.5)	3 (4.9)	3 (4.9)	-
PRISMS (54)	IFNβ-1a 22 µg TIW (189)	0.94	0.50	119 (63.0)	138 (73.0)	70 (37.0)	51 (27.0)	0.23 (1.30)	49 (25.9)	-	-	-	22 (11.6)	6 (3.2)	1 (0.5)
	IFNβ-1a 44 µg TIW (184)	0.88	0.38	101 (54.9)	126 (68.5)	83 (45.1)	59 (32.1)	0.74 (1.49)	47 (25.5)	-	-	-	19 (10.3)	9 (4.9)	0 (0.0)
	Placebo (187)	1.32	0.71	146 (78.1)	157 (84.0)	41 (21.9)	30 (16.0)	0.48 (1.30)	68 (36.4)	-	-	-	17 (9.1)	2 (1.1)	1 (0.5)
REGARD (60)	GA 20 mg OD (378)	0.29	0.17	-	144 (38.1)	-	234 (61.9)	-	-	33 (8.7)	-	27 (7.2)	54 (14.3)	19 (5.0)	-
	IFNβ-1a 44 µg TIW (386)	0.30	0.19	-	147 (38.1)	-	239 (61.9)	-	-	45 (11.7)	-	29 (7.6)	85 (22.0)	23 (6.0)	-
Saida 2012 (71)	Fingolimod 0.5 mg (57)	0.50	-	-	-	-	-	-	-	-	52 (91.2)	5 (8.8)	9 (15.8)	6 (10.5)	-
	Placebo (57)	0.99	-	-	-	-	-	-	-	-	45 (78.9)	3 (5.3)	6 (10.5)	3 (5.3)	-
TEMSO (70)	Teriflunomide 7 mg OD (61)	0.37	-	-	154 (42.1)	-	211 (57.7)	-	79 (21.6)	-	328 (89.1)	52 (14.1)	92 (25.1)	37 (10.1)	-

Study name	Treatment (n)	Mean ARR †	Mean ARR-ST†	Patients with relapse at 12 months, n (%)	Patients with relapse at 24 months, n (%)	Proportion relapse-free at 12 months, n (%)	Proportion relapse-free at 24 months, n (%)	EDSS score change at 24 months (mean±SD)	CDPS3M at 24 months, n (%)	CDPS6M at 24 months, n (%)	Any AE, n (%)	Any SAE, n (%)	All withdrawals, n (%)	Withdrawal due to AEs, n (%)	Withdrawals due to death, n (%)
	Teriflunomide 14 mg OD (57)	0.37	-	-	141 (39.3)	-	217 (60.4)	-	72 (20.1)	-	325 (90.8)	57 (15.9)	96 (26.7)	38 (10.6)	-
	Placebo (61)	0.54	-	-	184 (50.7)	-	179 (49.3)	-	99 (27.3)	-	315 (87.5)	46 (12.8)	104 (28.7)	39 (8.0)	-
TRANSFORMS (51)	Fingolimod 0.5 mg OD (429)	0.21	0.14	75 (17.4)	-	354 (82.1)	-	-	-	-	369 (86.0)	30 (7.0)	33 (7.7)	18 (4.2)	-
	IFNβ-1a 30 µg OW (431)	0.43	0.33	129 (29.7)	-	302 (69.4)	-	-	-	-	395 (91.6)	25 (5.8)	49 (11.3)	13 (3.0)	-
Wroe 2005 (65)	IFNβ-1b 250 µg QAD (65)	-	-	-	-	-	-	-	-	-	-	-	3 (4.6)	2 (3.1)	-
	Placebo (33)	-	-	-	-	-	-	-	-	-	-	-	0 (0.0)	0 (0.0)	-

†ARR was reported differently throughout the trials; unadjusted ARRs were therefore calculated using total number of relapses and total patient-years of treatment.
Abbreviations: AE, adverse event; ARR, annualised relapse rate; ARR-ST, annualised rate of relapses requiring steroids; CDPS3M, confirmed disability progression sustained for 3 months; CDPS6M, continued disability progression sustained for 6 months; EDSS, Expanded Disability Status Scale; SAE, serious adverse event.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Mixed treatment comparison

The aim of the mixed treatment comparison was to compare the relative efficacy of dimethyl fumarate with other treatments for RRMS, including IFNs, GA, natalizumab, and fingolimod. A systematic review was performed to identify evidence on the efficacy and safety of these therapies. Data for dimethyl fumarate were derived from the DEFINE and CONFIRM RCTs. Placebo was used as the common comparator by which to compare dimethyl fumarate and the other available therapies. In order to strengthen the placebo arm, data from comparators not of interest in the economic model (teriflunomide) were included in the SR and MTC. The rationale behind the inclusion of those studies was the fact that the trial populations were similar to those in the other trials; consequently, the additional heterogeneity they would introduce into the analysis would be out weighted by the value of information they would provide that would strengthen the overall analysis. The trials included for each endpoint are summarised in Table 32.

Indirect comparisons between interventions were performed through the mixed treatment comparison (MTC) method. Evidence networks were produced to identify comparative analyses that could be performed for MTC. MTC was performed if the network consisted of at least one closed loop.

The MTC was conducted via a frequentist approach using the PROC GLIMMIX procedure in SAS version 9.3. This methodology was used for the analysis for the following reasons:

- As statistical computation software, SAS is widely used and is the industry standard for analysis of clinical trial data over long time periods due to its ability to handle large datasets, and the flexibility it provides to the analyst in coding and reporting. Analysts are consequently extremely familiar with the embedded procedures and user interface, making it easier to create codes, debug the code and analysis, and create reports summarising outcomes in a traditional fashion.
- One of the important shortcomings of the frequentist method is that it does not account for correlations that might have existed between effect estimates when they areobtained from a single multi-arm trial. The PROC GLIMMIX procedure can address adjustment for multi-arm trials using a multiple logistic regression MTC model (114), as employed in this analysis.
- PROC GLIMMIX is a new alternative method for MTC that generates effect sizes with greater precision (i.e. narrower credible intervals) than the Bayesian approach (which typically uses WinBugs software) (115). PROC GLIMMIX has also demonstrated better evidence consistency than WinBugs, with closer estimates to direct analysis (116).

MTC models using the generalised linear mixed model (GLMM) method were designed to assess treatment efficacy using all available evidence, both direct and indirect. GLMM is an extension to the generalised linear model in which the linear predictor contains random effects in addition to the fixed effects (117). These models were built in the PROC GLIMMIX procedure of SAS version 9.3 (SAS Institute Corporation, NC, USA).

The models provided the following efficacy outputs for every possible treatment comparison:

- For Poisson (count) outcomes: Rate ratio for treatment A relative to treatment B with 95% CI
- For binomial outcomes: Risk ratio (RR) for treatment A relative to treatment B with 95% CI
- For continuous outcomes: Absolute difference and 95% CI between treatments A and B

The models for the three types of input data (Poisson, binomial, and continuous) are presented in Section 10.14.1 (Appendix 14).

Outcomes analysed

The outcomes analysed in the MTC are summarised in Table 33. It was not possible to analyse MRI outcomes across the trials due to variation in reporting of these outcomes.

Table 33: List of outcomes and analytic approach

Outcomes	Type of data	Information needed	Output statistics of mixed treatment comparison
Efficacy outcomes			
ARR	Poisson	Total number of relapses, person-years	ARR ratio, 95% CI of estimate
Annualised steroid-treated relapse rate			
Change in EDSS score from baseline at 24 months	Continuous	Evaluable N, Mean/median and SD/SE/CI/p value	Median absolute difference, 95% CI of estimate
Confirmed disability progression sustained for 3 months at 24 months	Binomial	Number of patients with outcome (n) ITT Number (N)	RR, 95% CI of estimate
Confirmed disability progression sustained for 6 months at 24 months			
Proportion of patients with relapse at 12 and 24 months			
Proportion of patients relapse free at 12 and 24 months			
Safety outcomes			
Any AEs	Binomial	Number of patients with outcome (n) evaluable/ITT number (N)	RR, 95% CI of estimate
Any SAEs			
Any GI disorder			
Abdominal pain			
Upper abdominal pain			
ALT increase			
Arthralgia			
Back pain			
Depression			
Diarrhoea			

Outcomes	Type of data	Information needed	Output statistics of mixed treatment comparison
Fatigue			
Flu-like symptoms			
Flushing			
Influenza			
Headache			
Leukopenia			
Nausea			
Pain in extremity			
Pruritus			
Rash			
Urinary tract infection			
Tolerability outcomes			
Discontinuation due to any cause	Binomial	Number of patients with outcome (n) ITT number (N)	RR, 95% CI of estimate
Discontinuation due to adverse events			
Discontinuation due to death			

Abbreviations: AE, adverse event; ALT, alanine transaminase; ARR, annualised relapse rate; ACB, atrioventricular conduction block; CI, confidence interval; EDSS, Expanded Disability Status Scale; GI, gastrointestinal; ITT, intent to treat; MTC, mixed treatment comparison; RR, risk ratio; SAE, serious adverse event; SD, standard deviation; SE, standard error; WMD, weighted mean difference.

As data were missing in some studies it was necessary to impute these data using derivations for dichotomous or continuous outcomes, or for skewed data.

Dichotomous outcomes

Dichotomous outcomes were generally presented as the number of patients analysed (N) and the number of patients with an outcome (n). Many times the proportion of patients with outcome (%) were reported with no mention of the number of patients analysed (N). Following the principle of ITT analyses, the number of patients randomised (ITT N) was used to derive the number of patients with outcome (n).

When the number of patients analysed (N) and the proportion of patients with outcome (%) are known, the number of patients with outcome (n) were calculated using this formula:

Continuous outcomes

Continuous outcome data were presented as mean/median with variance (standard deviation [SD], standard error of mean [SE], 95% CI). Many times these data were presented as mean/median with no SD. For such instances, imputation techniques were used to generate missing SD from SE or 95% CI. Similar to the technique used for

dichotomous variable, when number of patients analysed was missing, the number of patients randomised (ITT N) was used for analyses.

There are several ways to derive the SD when it is not reported:

- Derive directly from SE using (where n is the randomised number in the treatment arm) (118):

$$_$$

- Derive SD directly from the CI. It is assumed that the CI is estimated by the normal distribution. As rates can only be positive, a log-transformation will be necessary on the CI bounds prior to the calculations (are the respective lower and upper bounds of the 95% CI) (118):

$$\frac{_____}{_}$$

- Imputing SDs for changes from baseline: A special case of missing SD is for change from baseline. When there is not enough information available to calculate the SD for the change, they can be imputed from the SD values reported for baseline and endpoint data. A typically unreported number known as the correlation coefficient describes how similar the baseline and final measurements were across participants. The following technique will be used for imputing missing SD for change from baseline (118):
    - Calculate the correlation coefficient from a study that is reported in considerable detail:

$$\frac{_____}{_____}$$

    - Calculation of SD using an imputed correlation coefficient:

$$\frac{_____}{_____}$$

  Note that the second method is applicable both to correlation coefficients obtained using the first method and to correlation coefficients obtained in other ways (for example, by reasoned argument).

Poisson outcomes

For studies that did not report the total number of relapses and person-years in the publication, imputations were performed to derive the respective values. Total number of relapses was derived from the following variables:

- Using person-years and ARR
- From mean relapses per patient

To derive person years the following variables were used:

- Using number of relapses and ARR

Imputed as (study duration × the number of completers) + (half of study duration × number patients who withdrew from the study)

Covariate analysis

Covariate analysis was performed to verify the model, as outlined in Sections 10.14.2 and 10.14.3.

6.7.6 Please present the results of the analysis.

The MTC was performed only in the overall RRMS population, as it was not possible to perform an MTC for the subgroups defined in the NICE scope (inadequate response to therapy, intolerant to therapy, highly active RRMS, rapidly evolving severe RRMS). These subgroups have not been specifically examined in the majority of trials contributing to the MTC, and there is consequently a lack of data for each treatment to allow such a comparison. However, the overall populations in these trials include patients in these subgroups and are therefore indicative of efficacy in these groups. The results of the MTC are summarised briefly in Table 34, with complete results presented below.

Table 34: Summary of MTC results for dimethyl fumarate vs comparators *(Academic in confidence information removed)*

Comparator	ARR	ARR-ST	PPR 12 months	PPR 24 months	PPR-F 12 months	PPR-F 24 months	EDSS change at 24 months	CDPS3M	CDPS6M	Discont-inuation (any cause)	Discont-inuation (Death)
Fingolimod (Gilenya®)											
Glatiramer acetate (Copaxone®)											
IM IFNβ-1a 30 µg (Avonex®)											
Natalizumab (Tysabri®)											
Placebo											
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)											
SC IFNβ-1a 22 µg (Rebif® 22 µg)											
SC IFNβ-1a 44 µg (Rebif® 44 µg)											
Teriflunomide 7 mg (Aubagio® 7 mg)											
Teriflunomide 14 mg (Aubagio® 14 mg)											

↑ indicates dimethyl fumarate was significantly better for this outcome, ↓ indicates dimethyl fumarate was significantly worse for this outcome, - indicates comparison was not possible.

Abbreviations: ARR, annualised relapse rate; ARR-ST, annualised steroid-treated relapse rate; CDPS3M, confirmed disability progression sustained for 3 months; CDPS6M, confirmed disability progression sustained for 6 months; MRI, magnetic resonance imaging; ND, no statistical difference; PPR, proportion of patients with relapse; PPR-F, proportion of patients relapse free.

ARR

Dimethyl fumarate BID significantly reduced ARR when compared with placebo, GA 20 mg OD, both teriflunomide doses, and all IFNs. Natalizumab significantly reduced ARR when compared with dimethyl fumarate BID, while there was also a non-significant trend in favour of fingolimod over dimethyl fumarate BID. The results of the MTC are presented in Figure 21.

Figure 21: Results of the MTC for ARR *(Academic in confidence information removed)*

ARR <1 indicates better efficacy of intervention.
Abbreviations: ARR, annualised relapse rate; Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; tid, three times daily; tiw, three times weekly.

Annualised steroid-treated relapse rate

Dimethyl fumarate was significantly better than placebo, IFNβ-1a 30 µg and IFNβ-1a 22 µg for reducing the annualised rate of relapses requiring steroids (Figure 22). There was also a non-significant trend towards dimethyl fumarate BID when compared with GA 20 mg OD and all other IFNs. Natalizumab was found to be significantly better than dimethyl fumarate BID for this outcome, while there was also a non-significant trend in favour of fingolimod over dimethyl fumarate BID.

Figure 22: Results of the MTC for annualised steroid-treated relapse rate *(Academic in confidence information removed)*

RR <1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Proportion of patients with relapse at 12 and 24 months

No significant difference between dimethyl fumarate and any comparator was found at 12 months for this outcome (Figure 23). At 24 months dimethyl fumarate BID was found to be significantly better than placebo, all IFNs, GA, and teriflunomide 7mg for this outcome, with non-significant trends in favour of dimethyl fumarate when compared with teriflunomide 14 mg (Figure 24). A non-significant trend in favour of natalizumab and fingolimod, compared with dimethyl fumarate, was also observed at 24 months.

Figure 23: Results of the MTC for proportion of patients relapsed at 12 months *(Academic in confidence information removed)*

RR <1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Figure 24: Results of the MTC for proportion of patients relapsed at 24 months *(Academic in confidence information removed)*

RR <1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Patients remaining relapse free at 12 and 24 months

There was no significant difference between dimethyl fumarate and any active comparator at 12 months (Figure 25). At 24 months dimethyl fumarate BID was found to

be significantly better than placebo and IFNβ-1a 30 µg for this outcome (Figure 26). Non-significant trends in favour of dimethyl fumarate were observed at 24 months, compared with IFNβ-1b 250 µg, IFNβ-1a 22 µg, GA, teriflunomide 7 mg and teriflunomide 14 mg. A non-significant trend in favour of IFNβ-1a 44 µg compared with dimethyl fumarate was also observed. Natalizumab and fingolimod were found to be significantly better for this outcome at 24 months, compared with dimethyl fumarate.

Figure 25: Results of the MTC for patients remaining relapse free at 12 months *(Academic in confidence information removed)*

RR >1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Figure 26: Results of the MTC for patients remaining relapse free at 24 months *(Academic in confidence information removed)*

RR >1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Change in EDSS score from baseline at 24 months

IFNβ-1b 250 µg EOD was found to be significantly better than dimethyl fumarate for this outcome (Figure 27). No significant differences were found between dimethyl fumarate and any other comparator, although the effect sizes favoured IFNβ treatments and natalizumab.

Figure 27: Results of the MTC for change in EDSS score from baseline at 24 months *(Academic in confidence information removed)*

RR <1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Confirmed disability progression sustained for 3 months at 24 months

Dimethyl fumarate BID was significantly better then placebo for this outcome. There was no significant difference between dimethyl fumarate BID and any other comparator for this outcome, although the effect sizes favoured dimethyl fumarate when compared to all other therapies that report this outcome. The exception was natalizumab, for which there was a non-significant trend in favour of natalizumab compared to dimethyl fumarate (Figure 28).

Figure 28: Results of the MTC for confirmed disability progression sustained for 3 months at 24 months *(Academic in confidence information removed)*

RR <1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Confirmed disability progression sustained for 6 months at 24 months

There was no significant difference between dimethyl fumarate BID and any comparator for this outcome (Figure 29). When compared with placebo and IFNβ-1a 44 µg the effect sizes favoured dimethyl fumarate BID. When compared with IFNβ-1b 250 µg the effect size was against dimethyl fumarate BID.

Figure 29: Results of the MTC for confirmed disability progression sustained for 6 months at 24 months *(Academic in confidence information removed)*

RR <1 indicates better efficacy of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Safety

The results of the MTC for safety outcomes are summarised in Table 35. Flushing was found to occur significantly more with dimethyl fumarate BID, compared with placebo and GA. There were significantly fewer increases in alanine transaminase (ALT) levels with dimethyl fumarate BID, compared with IFNβ-1a 22 µg TIW, IFNβ-1a 44 µg TIW, IFNβ-1b 250 µg, and fingolimod. Other significant differences between dimethyl fumarate and comparators are summarised in Table 35.

Table 35: Results of the MTC for safety outcomes *(Academic in confidence information removed)*

Comparison	Any AEs	Any SAEs	Any GI disorder	Abdominal pain	ALT increase	Arthralgia	AV conduction block	Back pain	Bradycardia
Fingolimod 0.5 mg OD									
GA 20 mg OD									
IFNβ-1a 30 µg OW									
IFNβ-1a 22 µg TIW									
IFNβ-1a 44 µg TIW									
IFNβ-1b 250 µg EOD									
Natalizumab 300 mg OM									
Teriflunomide 7 mg OD									
Teriflunomide 14 mg OD									
Placebo									
Comparison									
Fingolimod 0.5 mg OD									
GA 20 mg OD									
IFNβ-1a 22 µg TIW									
IFNβ-1a 30 µg OW									
IFNβ-1a 44 µg TIW									

IFNβ-1b 250 µg EOD									
Natalizumab 300 mg OM									
Teriflunomide 7 mg OD									
Teriflunomide 14 mg OD									
Placebo									
Comparison									
Fingolimod 0.5 mg OD									
GA 20 mg OD									
IFNβ-1a 22 µg TIW									
IFNβ-1a 30 µg OW									
IFNβ-1a 44 µg TIW									
IFNβ-1b 250 µg EOD									
Natalizumab 300 mg OM									
Teriflunomide 14 mg OD									
Teriflunomide 7 mg OD									
Placebo									

Empty cells indicate unavailability of MTC results.

Abbreviations: AE, adverse event; ALT, alanine transaminase; ACB, atrioventricular conduction block; EOD, every other day; GA, glatiramer acetate; GI, gastrointestinal; IFN, interferon; OD: Once Daily; OM, once monthly; OW, once weekly; SAE, serious adverse event; TIW, three times weekly.

Tolerability: Discontinuation due to any cause

There was no significant difference between dimethyl fumarate and any comparator for this outcome (Figure 30). There was a non-significant trend in favour of dimethyl fumarate BID, when compared with IFNβ-1a 22 µg TIW, IFNβ-1a 44 µg TIW, and placebo, and against dimethyl fumarate, when compared with IFNβ-1b 250 µg EOD, GA, and fingolimod.

Figure 30: Results of the MTC for discontinuation due to any cause *(Academic in confidence information removed)*

RR <1 indicates better tolerability of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly.

Tolerability: Discontinuation due to death

There was no significant difference between dimethyl fumarate BID and any comparator for discontinuation due to death, although there was a non-significant trend in favour of dimethyl fumarate BID, compared with placebo, natalizumab, IFNβ-1a 44 µg TIW, IFNβ-1a 22 µg TIW, and GA 20 mg OD (Figure 31).

Figure 31: Results of the MTC for discontinuation due to death*(Academic in confidence information removed)*

RR <1 indicates better tolerability of intervention.
Abbreviations: Tecfidera, dimethyl fumarate; CI, credible intervals; EOD, every other day; GA, glatiramer acetate; IFN, interferon; MTC, mixed treatment comparison; od, once daily; q4w, every 4 weeks; RR, risk ratio; tid, three times daily; tiw, three times weekly

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see Section 6.2.7), please repeat the instructions specified in Sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in Sections 10.6 and 10.7, appendices 6 and 7.

The identification of non-RCT evidence is described in Sections 6.1 and 6.2. No relevant non-RCT evidence was identified.

6.9 Adverse events

Summary

Clinical studies

- The overall incidence of adverse events was similar to placebo in the dimethyl fumarate BID group (96% vs 95% in DEFINE and 94% vs 92% in CONFIRM)
- The most common adverse events with dimethyl fumarate BID were flushing and GI events, incidences were highest in the first month and decreased thereafter
    - Vascular disorders – flushing (38% and 31%) and hot flush (8% and 5%, respectively) in DEFINE and CONFIRM respectively
    - GI events – abdominal pain upper (10% and 10%), nausea (13% and 11%) and vomiting (10% and 7%), in DEFINE and CONFIRM respectively)
- Most reported adverse events were mild to moderate in severity, transient in nature and manageable
- The incidence of adverse events leading to discontinuations is low with dimethyl fumarate BID (DEFINE, 16%; CONFIRM, 12%) and comparable with placebo (DEFINE, 13%; CONFIRM, 10%)
- The incidence of serious adverse events was low with dimethyl fumarate BID (DEFINE 18%; CONFIRM 17%) and comparable to placebo (DEFINE 21%; CONFIRM 22%)
- Many MS treatments have a detrimental effect on the rate of infections as a result of their mechanism of action; however, dimethyl fumarate is not associated with an increased risk of serious infections; 2% with dimethyl fumarate in both studies comparable with placebo; 1-2%
- Decreased white blood cell and lymphocyte counts were observed; however, mean values remained within normal limits and were not associated with an increased risk of serious or opportunistic infections

The identification of clinical evidence is described in Sections 6.1 and 6.2. All trials relevant to this submission are listed in Table 7 in Section 6.2.4. The methodology, critical appraisal and results of relevant trials that are designed primarily to assess safety outcomes are presented in Section 6.9.1. Safety results from other studies, primarily designed to assess efficacy are described in Section 6.9.1.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key

aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

No trials were specifically designed to assess safety.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event.

DEFINE and CONFIRM

Adverse events were recorded in the DEFINE and CONFIRM Phase III trials, designed primarily to evaluate efficacy. The methodologies for these trials have previously been described in Section 6.3. Adverse events were defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. All adverse events were recorded on the patient's clinical report form, regardless of whether the patient discontinued the study treatment but remained in the study, and regardless of the severity of the event or suspected relationship to the study treatment.

A total of 2651 subjects were included in the safety population, defined as all subjects that received at least one dose of study treatment. The integrated analysis included 769 subjects treated with dimethyl fumarate BID and 771 subjects treated with placebo.

The overall incidence of AEs in DEFINE and CONFIRM was similar between the treatment groups (***DEFINE:*** dimethyl fumarate BID=96%, dimethyl fumarate TID=95%, and placebo=95%; ***CONFIRM:*** dimethyl fumarate BID=94%, dimethyl fumarate TID=92%, GA=87%, and placebo=92%). A summary of AEs in DEFINE and CONFIRM is given in Table 36.

Table 36: Summary of adverse events: DEFINE and CONFIRM

Adverse events Number (%) subjects	DEFINE			CONFIRM			
	Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=344)	GA (N=351)	Placebo (N=363)
≥ 1 AE	395 (96)	396 (95)	387 (95)	338 (94)	316 (92)	304 (87)	333 (92)
≥ 1 moderate or severe AE	311 (76)	326 (78)	290 (71)	233 (65)	228 (66)	210 (60)	245 (67)
≥ 1 SAE	74 (18)	65 (16)	86 (21)	61 (17)	54 (16)	60 (17)	79 (22)
≥ 1 treatment related AE	124 (30)	128 (31)	28 (7)	97 (27)	93 (27)	91 (26)	24 (7)
Discontinuation due to AEs	65 (16)	68 (16)	55 (13)	44 (12)	41 (12)	35 (10)	38 (10)
Withdrawal due to AEs	40 (10)	38 (9)	21 (5)	21 (6)	25 (7)	11 (3)	10 (3)
Discontinuation /withdrawal due to flushing or GI events	31 (8)	30 (7)	7 (2)	24 (7)	25 (7)	3 (<1)	1 (<1)

Abbreviations: AE, adverse event; BID, twice daily; GA, glatiramer acetate; SAE, serious adverse event; TID, three times daily.

Most common AEs (≥5% of patients)

DEFINE: The most common adverse events (Table 37) that occurred at an incidence ≥3% higher in the dimethyl fumarate BID group than placebo included:

- Vascular disorders (flushing [38% vs 5%] and hot flush [8% vs 2%])
- GI events (upper abdominal pain [10% vs 7%], dyspepsia [6% vs 3%], nausea [13% vs 9%], and vomiting [10% vs 6%])
- Skin events (erythema [5% vs 1%], pruritus [10% vs 5%], and rash [8% vs 3%])
- Clinical investigations (alanine aminotransferase increased [7% vs 3%] and albumin urine present [6% vs 3%])

The incidence of GI events and flushing was highest in months 0–3, and decreased over time to relatively low levels (Table 38). Multiple sclerosis relapses occurred more frequently in the placebo group (46%) than in the dimethyl fumarate BID group (27%).

CONFIRM: The most common adverse events (Table 37) that occurred at an incidence ≥3% higher in the dimethyl fumarate BID group than placebo included:

- Vascular disorders (flushing [31% vs 4%] and hot flush [5% vs 2%])
- GI events (abdominal pain [8% vs 4%], abdominal pain upper [10% vs 5%], diarrhoea [13 vs 8%], nausea [11% vs 8%], and vomiting [7% vs 4%])
- Skin events (pruritus [6% vs 3%], and rash [7% vs 4%])

The incidence of GI events and flushing was highest in months 0–3, and decreased over time to relatively low levels (Table 38). Multiple sclerosis relapses occurred more frequently in the placebo group (43%) than in the dimethyl fumarate BID group (31%).

The safety of dimethyl fumarate has also been monitored through the safety extension of DEFINE and CONFIRM, ENDORSE, which demonstrates that the favourable profile was maintained in the year following study completion (98).

Table 37: Adverse events occurring in ≥5% of patients: DEFINE and CONFIRM

SOC Adverse events, n (%)	DEFINE			CONFIRM			
	Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=344)	GA (N=351)	Placebo (N=363)
Any AE	395 (96)	396 (95)	387 (95)	338 (94)	316 (92)	304 (87)	333 (92)
Ear and labyrinth disorders							
Vertigo	13 (3)	29 (7)	15 (4)	9 (3)	13 (4)	15 (4)	22 (6)
Gastrointestinal disorders							
Abdominal pain	46 (11)	37 (9)	22 (5)	27 (8)	26 (8)	4 (1)	15 (4)
Abdominal pain upper	40 (10)	52 (13)	28 (7)	36 (10)	33 (10)	4 (1)	17 (5)
Constipation	14 (3)	18 (4)	19 (5)	-	-	-	-
Diarrhoea	62 (15)	78 (19)	55 (13)	45 (13)	50 (15)	14 (4)	28 (8)
Dyspepsia	23 (6)	24 (6)	12 (3)	12 (3)	16 (5)	6 (2)	8 (2)
Gastrointestinal disorder	9 (2)	20 (5)	6 (1)	-	-	-	-
Nausea	53 (13)	54 (13)	38 (9)	40 (11)	51 (15)	15 (4)	29 (8)
Vomiting	40 (10)	30 (7)	24 (6)	25 (7)	23 (7)	8 (2)	13 (4)
General disorders and administration site conditions							
Fatigue	57 (14)	63 (15)	54 (13)	37 (10)	33 (10)	30 (9)	33 (9)
Injection site erythema	-	-	-	0	0	31 (9)	0
Injection site pain	-	-	-	0	0	29 (8)	0
Pyrexia	16 (4)	19 (5)	21 (5)	11 (3)	25 (7)	17 (5)	19 (5)
Infections and infestations							
Bronchitis	21 (5)	26 (6)	18 (4)	14 (4)	22 (6)	16 (5)	14 (4)

SOC Adverse events, n (%)	DEFINE			CONFIRM			
	Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=344)	GA (N=351)	Placebo (N=363)
Gastroenteritis	28 (7)	21 (5)	21 (5)	-	-	-	-
Influenza	34 (8)	48 (12)	39 (10)	20 (6)	25 (7)	15 (4)	22 (6)
Nasopharyngitis	108 (26)	109 (26)	101 (25)	62 (17)	63 (18)	51 (15)	58 (16)
Rhinitis	12 (3)	16 (4)	19 (5)	-	-	-	-
Sinusitis	17 (4)	34 (8)	20 (5)	18 (5)	18 (5)	11 (3)	11 (3)
Upper respiratory tract infection	63 (15)	51 (12)	53 (13)	36 (10)	47 (14)	27 (8)	34 (9)
Urinary tract infection	55 (13)	54 (13)	53 (13)	52 (14)	41 (12)	46 (13)	42 (12)
Investigations							
Alanine aminotransferase increased	29 (7)	27 (6)	13 (3)	16 (4)	22 (6)	20 (6)	25 (7)
Albumin urine present	24 (6)	22 (5)	12 (3)	22 (6)	14 (4)	18 (5)	15 (4)
Protein urine present	-	-	-	18 (5)	7 (2)	15 (4)	10 (3)
Musculoskeletal and connective tissue disorders							
Arthralgia	46 (11)	37 (9)	39 (10)	20 (6)	27 (8)	17 (5)	26 (7)
Back pain	59 (14)	46 (11)	57 (14)	35 (10)	36 (10)	32 (9)	33 (9)
Muscle spasms	13 (3)	27 (6)	20 (5)	13 (4)	21 (6)	8 (2)	14 (4)
Muscular weakness	12 (3)	14 (3)	26 (6)	-	-	-	-
Musculoskeletal pain	11 (3)	10 (2)	21 (5)	-	-	-	-
Pain in extremity	37 (9)	29 (7)	29 (7)	21 (6)	26 (8)	21 (6)	29 (8)
Nervous system disorders							
Dizziness	19 (5)	22 (5)	23 (6)	-	-	-	-

SOC Adverse events, n (%)	DEFINE			CONFIRM			
	Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=344)	GA (N=351)	Placebo (N=363)
Headache	81 (20)	80 (19)	80 (20)	52 (14)	46 (13)	46 (13)	49 (13)
Hypoaesthesia	20 (5)	24 (6)	27 (7)	11 (3)	19 (6)	16 (5)	21 (6)
Multiple sclerosis relapse	111 (27)	114 (27)	189 (46)	110 (31)	85 (25)	119 (34)	155 (43)
Paraesthesia	35 (9)	38 (9)	38 (9)	21 (6)	21 (6)	15 (4)	31 (9)
Psychiatric disorders							
Depression	29 (7)	33 (8)	33 (8)	24 (7)	15 (4)	30 (9)	35 (10)
Insomnia	20 (5)	20 (5)	19 (5)	15 (4)	10 (3)	13 (4)	18 (5)
Renal and urinary disorders							
Haematuria	26 (6)	26 (6)	19 (5)	-	-	-	-
Microalbuminuria	21 (5)	17 (4)	11 (3)	14 (4)	19 (6)	15 (4)	13 (4)
Proteinuria	38 (9)	50 (12)	34 (8)	29 (8)	35 (10)	30 (9)	25 (7)
Respiratory, thoracic and mediastinal disorders							
Cough	22 (5)	19 (5)	18 (4)	16 (4)	18 (5)	9 (3)	17 (5)
Oropharyngeal pain	25 (6)	21 (5)	19 (5)	12 (3)	21 (6)	15 (4)	14 (4)
Skin and subcutaneous tissue disorders							
Erythema	20 (5)	33 (8)	5 (1)	16 (4)	21 (6)	6 (2)	5 (1)
Pruritus	42 (10)	34 (8)	19 (5)	20 (6)	24 (7)	7 (2)	11 (3)
Rash	34 (8)	27 (6)	13 (3)	24 (7)	28 (8)	8 (2)	13 (4)
Vascular disorders							

SOC Adverse events, n (%)	DEFINE			CONFIRM			
	Dimethyl fumarate BID (N=410)	Dimethyl fumarate TID (N=416)	Placebo (N=408)	Dimethyl fumarate BID (N=359)	Dimethyl fumarate TID (N=344)	GA (N=351)	Placebo (N=363)
Flushing	154 (38)	132 (32)	20 (5)	110 (31)	83 (24)	6 (2)	13 (4)
Hot flush	31 (8)	29 (7)	8 (2)	18 (5)	19 (6)	4 (1)	8 (2)

Abbreviations: AE, adverse event; CI, confidence interval; SOC, system organ class.

Table 38: Gastrointestinal events, flushing/hot flush over time in DEFINE and CONFIRM

Gastrointestinal events and flushing over time, n (%)	Months								
	0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24
DEFINE									
Dimethyl fumarate BID (N=410)									
GI events	149 (36)	41 (11)	31 (9)	41 (12)	25 (7)	18 (6)	17 (5)	16 (5)	2 (<1)
Flushing/hot flush	146 (36)	34 (9)	15 (4)	22 (5)	14 (4)	11 (3)	4 (1)	2 (<1)	0
Placebo (N=408)									
GI events	100 (25)	30 (8)	35 (9)	31 (9)	23 (7)	22 (7)	18 (6)	22 (8)	4 (2)
Flushing/hot flush	21 (5)	1 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (<1)	1 (<1)	2 (<1)	0
CONFIRM									
Dimethyl fumarate BID (N=359)									
GI events	107 (30)	30 (9)	29 (9)	18 (6)	12 (4)	14 (5)	12 (4)	8 (3)	1 (<1)
Flushing/hot flush	101 (28)	11 (3)	10 (3)	9 (3)	6 (2)	10 (3)	5 (1)	4 (1)	1 (<1)
Placebo (N=363)									
GI events	58 (16)	24 (7)	17 (5)	14 (4)	13 (4)	10 (4)	17 (6)	7 (3)	3 (2)
Flushing/hot flush	12 (3)	3 (<1)	3 (<1)	0	0	0	2 (<1)	1 (<1)	0

Abbreviations: BID, twice daily; GI, gastrointestinal

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem

Please refer to the summary box at the start of Section 6.9 for a summary of the safety profile of dimethyl fumarate.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Dimethyl fumarate BID is effective for the treatment of adults with RRMS, as demonstrated by the clinical findings from DEFINE and CONFIRM. When compared with placebo after 2 years, dimethyl fumarate BID significantly reduced relapse rate, proportion of patients relapsed, disability progression, and MRI lesion burden (Section 6.5.4). CONFIRM also included GA as a comparator arm, although the study was not statistically powered to detect a difference between dimethyl fumarate and GA. However, a direct comparison of dimethyl fumarate BID with GA demonstrated that dimethyl fumarate BID was more effective for reducing relapse rate (Section 6.6). Mixed treatment comparison also demonstrated that dimethyl fumarate BID is significantly better than all IFNs and GA for ARR and proportion of patients relapsed at 2 years, significantly better than IM IFNβ-1a 30 µg for annualised steroid treated relapse rate and patients remaining relapse free at 24 months, and significantly better than SC IFNβ-1a 22 µg TIW for annualised steroid treated relapse rate (Section 6.7.6).

The overall rate of AEs with dimethyl fumarate BID in DEFINE and CONFIRM was similar to placebo; the most common AEs were flushing and GI events, which generally settled with continued treatment. Discontinuation and SAE rates were low with dimethyl fumarate BID, and rates were not significantly different to placebo. Dimethyl fumarate BID was not associated with an increased risk of serious infections (Section 6.9).

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Both dimethyl fumarate RCTs were large, high-quality studies which examined the most commonly used outcomes in RRMS trials, in addition to a number of additional outcomes. The results for each outcome were generally consistent between the two trials, indicating the robustness of the evidence base. One possible limitation relates to the length of the trials (2 years); due to the high variability of the underlying disease course, it may be difficult to detect differences between comparators for some outcomes over this time period. However, given the problems inherent in running large RCTs over long time scales, 2 years is used in the majority of RRMS RCTs and is felt to be an appropriate time frame.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The outcomes examined in the DEFINE and CONFIRM trials were the same as set out in the scope (Section 5), with the exception of severity of relapse, and are therefore highly relevant to the decision problem. Relapses are likely to be the most obvious manifestations of disease activity and contribute to impairment and disease progression (103). An increased relapse frequency also leads to faster disease progression (104, 105); the reductions in relapse rate and proportion of

patients relapsed in DEFINE and CONFIRM are therefore likely to provide patients with significant benefits.

Physical and mental disability accumulates in patients with RRMS as they experience relapses and an increasing lesion burden (104, 105). Patients treated with dimethyl fumarate had significantly less disability progression in DEFINE, and a trend towards less disability progression in CONFIRM, compared with placebo. Reducing disability progression will consequently provide patients with significant benefits.

Brain and CNS lesions on MRI (T2, T1, and Gd+) are one of the main identifying characteristics of MS (104, 105). These may be present even when patients have no relapses or disability progression, and are consequently a useful marker for treatment efficacy (104, 105). Dimethyl fumarate significantly reduced T2, T1, and Gd+ lesion burden in DEFINE and CONFIRM, compared with placebo, indicating that it can effectively treat the inflammation which underlies the RRMS disease process.

Complete freedom from disease activity has been suggested as the ultimate goal of RRMS treatments, defined as no relapses, no disability progression, and no new/enlarging MRI lesions (119). This was examined in post-hoc analyses of DEFINE and CONFIRM, which demonstrated that dimethyl fumarate patients had significantly more freedom from disease at 2 years, compared with placebo.

Dimethyl fumarate also resulted in significantly improved QoL in many patients, compared with placebo, which may be a consequence of the significant clinical benefits provided by treatment.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Dimethyl fumarate has received a positive CHMP opinion and is awaiting Marketing Authorisation from the EMA for the treatment of adult patients with relapsing remitting multiple sclerosis (1). DEFINE and CONFIRM both enrolled a mixture of treatment-naïve and treatment-experienced RRMS patients with varying levels of disease activity; these trials consequently represent the indicated population. Dimethyl fumarate was used as it would be in clinical practice in both trials (240 mg BID); the only likely differences between the trials and clinical practice are therefore those apparent with all drugs, such as reduced frequency of monitoring and less stringent follow-up. These trials are consequently valid representations of the likely effects of dimethyl fumarate in the indicated population in clinical practice.

7 Cost-effectiveness

- A cohort-based Markov model was developed in Microsoft Excel, based on the ScHARR framework used in previous NICE appraisals of different MS therapies
- Treatment costs (acquisition, monitoring and administration) were obtained from published sources, while treatment effects (reduction in relapse rate and disability progression, AEs) were obtained from an MTC
- These were used to evaluate the costs and QALYs associated with each treatment
- Using the list price for dimethyl fumarate resulted in ICERs in the range £106,127 to £159,295. Dimethyl fumarate will, however, be supplied at a discounted PAS price
- Using the PAS price resulted in dimethyl fumarate dominating fingolimod (Gilenya®), IM IFNβ-1a 30 µg (Avonex®), SC IFNβ-1b 250 µg (Betaferon®/Extavia®), and SC IFNβ-1a 44 µg (Rebif® 22 µg), and ICERs of £19,057 and £18,581, compared with GA (Copaxone®) and SC IFNβ-1a 22 µg (Rebif® 22 µg), respectively
- The results of the analysis were verified in scenario analysis and univariate sensitivity analysis, where dimethyl fumarate was dominant against most comparators in the majority of cases
- Probabilistic sensitivity analysis demonstrated that, versus all comparators except glatiramer acetate, the probability of dimethyl fumarate being cost-effective was ≥70% at a willingness to pay threshold of £20,000/QALY

7.1 Published cost-effectiveness evaluations

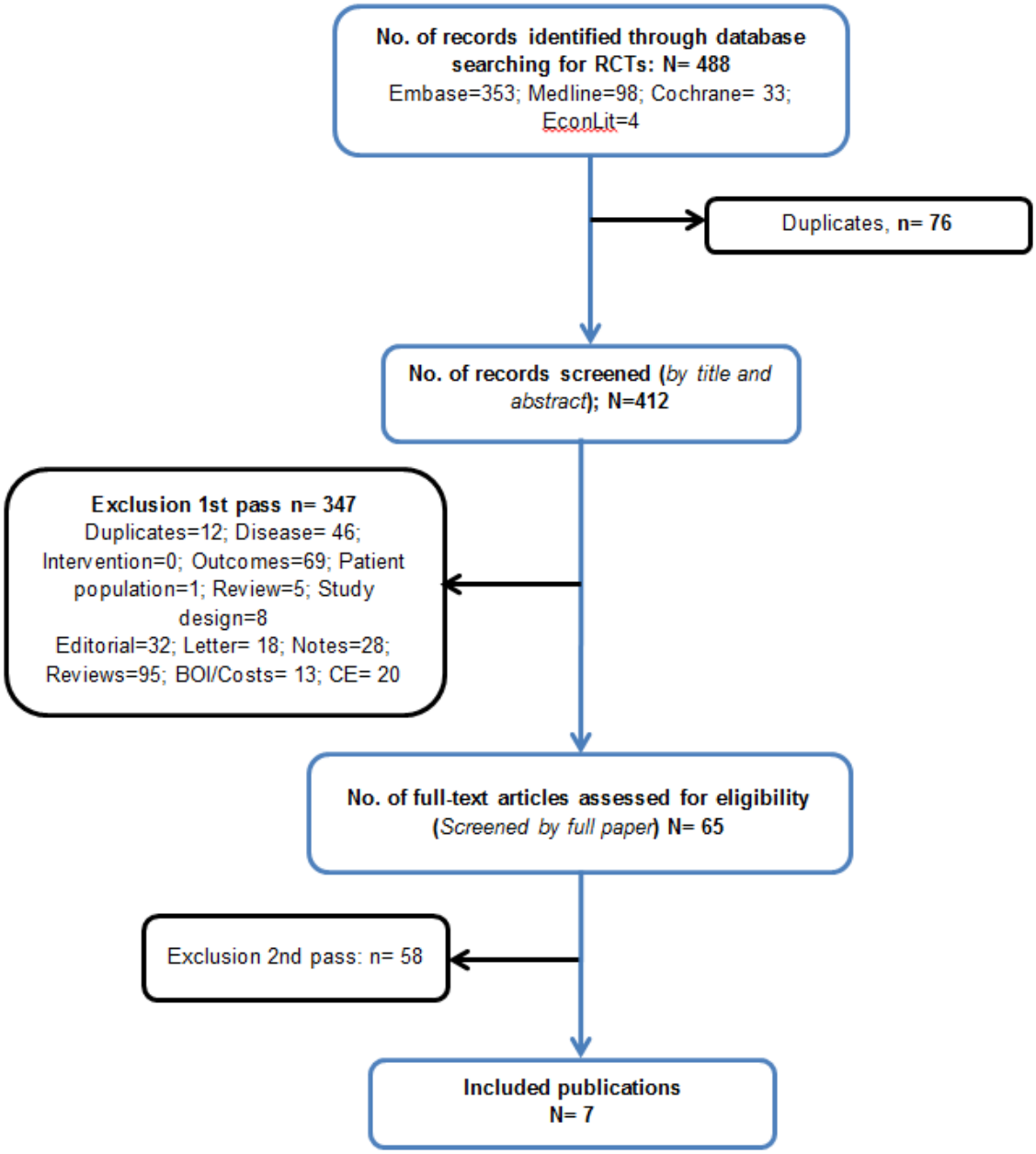
7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.

A systematic review of the published literature was conducted to identify cost-effectiveness studies relevant to the decision problem. The following electronic databases were searched: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), NHS EED and Econlit (Ovid).

Electronic searches were supplemented by hand searching the following sources: manufacturer databases, the Cost-Effectiveness Analysis (CEA) Registry, conference proceedings and NICE HTA submissions. Full details of the search are provided in Section 10.10.

In total, 488 papers were identified through the electronic searches. Following removal of duplicate papers, 412 titles and abstracts were reviewed. Sixty-five publications were reviewed in full, of which 58 were excluded, resulting in 7 seven relevant papers for final inclusion (Figure 32).

Figure 32: Schematic for the systematic review of cost-effectiveness evidence



Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided.

Of the 65 full text papers identified, seven were cost-utility analyses evaluating currently available pharmacological interventions in an active comparator setting, and reported an ICER. These seven studies were deemed relevant to this submission and are summarised in Table 39. A Markov model was used in three studies, a decision analytical in three studies and cost-utility analysis in one study.

Table 39: Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Chilcott, 2003 (120)	2003	UK	Cost utility analysis: A Markov model with time horizon of 20 years in the base-case, five disease states (derived from the Kurtzke EDSS) and 1-year cycle length.	Patients with RRMS or SPMS, meeting Association of British Neurologists criteria for treatment with IFNβ or glatiramer acetate	Not reported	Not reported	All vs BSC Base case, discounted at 6% for costs and 1.5% for benefits: Avonex: £42,041 Rebif 22 µg: £60,963 Rebif 44 µg: £71,732 Betaferon: £49,664 Copaxone: £97,636 Discounted at 6% for costs and 6% for benefits: Avonex: £73,137 Rebif 22 µg: £105,718 Rebif 44 µg: £124,034 Betaferon: £86,127 Copaxone: £168,539
Forbes, 1999 (121)	1999	UK	Cost-utility analysis: Population based cost-utility model. Effectiveness modelled using an RCT of IFNβ	132 ambulatory patients with diagnosed SPMS (from Jan 1993 to December 1995). Subset of population cohort either admitted to the neurology unit or referred to neurology outpatient clinics identified for more active disease (neurology subset).	Overall population: 0.397 Neurology subset: 0.357	Not reported	IFNβ-1b vs BSC in SPMS: Overall population: £1,024,393 Neurology subset: £883,209
Parkin, 1998 (including 1999 update) (122)	1998	UK	Cost utility analysis: two decision analytic models; one to calculate costs of treatment, cost savings and QALY gains from reductions in the number of relapses and one model of EDSS health states, to model	Hypothetical cohort of RRMS patients (1998 HTA) and for October 1999 update, RRMS and SPMS patients	QALY gains: Undiscounted (5 years): Standard care: -0.204 IFNβ-1b: -0.145	Undiscounted (5 years): Standard care: £11, 000 IFNβ-1b: £60,300 6% discounting (5 years): Standard care: £10,000 IFNβ-1b: ££53,600	IFNβ-1b vs BSC (5 years, no progression): Undiscounted: £831,400 Costs only discounted: £736,200 Costs and QALYs discounted: £809,900

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			disease and disability progression. Both models modelled time horizons of 5-years (covering trial evidence duration) and 10 years (extrapolation). A subsequent update of the model (October 1999) is also reported, based on newer trial evidence.		6% discounting (5 years): Standard care: -0.184 IFNβ-1b: -0.130 Undiscounted (10 years): Standard care: 5.32 IFNβ-1b: 5.65 October 1999 update: Using PRISMS Study Group RRMS data for 5-year model: Standard care: 3.41 IFNβ-1b: 3.52 Using PRISMS Study Group RRMS data for 10-year model: Standard care: 6.66 IFNβ-1b: 6.85 Using European Study Group SPMS patients for 5-year model: Standard care: 2.54 IFNβ-1b: 2.61	6% discounting (10 years): Standard care: £29,900 IFNβ-1b: £104,700 October 1999 update: Using PRISMS Study Group RRMS data for 5-year model: Standard care: £17,140 IFNβ-1b: £59,590 Using PRISMS Study Group RRMS data for 10-year model: Standard care: £25,670 IFNβ-1b: £101,140 Using European Study Group SPMSD data for 5-year model: Standard care: £13,500 IFNβ-1b: £58,210 Using European Study Group SPMSD data for 10-year model: Standard care: £23,300 IFNβ-1b: £101,655	IFNβ-1b vs BSC (5 years, incorporating changes in progression): £328,300 IFNβ-1b vs BSC (10 years, costs only discounted): £228,300 October 1999 update, using PRISMS Study Group RRMS data and European Study Group SPMS data: PRISMS: £375,100 and £393,300 over 5 and 10 years, respectively European Study Group: cost per QALY gained of £667,800 and £587,200 over 5 and 10 years, respectively

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					Using European Study Group for SPMS patients for 10-year model: Standard care: 4.79 IFNβ-1b: 4.92		
Parkin, 2000 (123)	2000	UK	Cost-utility: Decision analytical model, modelling a hypothetical cohort based on EDSS (baseline 3). Progression probabilities, taken from the natural history literature, with treatment effect taken from published sources. Discounting at 6% for costs and benefits. The model considers both no effect of treatment on disease progression and a treatment effect on disease progression.	Patients with RRMS; 40 patients who had a relapse in previous 6 months (recent relapse) and 62 who had not (remission group); median age 42 (range 25-65), 28% men.	5 year model (no modelling of disease progression): IFNβ-1b vs BSC: 0.054 net gain 5 year model (with modelling of disease progression): IFNβ-1b vs BSC: 0.13 net gain 10 year (with modelling of disease progression): IFNβ-1b vs BSC: 0.33	5 year model (with no modelling of disease progression): BSC: £10,000 IFNβ-1b: £53,600	5 year model (with no modelling of disease progression): IFNβ-1b vs BSC: £809,900 5 year model (with modelling of disease progression): IFNβ-1b vs BSC: £328,300
Gani, 2008 (124)	2008	UK	Cost-utility: Markov model, 30 year time horizon, based on Chilcott et al (2003) model, based on EDSS score, reparameterised for a HARRMS patient population, cycle length: 1 year. Discounting at 3.5%.	HARRMS patients (an RRMS subset); defined as patients with rapidly evolving severe RRMS, having 2 or more disabling relapses in the previous year, and with 1 or gadolinium-enhancing MRI brain lesions or a significant increase in T2	Natalizumab: 7.4 IFNβ (pooled): 5.5 GA: 5.1 BSC: 4.7	Natalizumab: £449,500 IFNβ (pooled): £445,200 GA: £444,800 BSC: £427,100	Natalizumab vs IFNβ: £2,300 Natalizumab vs GA: £2,000 Natalizumab vs BSC: £8,200

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				lesion load compared with a previous recent MRI. Mean age: 36 years, mean EDSS: 2.5.			
Nuijten, 2002 (125)	2002	UK	Cost utility analysis: Markov process model analysis, from UK societal and NHS perspective, lifetime time horizon, 3 yearly cycles, 4 health states based on EDSS score.	Hypothetical cohort of RRMS patients, 30 year old females	No discounting: IFNβ-1b: 28.2 BSC: 24.9	Discounted costs, health payer perspective (6%): IFNβ-1b: £221,436 BSC: £51,214 Undiscounted costs, health payer perspective: IFNβ-1b: £659,980 BSC: £210,824 Discounted costs, societal perspective (6%): IFNβ-1b: £473,115 BSC: £322,499 Undiscounted costs, societal perspective: IFNβ -1b: £1,530,717 BSC: £1,209,409	IFNβ-1b vs BSC, costs only discounted at 6%, payer perspective : £51,582
Phillips, 2001 (126)	2001	UK	Cost-utility analysis: based largely on Parkin et al 2000, with 20-year time horizon, model based on EDSS, including a sensitivity analysis of a 10 year horizon, from three perspectives (direct costs, direct + indirect costs, direct + indirect + informal care). Discounting at 6%.	Hypothetical cohort of RRMS patients at EDSS level 3	Societal perspective, 20 year horizon: IFNβ-1b: 10.8 BSC: 5.71 Societal perspective, 10 year horizon: IFNβ-1b: 6.19 BSC: 4.43	Direct costs only, 20 year horizon: IFNβ-1b: £163,084 BSC: £93,429 Direct + indirect costs, 20 year horizon, base case: IFNβ-1b: £244,294 Standard care: £ 203,113 Direct+indirect+informal costs, 20 year horizon: IFNβ-1b: £281,100 BSC: £265,773	Direct costs perspective, 20 year horizon : IFNβ-1b: £13,700 Direct+indirect costs perspective, 20 year horizon : IFNβ-1b: £8,100 Direct+indirect+informal care costs perspective, 20 year horizon : IFNβ-1b: £3,000

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						Direct costs only, 10 year horizon: IFNβ-1b: £99,484 BSC: £45,886 Direct + indirect costs, 10 year horizon,: IFNβ-1b: £146,516 BSC: £ 106,556 Direct+indirect+informal costs, 10 year horizon, base case: IFNβ-1b: £161,067 BSC: £135,427	Direct costs perspective, 10 year horizon : IFNβ-1b: £30,500 Direct+indirect costs perspective, 10 year horizon: IFNβ-1b: £22,800 Direct+indirect+informal care costs perspective, 10 year horizon: IFNβ-1b: £14,600

Abbreviations: BSC, best supportive care; GA, glatiramer acetate; EDSS, Expanded Disability Status Scale; HARRMS, highly active relapsing-remitting multiple sclerosis; ICER, incremental cost-effectiveness ratio; IFN, interferon; NHS, National Health Service; QALY(s), quality-adjusted life year(s); QoL, quality of life; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996 BMJ 313 (7052): 275–83), or Philips Z, et al. (2004 Health Technology Assessment 8: 36). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, appendix 11.

A complete quality assessment for each RCT is provided in Section 10.11.

7.2 De novo analysis

Patients

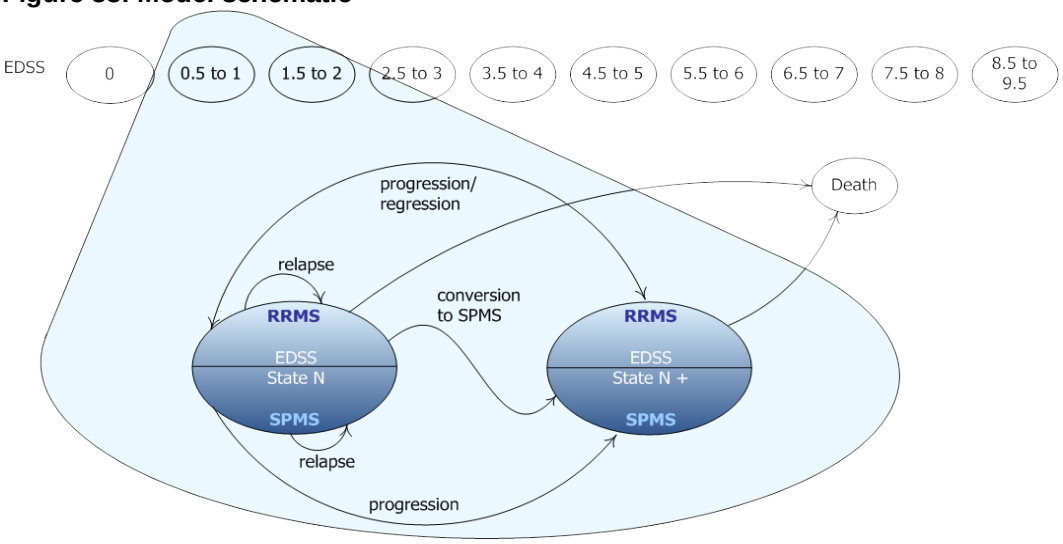
7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.4 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

Based on the licensed indication for dimethyl fumarate, the model considers all adult (≥ 18 years old) patients with RRMS with EDSS score < 7 (1).

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Patient flow through the model is shown in Figure 33. A definition of the scales used in the EDSS is provided in Section 7.3.1 Table 43.

Figure 33: Model schematic



Adapted from Gani et al (124)
Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. State N is a patient's EDSS state.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in Section 2.5.

There is currently no well-defined clinical pathway for the treatment of patients with MS (see Section 2.5). Treatment choices are based on efficacy and safety concerns, as well as patient

preference, therefore, a modelling approach was selected which reflected this and facilitated the use of the evidence available.

A cohort-based Markov model was developed in Microsoft Excel, based on the extensively validated model developed by ScHARR for NICE (120), which has been used in three previous health technology assessments (120, 124, 127). Evidence of disability progression in MS is most commonly based on changes in EDSS score (4, 104), as are QoL, costs, and treatment decisions (23, 128). Therefore, a Markov modelling approach was deemed appropriate as it allows patients to progress through a series of disability states. The model structure was also fully aligned with two of the primary objectives of treatment in relapsing MS: prevention of relapses and avoidance of disability progression.

Disease progression in the model reflects that observed in clinical practice. The most common form of MS is RRMS (13) and it is characterised by relapses, separated by periods of remission. Therefore, patients enter the model from a baseline RRMS state and may either move to a higher or lower disability state (based upon the EDSS (129)) or remain in the same state. Patients with RRMS will eventually enter a period of steady progression of neurological damage with or without relapses, known as SPMS. Therefore, in the model patients may progress to SPMS, from where they may enter a higher EDSS state or remain the same but may not return to a lower (better) disability status. The probability of changing EDSS state or experiencing a relapse was fixed for each EDSS range based on natural history data (underlying disease progression) and clinical trial data (disease progression with treatment) (Section 7.3.2). Each EDSS state for RRMS and SPMS is associated with a cost and utility whilst relapses were associated with a cost and disutility. Mortality was assumed to be equivalent between RRMS and SPMS and dependent on EDSS state (16).

Treatments were assumed to delay the progression of disease and reduce the frequency of relapses in RRMS. Progression to SPMS is included as a treatment discontinuation rule in the model, in line with clinical guidelines in the UK (22). Patients receiving treatment for MS may experience tolerability issues (1, 23-28); therefore various AEs were associated with each treatment in the model and incurred costs and disutilities.

Using the Markov model structure, it was possible to capture the accumulated costs and QALYs for patients based on their baseline EDSS and RRMS/SPMS status, treatment-related costs, AE costs and disutilities, and the efficacy of treatment regarding disease progression and relapses.

7.2.4 Please define what the health states in the model are meant to capture.

The health states in the model represent typical disease progression in patients with RRMS. Patients may experience changes in the degree of disability they experience, represented by the various EDSS states (Figure 33), and may progress to SPMS, from where they will experience increasing (but not decreasing) disability. Utilities and costs are associated with specific EDSS states (and time spent in these states) in both RRMS and SPMS.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in Section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to Section 2.1.

Relapsing-remitting MS (RRMS) is a progressive, chronic, disabling disease characterised by relapses and remission (See Section 2.1). Patients eventually enter a period of steady progression of neurological damage with or without relapses, known as SPMS. In the Markov model, the main aspects of the disease (i.e. relapse. remission, progression, transition from RRMS to SPMS, and

treatment) were captured using changes in EDSS. Parameters reflecting the natural history of MS were based on disability progression/regression rates, MS relapse rates, and mortality rates. The response to treatment was modelled by changes to the progression/regression risks and relapse rates, as well as changes to the overall costs of treatment and utilities. The Markov approach adopted in this submission is typical of modelling in RRMS, and similar models have been used in previous NICE STAs (120, 124, 127).

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported.

Table 40: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	30 years	30 years was chosen as it represents a lifetime horizon in the relevant population (RRMS patients, with average age of ~38 years old), and the benefits of delaying disease progression associated with DMTs are expected to persist over a lifetime. This is in line with NICE guidance.	(130)
Cycle length	1 year	Aligned with trial measurement period	(130)
Half-cycle correction	Yes	NICE reference case	(130)
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	(130)
Discount of 3.5% for utilities and costs	Yes	NICE reference case	(130)
Perspective (NHS/PSS)	NHS.PSS	NICE reference case	(130)

Abbreviations: DMT, disease-modifying therapy; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in Sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

See Table 41 for a list of the interventions considered in the model. Dimethyl fumarate, IFN, and GA are implemented as per their marketing authorisation. Natalizumab and fingolimod are restricted to patients with rapidly evolving severe disease or patients with highly active disease despite treatment, respectively, by NICE guidance (20, 21). However, given the lack of data allowing a comparison of all treatments for these subgroups the interventions were evaluated only in the overall patient population.

Table 41: Interventions considered in the model

Brand name	Generic name	Dosage	Frequency
Avonex®	IFNβ-1a	IM 30 µg	OW
Betaferon®/Extavia®	IFNβ-1b	SC 250 µg	EOD
Copaxone®	Glatiramer acetate	SC 20 mg	OD
Gilenya®	Fingolimod	Oral pill, 0.5 mg	OD
Rebif®	IFNβ-1a	SC 22 µg	TIW
Rebif®	IFNβ-1a	SC 44 µg	TIW
Tecfidera®	Dimethyl fumarate	Oral capsule, 240 mg	BID
Tysabri®	Natalizumab	IV infusion, 300 mg	OM

Abbreviations: BID, twice daily; EOD, every other day; IFN, interferon; IM, intramuscular; IV, intravenous; OD, once daily; OM, once monthly; OW, once weekly; TIW, three times weekly.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No additional treatment continuation rule has been assumed in the model, beyond the requirements of the marketing authorisation. It is assumed that treatment will be administered until the patient progresses to SPMS, dies, or discontinues treatment.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Baseline patient characteristics

Patient characteristics at baseline were pooled from the BG-12 BID and placebo arms of the pivotal clinical trials DEFINE and CONFIRM, and are shown in Table 42. An explanation of the scales used in the EDSS is provided in Table 43.

Table 42: Baseline characteristics used in the model

Characteristic		Overall population
Age (years)		37.8
Female:male ratio		2.5
EDSS score (%)	0	5.05
	1	8.52
	2	34.08
	3	22.94
	4	20.64
	5	8.65
	6	0.13
	7	0.00
	8	0.00
	9	0.00

Abbreviations: EDSS, expanded disability status scale; Tx, treatment.

Table 43: The progressive classifications of disease burden using the EDSS

Score	Description
0.0	Normal neurologic examination
1.0	No disability, minimal signs on 1 of 7 functional systems[†]
1.5	No disability, minimal signs on 2 functional systems
2.0	Minimal disability in 1 functional system
2.5	Minimal disability in 2 functional systems
3.0	Moderate disability in 1 functional system or mild disability in 3-4 functional systems, although fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 functional system and mild disability in 1-2 functional systems or moderate disability in 2 functional systems or mild disability in 5 functional systems
4.0	Fully ambulatory without aid, up and about 12 hours a day despite relatively severe disability. Able to walk 500 meters without aid
4.5	Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk 300 meters without aid
5.0	Ambulatory without aid for about 200 meters. Disability impairs full daily activities
5.5	Ambulatory for 100 meters. Disability precludes full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk 100 meters with or without resting
6.5	Constant bilateral support (canes, crutches, or braces) required to walk 20 meters without resting
7.0	Unable to walk beyond 5 meters, even with aid. Essentially restricted to wheelchair, wheels self, transfers alone. Active in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps, restricted to wheelchair, may need aid to transfer. Wheels self, but may require motorized chair for full day's activities
8.0	Essentially restricted to bed, chair, or wheelchair but may be out of bed much of the day. Retains self-care functions, generally effective use of arms
8.5	Essentially restricted to bed much of the day. Some effective use of arms, retains some self-care functions
9.0	Helpless bed patient, can communicate and eat
9.5	Unable to communicate effectively or eat/swallow
10.0	Death

Source: Kurtzke 1983 (129).

[†]Functional tests are pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other.

Relapse rates

Relapse rates per person per year were obtained from pooled baseline data from the pivotal dimethyl fumarate trials, which documented ARR in the 12 months prior to enrolment in the study. Data with adequate sample sizes were only available up to EDSS 5; the ARR for EDSS scores > 5 were therefore computed based on the relative increases in ARR reported by Patzold et al (131). As Patzold et al reported ARR by year from diagnosis (Table 44), it was necessary to convert this into an ARR for each EDSS state. This was achieved by taking the mean number of relapses per year for each state from the UK MS survey (Table 45) (128, 132) and multiplying by the relative relapse rates per person per year reported by Patzold et al (Table 44) to give the total number of relapses by EDSS state by year since diagnosis (Table 46). Average relapse rates per year (Table

44) were then derived by taking the total number of relapses in each EDSS state (sum of each row in Table 46) and dividing by the number of patients observed in this state in the UK MS Survey (sum of each row in Table 45). Owing to the small number of records in EDSS states 7, 8 and 9, these data were pooled together, and the average relapse rate per year calculated by taking the total number of relapses in EDSS states 6.5 - 9 (sum of last four rows in Table 46), and dividing by the number of patients observed in these states in the UK MS Survey (sum of last four rows in Table 45). The ARR by EDSS state data used in the model are given in Table 48.

Table 44: ARR per year since diagnosis in Patzold et al

Years since diagnosis	Annual relapse rate
1	1.85
2	1.10
3	1.00
4	0.85
5	0.65
6-7	0.75
8-9	0.25
10-11	0.60
12-13	0.28
14-15	0.30
16+	0.20

Table 45: Total patients with relapse per health state by year since diagnosis in the UK MS survey

Years since diagnosis	1	2	3	4	5	6-7	8-9	10-11	12-13	14-15	16+
RRMS											
EDSS 0	2	2	1	2	6	6	3	2	0	1	3
EDSS 1	11	16	18	11	16	22	15	10	3	10	18
EDSS 2	11	16	7	17	14	13	19	19	9	5	22
EDSS 3	6	4	4	5	7	9	4	1	5	6	6
EDSS 4	6	15	7	12	13	24	8	13	6	2	17
EDSS 5	2	5	12	9	13	18	11	10	4	7	23
EDSS 6	2	3	3	5	2	6	11	2	2	6	20
EDSS 6.5	1	0	2	0	3	3	4	1	2	2	9
EDSS 7	1	0	0	0	0	0	1	1	1	0	3
EDSS 8	0	0	0	0	1	2	1	0	0	0	1
EDSS 9	1	0	0	0	0	0	0	0	0	0	1
SPMS											
EDSS 2	0	0	0	1	2	2	0	0	0	0	5
EDSS 3	2	0	1	1	0	4	0	1	1	0	1
EDSS 4	1	2	3	3	0	6	6	2	6	1	7
EDSS 5	6	6	5	6	7	14	17	15	10	11	35
EDSS 6	3	5	8	14	11	20	23	21	17	14	74
EDSS 6.5	2	1	3	4	5	18	16	11	19	12	78
EDSS 7	0	1	0	0	3	8	10	9	7	8	63
EDSS 8	0	0	0	0	3	5	4	7	4	5	46
EDSS 9	0	0	0	0	0	1	2	1	2	0	2

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 46: Number of relapses per health state by year since diagnosis

Years since diagnosis	1	2	3	4	5	6-7	8-9	10-11	12-13	14-15	16+
RRMS											
EDSS 0	3.7	2.2	1.0	1.7	3.9	4.5	0.8	1.2	0.0	0.3	0.6
EDSS 1	20.4	17.6	18.0	9.4	10.4	16.5	3.8	6.0	0.8	3.0	3.6
EDSS 2	20.4	17.6	7.0	14.5	9.1	9.8	4.8	11.4	2.5	1.5	4.4
EDSS 3	11.1	4.4	4.0	4.3	4.6	6.8	1.0	0.6	1.4	1.8	1.2
EDSS 4	11.1	16.5	7.0	10.2	8.5	18.0	2.0	7.8	1.7	0.6	3.4
EDSS 5	3.7	5.5	12.0	7.7	8.5	13.5	2.8	6.0	1.1	2.1	4.6
EDSS 6	3.7	3.3	3.0	4.3	1.3	4.5	2.8	1.2	0.6	1.8	4.0
EDSS 6.5	1.9	0.0	2.0	0.0	2.0	2.3	1.0	0.6	0.6	0.6	1.8
EDSS 7	1.9	0.0	0.0	0.0	0.0	0.0	0.3	0.6	0.3	0.0	0.6
EDSS 8	0.0	0.0	0.0	0.0	0.7	1.5	0.3	0.0	0.0	0.0	0.2
EDSS 9	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2
SPMS											
EDSS 2	0.0	0.0	0.0	0.9	1.3	1.5	0.0	0.0	0.0	0.0	1.0
EDSS 3	3.7	0.0	1.0	0.9	0.0	3.0	0.0	0.6	0.3	0.0	0.2
EDSS 4	1.9	2.2	3.0	2.6	0.0	4.5	1.5	1.2	1.7	0.3	1.4
EDSS 5	11.1	6.6	5.0	5.1	4.6	10.5	4.3	9.0	2.8	3.3	7.0
EDSS 6	5.6	5.5	8.0	11.9	7.2	15.0	5.8	12.6	4.8	4.2	14.8
EDSS 6.5	3.7	1.1	3.0	3.4	3.3	13.5	4.0	6.6	5.3	3.6	15.6
EDSS 7	0.0	1.1	0.0	0.0	2.0	6.0	2.5	5.4	2.0	2.4	12.6
EDSS 8	0.0	0.0	0.0	0.0	2.0	3.8	1.0	4.2	1.1	1.5	9.2
EDSS 9	0.0	0.0	0.0	0.0	0.0	0.8	0.5	0.6	0.6	0.0	0.4

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 47: ARR by EDSS state calculated for Patzold et al from Table 44

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

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 48: ARR by EDSS state used in the model

EDSS	Annual relapse rate	Sample size
0	1.26	135
1	1.32	640
2	1.32	769
3	1.35	665
4	1.36	339
5	1.43	97
6	1.18	N/A - Computed
7	1.23	N/A - Computed
8	1.23	N/A - Computed
9	1.23	N/A - Computed

Abbreviations: ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale.

Mortality

Mortality has been shown to be significantly higher in patients with MS than in the general population (15-17); mortality rates for the general population of England, adjusted by the factors reported in Pokorski et al, were therefore assigned to each age and EDSS state in the model (16, 133). It was assumed that the probability of mortality for each state was equivalent across the SPMS and RRMS cohorts. Pokorski et al report mortality multipliers for three EDSS states, ≤ 3.5, 4–7, and ≥ 7.5; a linear interpolation of this data was therefore used to determine the probability of mortality for each state, with a multiplier of 1.0 assumed for EDSS 1 (Table 49).

Table 49: Mortality multipliers reported in the literature and interpolated for use in the model

EDSS state	Mortality multiplier (Pokorski et al (16))	EDSS state	Mortality multiplier used in model
0–3.5	1.6	0	1
		1	1.3
		2	1.6
		3	1.68
4–7	1.84	4	1.76
		5	1.84
		6	2.71
		7	3.57
7.5+	4.44	8	4.44
		9	5.31

Abbreviations: EDSS, Expanded Disability Status Scale.

Treatment efficacy

Efficacy inputs for each treatment for disability progression sustained for 3 months and ARR were derived from the MTC described in Section 6.7, and are summarised in Table 50. These effects apply to RRMS-RRMS transitions only, as patients with SPMS were assumed not to receive treatment. The effect of treatments on RRMS–SPMS transitions was discussed in the fingolimod NICE submission with the conclusion that, in the absence of evidence supporting a treatment

effect, it should be assumed that RRMS treatment has no effect on RRMS–SPMS transitions (21). In the MTC analysis, three disability related efficacy outcomes were analysed; confirmed disability progression sustained for 3 months at 24 months, confirmed disability progression sustained for 6 months at 24 months, and change in EDSS score at 24 months. For the health economic model, confirmed disability progression sustained for 3 months at 24 months was used as the efficacy input since this outcome was reported by more studies than the 6-month sustained progression, and thus resulted in stronger evidence network for analysis in the indirect comparison. The change in EDSS score at 24 months was not used in the health economic assessment as this outcome was reported for the overall trial population and did not account for the EDSS score of the patient at the time of assessment. Therefore it cannot account for the potential differences between different EDSS levels in terms of the size of the change (one of the drivers of the health economic assessment).

Table 50: Treatment effect on disability progression and ARR used in the model *(Academic in confidence information removed)*

Treatment	Relative risk for disability progression† (CrI)	ARR† (CrI)
Dimethyl fumarate		
Fingolimod		
Glatiramer acetate		
IM IFNβ-1a 30 µg		
SC IFNβ-1b 250 µg		
Natalizumab		
SC IFNβ-1a 22 µg		
SC IFNβ-1a 44 µg		

† Compared with placebo. ‡ No 3-month data available. Assumed to be the average of Rebif 22 µg and Rebif 44 µg.
Abbreviations: ARR, annualised relapse rate; CrI, credible interval; IFN, interferon; IM, intramuscular; SC, subcutaneous.

Adverse events

The following AEs were included in the model:

- Most common AEs on dimethyl fumarate label (≥ 5% incidence in any treatment group in DEFINE and CONFIRM)
- Common dimethyl fumarate AEs on label that have been reported in published evidence and extracted in the systematic review (SR) (Section 6.1)
- AEs included in the model were only those reported in dimethyl fumarate studies
- Any AE occurring at an incidence ≥ 3 percentage points higher in the total dimethyl fumarate group than in the placebo group. This rationale was also used to identify AEs in the SR.

The treatment-specific annual incidence of AEs was calculated from the SR, using a weighted average across studies. For each common included adverse event, the number of serious events as reported from the systematic review was used to calculate the proportion of events that were serious for patients on each treatment in the model. Separate quality of life and cost implications were assigned to these serious events. The percentage of AEs which were deemed to be serious was determined from:

- **Dimethyl fumarate**: data from the dimethyl fumarate BID arms of DEFINE and CONFIRM (66, 67). Where data were available from more than one study regarding the same event, a weighted average was taken.

- **Fingolimod**: data from the fingolimod 0.5 mg arm of the TRANSFORMS and FREEDOMS studies (51, 58). Where data were available from more than one study regarding the same event, a weighted average was taken.
- **GA**: data from CONFIRM (67).
- **Avonex**: data from the IFNβ-1a arm of the TRANSFORMS study (51).
- **Natalizumab:** data from the natalizumab arm of the AFFIRM trial (62)
- **Other treatments**: no data on the proportion of AEs which were serious were available for the other comparators from the SR. It was therefore conservatively assumed that no AEs were serious for these treatments.

The incidence of AEs for each treatment (and the proportion of these which were serious), which was used in the model are given in Table 51.

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Table 51: Incidence of AEs and proportion of AEs which were serious used in the model *(Academic in confidence information removed)*

Adverse events	Dimethyl fumarate		Avonex		Rebif 22 µg		Rebif 44 µg		Betaferon		GA		Natalizumab		Fingolimod	
	Incid.	% SAE	Incid.	% SAE	Incid.	% SAE	Incid.	% SAE	Incid.	% SAE	Incid.	% SAE	Incid.	% SAE	Incid.	% SAE
Abdominal pain			NA		NA		NA		NA		0.0062	0.00	0.0566	NA	NA	
Abdominal pain upper			NA		NA		NA		NA		0.0062	NA	NA		NA	
ALT increased			0.0378	NA	0.1062	NA	0.0730	NA	0.0551	NA	0.0177	NA	0.0253	NA	0.04888	NA
Arthralgia			0.0557	NA	NA		0.0259	NA	0.0615	NA	0.0370	0.00	0.0999	NA	0.0319	NA
ACB			0.0023	100.00%	NA		NA		NA		0.0031	NA	NA		0.0100	100.00
Back pain			0.0534	NA	NA		0.0361	NA	0.0520	NA	0.0469	0.00	NA		0.0606	4.00
Bradycardia			0.0000	0.00%	NA		NA		NA		0.0031	0.00	NA		0.0066	72.35
Chest pain			NA		NA		NA		NA		0.0175	NA	0.0250	NA	0.0047	0.00
Cough			0.0371	NA	NA		NA		NA		0.0140	NA	NA		0.0493	NA
Depression			0.1251	NA	0.1121	NA	0.1032	NA	0.0841	NA	0.0492	6.67	0.0999	NA	0.0443	0.00
Diarrhoea			0.0578	NA	NA		NA		NA		0.0218	NA	NA		0.0677	NA
Fatigue			0.1684	NA	0.1803	NA	0.1824	NA	0.1177	NA	0.0761	NA	0.1453	NA	0.0805	NA
Flu-like symptoms			0.4132	NA	0.3373	NA	0.3684	NA	0.3703	NA	0.0468	NA	NA		0.0350	NA
Flushing			NA		NA		NA		NA		0.0163	NA	NA		NA	
Gastroenteritis			NA		NA		NA		NA		0.0077	NA	0.0566	1.45	NA	
Headache			0.2307	NA	0.4091	NA	0.3055	NA	0.2266	NA	0.0896	0.00	0.2123	NA	0.1655	0.00
Influenza			0.2163	NA	NA		0.0259	NA	0.0484	NA	0.0349	0.00	0.0893	0.96	0.0618	NA
Leukopenia			0.0209	NA	0.0685	NA	0.1153	NA	0.0717	NA	NA		NA		0.0071	NA
Lower RTIs			NA		NA		NA		NA		0.0015	NA	0.00893	NA	0.495	NA
Nausea			0.0947	NA	NA		0.0361	NA	0.0416	NA	0.0408	NA	NA		0.0763	NA
Pain in extremity			0.0650	NA	NA		NA		0.0478	NA	0.0467	NA	NA		0.0413	NA
Pruritus			NA		NA		NA		NA		0.0645	NA	0.0201	NA	NA	
Rash			0.0242	NA	NA		0.0969	NA	NA		0.0201	NA	0.0566	NA	NA	
UTI			0.0454	NA	NA		0.0244	NA	0.0458	NA	0.0493	0.00	0.1052	NA	0.0563	5.88

Abbreviations: ACB, atrioventricular conduction block; AE, adverse event; ALT, alanine transaminase; RTI, respiratory tract infection; UTI, urinary tract infection; NA, not available (indicates where data was not reported or found in systematic review).

Discontinuations

Risk of discontinuation for each treatment was sourced from the systematic review and the MTC described in Section 6.7 (Table 52). In the base case, constant all-cause discontinuations were assumed for all treatments, for all years up to the specified time horizon. The baseline risk of discontinuation on placebo from the included studies, along with the relative risk of discontinuation on each treatment as compared with placebo, was used to calculate the risk of withdrawal on each treatment. The all-cause annual discontinuation risk for placebo was averaged for each treatment arm over all identified studies from the SR. For each study in the SR, the annual all-cause probability of discontinuation was calculated from data extracted from the literature for the sample size, number of discontinuations, and duration of the study. The contribution of each study to total discontinuation was weighed by the sample size. Following discontinuation, patients were assumed to follow natural disease progression.

Table 52: Annual discontinuation risk used in the model *(Academic in confidence information removed)*

Treatment	Relative risk vs placebo[†]	Annual discontinuation risk
Dimethyl fumarate		
Fingolimod		
Glatiramer acetate		
IM IFNβ-1a 30 µg		
SC IFNβ-1b 250 µg		
Natalizumab		
Placebo		
SC IFNβ-1a 22 µg		
SC IFNβ-1a 44 µg		

[†]From SR and MTC. [‡] From studies included in SR.
Abbreviations: IFN, interferon; IM, intramuscular; SC, subcutaneous.

Treatment waning effect

DEFINE and CONFIRM were performed over 2 years, and there is consequently no data on treatment efficacy after this period. As no data on dimethyl fumarate use over a lifetime exists, it was conservatively assumed that efficacy diminished immediately after the trial period. Waning assumptions have previously been discussed by NICE in the fingolimod submission; the recommendations from the this submission were consequently used (21). It was therefore assumed that a waning effect occurs for all treatments after 2 years in the base case (Table 51).

Table 53: Waning effect used in the model

Year	1	2	3	4	5	6	7	8	9	10+
Treatment efficacy (Waning effect)	100%	100%	75%	75%	75%	50%	50%	50%	50%	50%

7.3.2 *Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.*

Three independent transition probability matrices were used in the model:

- Transition matrix of movement between EDSS states within RRMS (EDSS 0-9)
- Transition matrix of RRMS to SPMS (EDSS 1-9)
- Transition matrix of movement between EDSS states within SPMS (EDSS 1-9)

RRMS-RRMS transitions

Annual transition probabilities within RRMS health states are shown in Table 54. These were sourced from the placebo arms of the pivotal trials of dimethyl fumarate up to EDSS 7, with the Ebers London Ontario Multiple Sclerosis registry used as a supplement for EDSS 8–9 due to the limited number of observations for these states in DEFINE and CONFIRM (29, 30). The dimethyl fumarate and London Ontario matrix was derived using the Multi State Markov (MSM) package in the statistical software R through maximum likelihood estimation. In order to combine the matrices and values for both data sets a scaling factor was used to allow the inclusion of values within the combined matrix (rows are required to sum to one in order to ensure that patients are not lost or gained between transitions). The dimethyl fumarate transition probabilities were scaled by equal proportions to force the rows to sum to one.

The MSM method estimates the progression rates between disability states. It uses longitudinal individual patient data from patients with degenerative conditions. Each observation is treated independently using degeneration over a period of time to predict progression. The model makes the following assumptions:

- Transition rates are similar across studies.
- The probability of transition from one state to another is constant and independent of the time spent within the state. However, the model approximates the observed mean time spent in each state.

Table 54: Annual transition probability matrix *(Academic in confidence information removed)*

EDSS from/to†	0	1	2	3	4	5	6	7	8	9
0										
1										
2										
3										
4										
5										
6										
7										
8										
9										

†Rows indicate initial EDSS state, columns indicate new EDSS state. SOURCE: London Ontario (academic in confidence) and dimethyl fumarate clinical trial data
Abbreviations: EDSS, Extended Disability Status Scale

RRMS–SPMS transitions

Transition probabilities describing the probability of progressing from RRMS to SPMS health states are detailed in Table 55. These probabilities are applied to the RRMS population in order to estimate the proportion of patients who are expected to progress to a greater SPMS EDSS state during the given cycle (e.g. from EDSS 5 to EDSS 6). The RRMS to SPMS transition probabilities are estimated from the London Ontario dataset.

Table 55: Annual transition probabilities for RRMS-SPMS *(Academic in confidence information removed)*

RRMS EDSS	Probability of transition to SPMS (one EDSS higher)
1	
2	
3	
4	
5	
6	
7	
8	
9	

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

SPMS–SPMS transitions

Patients with SPMS were excluded from DEFINE and CONFIRM; annual transition probabilities within SPMS health states were therefore obtained from an analysis of the London Ontario dataset using an MSM model using the same method as for RRMS-RRMS probabilities (Table 56).

Table 56: Annual transition probabilities: SPMS-SPMS *(Academic in confidence information removed)*

EDSS from/to*	1	2	3	4	5	6	7	8	9
1									
2									
3									
4									
5									
6									
7									
8									
9									

Abbreviations: EDSS, Extended Disability Status Scale
[†]Rows indicate initial EDSS state, columns indicate new EDSS state. SOURCE: London Ontario (academic in confidence) and dimethyl fumarate clinical trial data.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Patients with RRMS will generally have a low EDSS score at diagnosis and will progress through the various EDSS states over time. The impact of time on transition probabilities is therefore captured in the data used to inform the transition probabilities for EDSS states. The probability of transition from one state to another is constant and independent of the time spent within the state. However, the model approximates the observed mean time spent in each state.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcome measures were not considered in this appraisal.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the details.

Clinical experts were not used to assess the applicability of values or to estimate values.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table.

Table 57: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Time horizon	30 years	Scenario analysis: 1–50 years	Section 7.2.6, SA: Section 7.6.1
Baseline characteristics			
Age	37.8 years	None	Section 7.3.1
Female:male ratio	2.5	None	Section 7.3.1
EDSS score distribution	See Table 42	None	Section 7.3.1
Disease progression			
ARR by EDSS state	See Table 48	Univariate: ±20% PSA: log-normal distribution with SE=10%	Section 7.3.1 SA: Sections 7.6.2–7.6.3
Mortality multiplier by EDSS state	See Table 49	Scenario: set to general population mortality	Section 7.3.1 SA: Section 7.6.1
RRMS–RRMS transition probabilities	See Table 54	PSA: Dirichlet distribution Scenario: London Ontario transition matrix used instead of combined dimethyl fumarate and London Ontario matrix (Table 73)	Section 7.3.2 SA: Section 7.6.1 and Section 7.6.3
RRMS–SPMS transition probabilities	See Table 55	PSA: beta distribution	Section 7.3.2 SA: Sections 7.6.3
SPMS–SPMS transition probabilities	See Table 56	PSA: Dirichlet distribution	Section 7.3.2 SA: Sections 7.6.3
Treatments			
Treatment efficacy	See Table 50	One-way: ±20% Two-way: upper and lower CIs calculated in MTC PSA: upper and lower CIs calculated in MTC	Section 7.3.1 SA: Sections 7.6.2–7.6.3
AEs	See Table 51	None	Section 7.3.1
Discontinuation rate	See Table 52	One-way: ±20% Two-way: ±20% PSA: beta with SE=10%	Section 7.3.1 SA: Sections 7.6.2–7.6.3
Treatment waning effect	See Table 53	Scenario: no waning effect	Section 7.3.1 SA: Section 7.6.1
Utilities			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
EQ-5D score by EDSS state, relapse status, and RRMS/SPMS state	See Table 63	Univariate: ±20% PSA: beta with SE=10%	Section 7.4.9 SA: Sections 7.6.2–7.6.3
Disutility associated with treatment	See Table 62	PSA: beta with SE=10%	Section 7.4.8 SA: Sections 7.6.3
Caregiver disutility	See Table 64	Scenario: no caregiver disutility	Section 7.4.9 SA: Section 7.6.1
Costs			
Treatment acquisition	See Table 65	PSA: gamma distribution with SE: 10%	Section 7.5.5 SA: Sections 7.6.3
Treatment administration	See Table 66	PSA: gamma distribution with SE: 10%	Section 7.5.5 SA: Sections 7.6.3
Treatment monitoring	See Table 67	PSA: gamma distribution with SE: 10%	Section 7.5.5 SA: Sections 7.6.3
EDSS state costs	See Table 70	Univariate: ±20% PSA: gamma distribution with SE: 10%	Section 7.5.6 SA: Sections 7.6.2–7.6.3
Relapse costs	See Table 71	Univariate: ±20% PSA: gamma distribution with SE: 10%	Section 7.5.6 SA: Sections 7.6.2–7.6.3
AE treatment costs	See Table 72	PSA: gamma distribution with SE: 10%	Section 7.5.7 SA: Sections 7.6.3
Discount rate	3.5%	Scenarios: Costs and benefits at 0% Costs and benefits at 6% Costs at 0%, benefits at 6% Costs at 6% and benefits at 0% Costs at 1.5% and benefits at 3.5% Costs at 3.5% and benefits at 1.5%	Section 7.2.6 SA: Section 7.6.1

Abbreviations: AE, adverse event; CI, confidence interval; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life 5 Dimensions; MTC, mixed treatment comparison; PPMS, primary-progressive multiple sclerosis; PSA, probabilistic sensitivity analysis; RRMS, relapsing-remitting multiple sclerosis; SA, scenario/sensitivity analysis; SE, standard error; SPMS, secondary-progressive multiple sclerosis.

7.3.7 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.*

The DEFINE and CONFIRM clinical trials reported on the efficacy of dimethyl fumarate over 2 years; it was therefore necessary to extrapolate treatment efficacy past this point for the 30 year time horizon used in the model. No waning effect was observed at 2 years in DEFINE or CONFIRM; however, there is uncertainty as to whether efficacy is maintained long term. This has previously been discussed by the evidence review group for the fingolimod NICE submission, where it was felt that a waning effect should have been considered as there is uncertainty as to whether treatment effects would be maintained long-term (21). A waning effect is therefore used for all treatments in the current model, described in Table 53. Costs were assumed to be dependent on a patient's EDSS state, RRMS/SPMS state, relapse status, and treatment. The model therefore varies the costs associated with each patient over time (Section 7.3.3).

7.3.8 *Provide a list of all assumptions in the de novo economic model and a justification for each assumption.*

Assumption	Justification	Reference to section:
All patients in a particular health state have the same probability of transitioning, regardless of any previous experience.	Inherent limitation of Markov models	Section 7.2.5
Costs and utilities applied to a mid-year estimate of the cohort distribution.	To avoid over- or under-estimation in the model.	Sections 7.4.9 and 7.5.6
Disability progression and relapses modelled independently, with independent treatment effects applied to each.	No definitive link between treatment effects on relapses and disability progression has been established in the literature.	Section 7.3.1
No switching between DMTs	There is no definitive treatment pathway for patients with RRMS; patients may initiate treatment with IFN, GA, or dimethyl fumarate, or natalizumab or fingolimod if they experience rapidly evolving severe disease. Patients may then switch back and forth between these treatments as decided by their physician, as a result of efficacy adverse event concerns. In the absence of a definitive treatment pathway, it was assumed that all patients remained on their original treatment.	Section 7.3.1
Patients who drop out of treatment are assumed to follow natural disease progression	No evidence exists to support treatment effects continuing following treatment discontinuation.	Section 7.3.1
Adverse events included in the model are only those present in	Conservative assumption which reduces the number of AEs for comparators, but not dimethyl	Section

Assumption	Justification	Reference to section:
the dimethyl fumarate trial	fumarate	7.3.1
Transitions to EDSS state 10 (MS related death) not included in transition matrices.	Mortality multiplier by MS state used to account for increased mortality.	Section 7.3.1
Relapses are not divided into different levels of severity for costs and utilities.	Mean costs and utilities are used for each EDSS state. Relapses are allowed to have differing quality of life impact depending on the EDSS state, which could be interpreted as a measure of relapse severity	Sections 7.4.9 and 7.5.6
Waning effect on treatment efficacy over time.	There is uncertainty as to whether the treatment effects observed in clinical trials are maintained long-term. This was deemed appropriate by the ERG for the fingolimod STA.	Section 7.3.1
Treatments have no direct effect on the risk of conversion to SPMS	Treatments may delay conversion to SPMS by delaying disability progression; however, there is no definitive evidence to support this. This assumption was deemed appropriate by the ERG for the fingolimod STA.	Section 7.3.2
Patients withdraw from treatment when they reach EDSS ≥ 7, or when they convert to SPMS	In accordance with treatment guidelines	Section 7.3.1

Abbreviations: AE, adverse event; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; ERG, Evidence Review Group; GA, glatiramer acetate; IFN, interferon; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis; STA, Single Technology Appraisal.

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Physical and mental disability is a defining symptom of RRMS, and will result in diminished QoL (4, 128). Patients also experience periods of diminished HRQL from which they may recover as a result of relapses (128).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition

Patients face increasing levels of physical and mental disability as the disease progresses, which result in declining HRQL with increasing EDSS score (128).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in Section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

Utility weights for RRMS EDSS states were derived from all arms in DEFINE and CONFIRM, by pooling observations for each EDSS state (0-9) and calculating the mean EQ-5D index score for each state (Table 58). Use of EQ-5D is consistent with the reference case.

Table 58: EQ-5D scores for each EDSS state derived from DEFINE and CONFIRM

EDSS score	EQ-5D index score (mean)	EQ-5D index score (SD)	Observations
0	0.88	0.17	513
1	0.83	0.19	846
2	0.78	0.19	3241
3	0.69	0.22	2185
4	0.63	0.22	2104
5	0.54	0.24	826
6	0.46	0.28	387
7	0.34	0.33	109
8	0.002	0.46	18
9	-0.17	0.29	11

Abbreviations: EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life 5 dimensions; SD, standard deviation.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide details.

As HRQL data were obtained using the EQ-5D from the DEFINE and CONFIRM clinical trials, no mapping was necessary for RRMS patients. Utilities for SPMS patients and patients with relapse were derived through the relationship between RRMS and SPMS utilities in the UK MS Survey (Table 59) (128, 132). The disutility scores obtained from the difference in utility score for relapse and no relapse for each EDSS state (Table 59) were subtracted from the utility scores which were derived from the dimethyl fumarate clinical trials as shown in Table 63 (Section 7.4.9).

Table 59: Utility scores reported in the UK MS survey

Clinical presentation	Disease type	EDSS state									
		0	1	2	3	4	5	6	7	8	9
No relapse	RRMS	0.909	0.844	0.745	0.611	0.654	0.558	0.495	0.437	-0.007	-0.151
	SPMS	0.865	0.800	0.701	0.568	0.610	0.514	0.451	0.393	-0.051	-0.195
Relapse	RRMS	0.900	0.835	0.735	0.602	0.645	0.548	0.485	0.427	-0.016	-0.160
	SPMS	0.856	0.791	0.692	0.559	0.601	0.505	0.442	0.384	-0.060	-0.204

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

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic review was conducted to identify HRQL studies from the published literature relevant to the decision problem, in particular those which considered EQ-5D health state utility values (in line with the NICE preferred method) relating to patients with RRMS.

The following electronic databases were searched:

- Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations
- EMBASE (Ovid)
- The Cochrane library including NHS EED

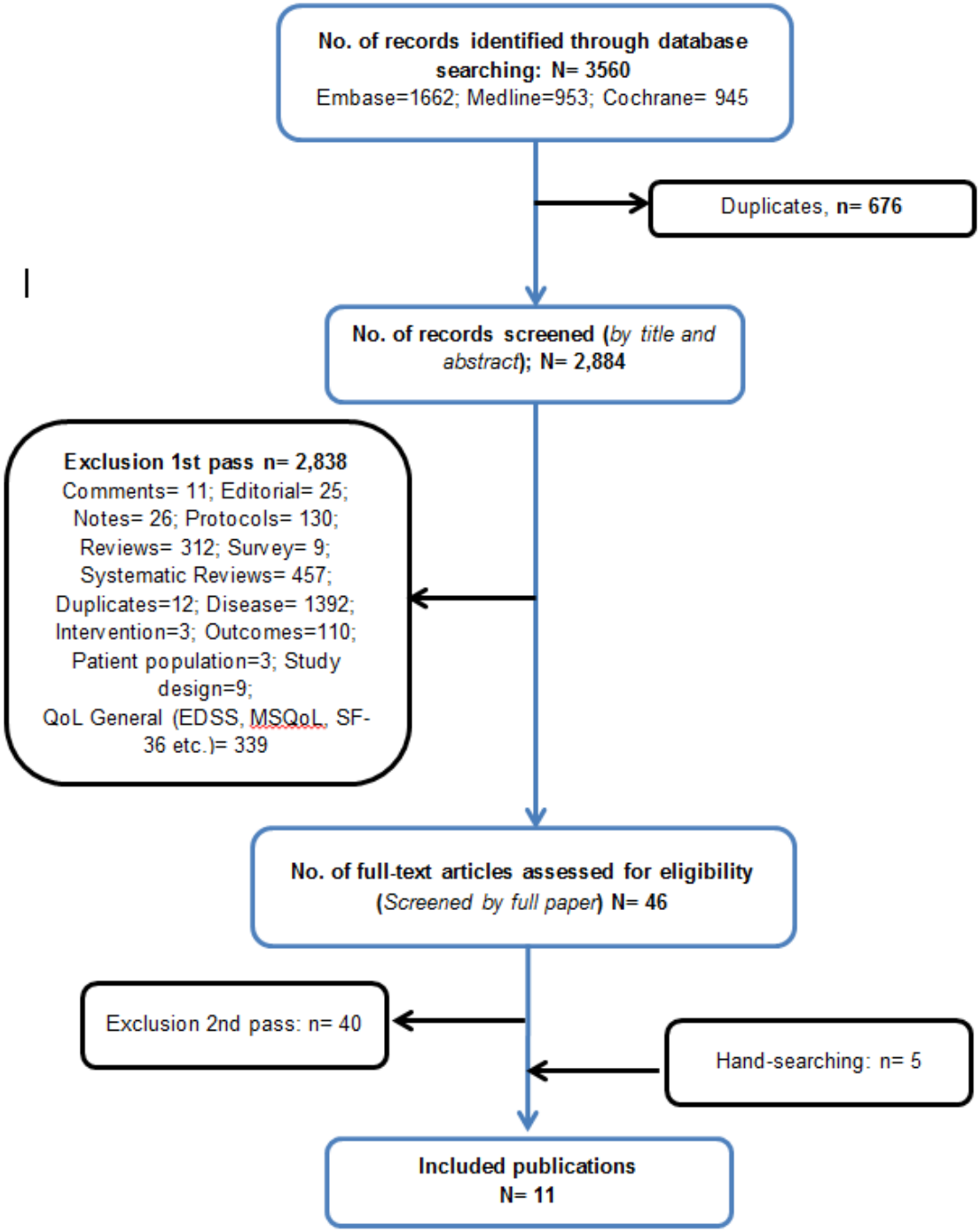
Electronic searches were supplemented by hand searching of the following sources:

- Primary sources of utilities used in economic evaluations
- Manufacturer databases
- Research Papers in Economics (RePEc)
- The EQ-5D website
- The Cost-Effectiveness Analysis (CEA) Registry
- Conference proceedings
- NICE HTA submissions.

Full details of the search are provided in Section 10.12

In total, 3,560 papers were identified through the electronic searches. Upon the removal of duplicate papers, 2,884 titles and abstracts were reviewed. 46 were ordered for full paper review, of which 40 were excluded, resulting in 11 relevant papers (including five identified via hand-searching) for final inclusion (Figure 34).

Figure 34: Schematic for the systematic review of HRQL evidence



7.4.6 Provide details of the studies in which HRQL is measured.

Details of the studies in which HRQL was measured are provided in Table 60.

Table 60: Table of included QoL studies

Study	Country	Population	Intervention(s)	Sample size	Elicitation method	Health states	Utility score
Gottberg 2006 (136)	Sweden	Female: 74% Mean age (years): 51 RRMS: 42% SPMS: 48% PPMS: 10% EDSS 0–3: 25% EDSS 3.5–5.5: 21% EDSS 6–6.5: 28% EDSS >7: 25% EDSS not reported: 1%	68% treated with a DMT	152	EQ-5D	Mean of all patients (SD)	0.5 (0.39)
Hemmett 2004 (137)	UK	Mean age: 51.9 Group 1: benign (infrequent relapses with long intervals between relapses) Group 2a: relapsing disease (currently in relapse at the time of participation) Group 2b: relapsing disease (not currently in relapse during participation) Group 3: PPMS	8.4% receiving IFNβ	Total: 1554 Group 1: 186 Group 2a: 465 Group 2b: 239 Group 3: 474	EQ-5D	Group 1 (mean)	0.73
						Group 2 (mean)	0.48
						Group 3 (mean)	0.4
						Group 4 (mean)	0.33
Kobelt 2001 (138)	Germany	Female: 73% Mean age (years): 41.9 Benign: 17.8% RRMS: 23.2% SPMS: 23.7% PPMS: 20.2%	13% receiving IFN or GA	737	EQ-5D	Mean of all patients (SD)	0.555 (0.331)

		Relapsing-progressive: 11.5% Disease type not reported: 3.6% EDSS <3: 43.6% EDSS 3.5–6: 27.5% EDSS >6.5: 28.9%					
McCrone 2008 (139)	UK	Female: 72.2% Mean age (years): 54.5 Benign: 0.7% RRMS: 39.7% SPMS: 37.7% PPMS: 21.8%	11.1% receiving IFN (24.6% in RRMS population) 1.7% receiving GA	1,843	EQ-5D	Mean of all patients (SD)	0.41 (0.34)
Orme 2007 (128)	UK	Female: 74.5% Mean age (years): 51.4 RRMS: 35.5% SPMS: 37.2% PPMS: 27.3%	Figures not provided	2,048	EQ-5D	Mean of all patients (SD)	0.491 (0.32)
Putzki 2009 (140)	Germany	Female: 72.8% Mean age (years): 37.6 Treatment-naïve patients with RRMS	IM IFNβ-1a	670	EQ-5D	Baseline, mean (95% CI)	0.75 (0.74–0.76)
						1 year of treatment (95% CI)	0.77 (0.75–0.78)
Henriksson 2001 (141)	Sweden	Female: 72.8% Mean age (years): 37.6 RRMS: 34% SPMS: 37% PPMS: 26% Disease type not reported:3%	42% received IFN	413	EQ-5D	Overall	0.42
						EDSS 0–3.0	0.68
						EDSS 3.5–6.0	0.52
						EDSS ≥6.5	0.17

		Female (%)	**Mean age, years**	**Mean EDSS score**	**Patients receiving DMTs:**	N	EQ-5D	Mean score	
Kobelt 2006 (142)	Austria	70.4	50	4.4	39.8%	1,019		Overall	0.719
								EDSS ≥6.5	0.447
	Belgium	68	48.1	4.2	49.7%	799		Overall	0.649
								EDSS ≥6.5	0.384
	Germany	72.2	45.1	3.8	50.3%	2,973		Overall	0.721
								EDSS ≥6.5	0.440
	Italy	65.8	46.1	4.6	42.6%	921		Overall	0.677
								EDSS ≥6.5	0.442
	Netherlands	69.1	46.7	3.9	35.5%	1,549		Overall	0.694
								EDSS ≥6.5	0.477
	Spain	64.2	44.7	4.5	52.4%	1,848		Overall	0.717
								EDSS ≥6.5	0.431
	Sweden	73	53.4	5.1	42.6%	1,339		Overall	0.696
								EDSS ≥6.5	0.462
	Switzerland	63.8	52.5	4.5	37.9%	1,101		Overall	0.767
								EDSS ≥6.5	0.540
	UK	74.5	51.4	5.1	20.6%	2,048		Overall	0.725
								EDSS ≥6.5	0.477
Kobelt 2000 (143)	UK	Female: 70.6% Mean age (years): 44.3 Benign: 10.7% RRMS: 21.5% SPMS: 26.8% PPMS: 10.2% No disease type answered:			2.6% received IFN	570	EQ-5D	All patients, mean (SD)	0.487 (0.328)
								Relapse in past years, mean (SD)	0.542 (0.287)
								No relapse in past year, mean (SD)	0.430 (0.358)
								Relapse in past 2 months, mean (SD)	0.457 (0.344)

		4.6% EDSS ≤3: 31.1 EDSS 3.5–6: 27.3 EDSS ≥6: 38.8				No relapse in past 2 months, mean (SD)	0.497 (0.325)
						EDSS ≤3, mean	0.698
						EDSS 3.5–6, mean	0.574
						EDSS ≥6, mean	0.277
Parkin 2000 (123)	UK	Female: 66% Mean age (years): 42 In remission: 48% In relapse: 52%	Results of QoL survey in general MS population fitted to clinical trial data for IFNβ-1b using the EDSS	50	EQ-5D	IFNβ-1b, mean (SD)	0.870 (0.200)
						Placebo, mean (SD)	0.856 (0.195)
						Severe disease[†], mean (SD)	0.359 (0.341)
Kobelt 2006 (144)	UK	Female: 74.5% Mean age (years): 51.4 RRMS: 35.5% Progressive MS: 64.5%	20.6% receiving DMTs	2,048	EQ-5D	All patients, mean (SD)	0.51 (0.29)

[†]No description provided in paper.

Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life 5 Dimensions; GA, glatiramer acetate; IFN, interferon; MS, multiple sclerosis; PPMS, primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary-progressive multiple sclerosis.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

EQ-5D scores at baseline in the placebo group in DEFINE and CONFIRM were 0.69 and 0.71, respectively (66, 67). This is higher than in the majority of the studies reported in Table 60; however, this is likely due to the recruitment of patients with SPMS and PPMS in most of these studies, while DEFINE and CONFIRM recruited only patients with RRMS. Many of these studies in Table 60 also included a large proportion of patients with high EDSS scores, with > 50% having EDSS scores ≥ 3.0 (where this was reported). In contrast, approximately 50% of patients in DEFINE and CONFIRM had EDSS scores ≤ 2.0 at baseline. Given the inverse relationship between EDSS score and EQ-5D score established by Henriksson et al (141) and Kobelt et al (142, 143), the large number of patients with EDSS scores ≥ 3.0 in these studies may therefore be responsible for the lower EQ-5D scores observed.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

The HRQL impact and duration associated with each AE is given in Table 61. This was used to calculate the disutility associated with each treatment per model cycle (Table 62).

Table 61: QoL impact and duration of AEs

Adverse event	Non-serious			Serious		
	Disutility per event	Source of disutility	Duration (days)	Disutility per event	Source of disutility	Duration (days)
Abdominal pain	0	KOL opinion	10.5†	0	KOL opinion	24.5†
Abdominal pain upper	0	KOL opinion	10.5 †	0	KOL opinion	24.5†
ALT increased	0	Assumption	28 †	0	Assumption	28†
Arthralgia	0	Assumption	10.5†	-0.25	Assumption: same as non-serious back pain	24.5†
ACB	-0.289	Gilenya® NICE submission in support of TA254 (135)	1‡	-0.289	Gilenya® NICE submission in support of TA254 (135)	1‡
Back pain	-0.25	Parson 2006 (145)	10.5†	-0.50	Assumption	24.5†
Bradycardia	0	Assumption	14‡	0	Assumption	14‡
Chest pain	-0.25	Assumption	7§	-0.50	Assumption	14§
Cough	0	Assumption	7§	--	--	14§
Depression	-0.1646	Weighted average of values from NICE clinical guideline 23 (146)	75†	-0.56	Weighted average of values from NICE clinical guideline 23 (146)	365.25†
Diarrhoea	0	Assumption	10.5†	--	--	24.5†
Fatigue	0	Assumption	168‡	--	--	168‡

Adverse	Non-serious			Serious		
Flu-like symptoms	-0.63	Assumption (same loss of utility as influenza)	1 day a week for 6 months[§]	-0.63	Assumption (same loss of utility as influenza)	1 day a week, all year[§]
Flushing	0	Assumption	10.5[†]	0	Assumption	24.5[†]
Gastroenteritis	-0.071	Inverse of gain in QoL of patients treated for IBS (147)	10.5[†]	-0.071	Inverse of gain in QoL of patients treated for IBS (147)	24.5[†]
Headache	-0.140	Xu 2011 (mild migraine pain) (148)	10.5[†]	-0.493	Xu 2011 (severe migraine pain) (148)	24.5[†]
Influenza	-0.63	van Hoek 2011 (149)	8.75[‡]	-0.67	van Hoek 2011 (149)	8.75[‡]
Leukopenia	0	Assumption	28[§]	--	--	168[§]
Lower RTIs	-0.05	Disutility for sore throat (150)	11.7[¶]	--	--	11.7[¶]
Nausea	0	Assumption	10.5[†]	0	Assumption	24.5[†]
Pain in extremity	-0.25	Assumption	7[‡]	--	--	28[‡]
Pruritus	0	Assumption	10.5[†]	0	Assumption	24.5[†]
Rash	0	Assumption	28[‡]	--	--	168[‡]
UTI	-0.1	Natalizumab NICE submission TA127 (134)	5[§]	-0.1	Natalizumab NICE submission TA127 (134)	5

[†]Midpoint of KOL estimate. [‡]As for source of disutility. [§]KOL estimate. [¶]Moore et al, 2008 (151)
Abbreviations: ACB, atrioventricular conduction block; AE, adverse event; ALT, alanine transaminase; RTI, respiratory tract infection; UTI, urinary tract infection; NA, not available (indicates where data was not reported or found in systematic review).

Table 62: Disutility associated with each treatment due to AEs in the model

Treatment	Disutility
Dimethyl fumarate	-0.004
Fingolimod	-0.005
Glatiramer acetate	-0.006
IM IFNβ-1a 30 µg	-0.016
Natalizumab	-0.006
SC IFNβ-1b 250 µg	-0.014
SC IFNβ-1a 22 µg	-0.016
SC IFNβ-1a 44 µg	-0.014

Abbreviations: IFN, interferon; IM, intramuscular; SC, subcutaneous.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

QoL data were derived from the pooled data from DEFINE and CONFIRM (Section 7.4.3, Table 58). SPMS utilities were derived from the dimethyl fumarate clinical trial data through the relationship between RRMS and SPMS utilities in the UK MS Survey

(Section 7.4.4, Table 59). The utilities used in the model for each health state are shown in Table 63. Costs are applied to a mid-year estimate of the cohort distribution.

Table 63: Utility scores used in the model

Clinical presentation	Disease type	EDSS state									
		0	1	2	3	4	5	6	7	8	9
No relapse	RRMS	0.8752	0.8342	0.7802	0.6946	0.6253	0.5442	0.4555	0.3437	0.0023	-0.1701
	SPMS	0.8315	0.7905	0.7365	0.6509	0.5816	0.5005	0.4118	0.3000	-0.0413	-0.2138
Relapse	RRMS	0.8660	0.8250	0.7710	0.6855	0.6161	0.5350	0.4463	0.3346	-0.0068	-0.1793
	SPMS	0.8223	0.7814	0.7274	0.6418	0.5725	0.4913	0.4027	0.2909	-0.0505	-0.2229

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

RRMS is a chronic condition which can lead to severe disability, and patients may therefore require assistive care (152). Caring for RRMS patients can have an impact upon the QoL of carers (153, 154), and the impact of should therefore be considered when evaluating RRMS therapies. As in the submissions to NICE in support of TA127 for natalizumab and TA254 for fingolimod (134, 135), the disutility associated with caregivers was therefore considered, using values from the UK MS survey. The maximum disutility for a caregiver of a person with MS was therefore assumed to be 0.14, based on a mean caregiver utility of 0.84 quoted in the NICE assessment of treatment for Alzheimer's disease (TA111) (155).

Table 64: Disutility associated with caregivers in the model

Disutility associated with caregivers	Disease type	EDSS state									
		0	1	2	3	4	5	6	7	8	9
	RRMS	0.0000	0.0014	0.0032	0.0091	0.0090	0.0199	0.0272	0.0534	0.1070	0.1400
	SPMS	--	--	0.0032	0.0091	0.0090	0.0199	0.0272	0.0534	0.1070	0.1400

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

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide details.

Clinical expert opinion was used to help determine treatment-specific AEs, and to validate the disutility for each treatment per cycle. This was obtained from Professor David Bates for the clinical inputs (Department of Neurology, The Royal Victoria Infirmary, Newcastle) and Marta Soares for model validation (Research Fellow, Team for Economic Evaluation and Health Technology Assessment, Centre for Health Economics, University of York).

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The HRQL associated with each health state is assumed to be constant; estimates of the variance of utility values used for these health states were investigated through sensitivity analysis.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects were excluded.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Baseline quality of life was distributed according to patients' EDSS scores in DEFINE and CONFIRM (Table 42).

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL changes over time based on the underlying disease progression through EDSS and RRMS/SPMS states (Table 54–Table 56), which can be slowed through treatment (Table 50).

7.4.15 Have the values in Sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values have not been amended.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to Section 2.

In line with the recent NICE appraisals of natalizumab and fingolimod (20, 21), the following range of cost inputs were considered:

- Drug acquisition costs (British National Formulary (BNF) 64 (156))
- Treatment administration costs (Department of Health 2011–2012 reference costs (31), Table 66)
- Resource use costs (see Table 69)
- Treatment monitoring costs (Department of Health 2011–2012 reference costs and National Tariff (31, 32), Table 68)
- Treatment-related AEs (see Table 72)

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Both NHS reference costs and PbR tariffs were used for the relevant cost inputs, as in the Biogen submission to NICE in support of the natalizumab STA (134).

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.

A systematic review of resource use in RRMS was not conducted given the availability of data from the UK MS survey, which included 115 different resources (128). The unit costs associated with these resources were updated using the most recent NHS reference costs, BNF costs, Personal Social Services Research Unit (PSSRU) costs, and PbR tariffs (31, 32, 156, 157).

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide details.

Clinical expert opinion was used to help determine treatment-specific AEs, and to validate the disutility for each treatment per cycle. This was obtained from Professor David Bates for the clinical inputs (Department of Neurology, The Royal Victoria Infirmary, Newcastle) and Marta Soares for model validation (Research Fellow, Team for Economic Evaluation and Health Technology Assessment, Centre for Health Economics, University of York).

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to Sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

Annual treatment acquisition costs were calculated using the cost per dose and dosing recommendations from the British National Formulary (Table 65) (158).

Table 65: Annual treatment costs used in the model *(Commercal in confidence information removed)*

Treatment	Administration	Doses per year	Unit cost per dose	Annual acquisition cost (156)
Dimethyl fumarate (Section 1.10)	BID	730.5	No info	£17,900 (List price) £ PAS price)
Fingolimod	OD	365.25	£52.50	£19,176
Glatiramer acetate	OD	365.25	£18.73	£6841
IM IFNβ-1a 30 µg	OW	52.18	£163.50	£8,531
Natalizumab	OM	13	£1,130	£14,690
SC IFNβ-1b 250 µg	EOD	182.63	£39.78	£7,265
SC IFNβ-1a 22 µg	TIW	156.18	£52.06	£8,149
SC IFNβ-1a 44 µg	TIW	156.18	£67.77	£10,608

Abbreviations: IFN, interferon; IM, intramuscular; PAS, patient access scheme; SC, subcutaneous.

The annual administration cost was calculated from the cost per administration (based on relevant resource use) multiplied by the number of administrations per year (Table 66).

Table 66: Administration costs for each treatment used in the model

Treatment	Annual administration cost (first year)	Resource use	Annual administration cost (second year)	Resource use
IM IFNβ-1a 30 µg **SC IFNβ-1a 22 µg** **SC IFNβ-1a 44 µg** **SC IFNβ-1b 250 µg** **Glatiramer acetate**	£99.00	3 hours of day nurse's time to teach self administration (31)	£0	None
Dimethyl fumarate **Fingolimod**	£0	None	£0	None
Natalizumab	£6,224.40	Day admission: weighted average cost per day of AA30A and AA30B (day case) (31)	£6,224.40	Day admission: weighted average cost per day of AA30A and AA30B (day case) (31)

Abbreviations: IFN, interferon; IM, intramuscular; SC, subcutaneous.

The annual cost of monitoring whilst on treatment is considered separately for the first year on treatment, and the subsequent years (Table 67). The monitoring required was obtained from the relevant product indications (23-28, 159), with unit costs obtained from national tariffs and reference costs produced by NHS England and Wales (Table 68).

Table 67: Annual cost of monitoring for each treatment

Treatment	Cost (year 1)	Resource use	Cost (subsequent years)	Resource use
IM IFNβ-1a 30 µg **SC IFNβ-1b 250 µg** **SC IFNβ-1a 22 µg** **SC IFNβ-1a 44 µg**	£1,776.86	3 Neurology visits 3 full blood counts 3 liver function tests	£594.75	1 Neurology visits 2 full blood count test 2 liver function tests
Dimethyl fumarate	£1,780.55	3 Neurologist visits 3 full blood counts 3 liver function tests 3 renal function tests	£597.21	1 Neurology visits 2 full blood count test 2 liver function tests 2 renal function tests
Fingolimod	£2,431.09	3 Neurology visits 3 full blood counts 3 liver function tests 1 basic metabolism test 1 ophthalmology visit 1 patient observation after first administration by healthcare professional (assumed to include additional monitoring required by the European protection agency after first administration, e.g. cardiac monitoring: ECG, blood pressure monitoring, etc)	£597.21	1 Neurology visit 2 full blood count test 2 liver function tests 2 basic metabolism tests
Glatiramer acetate	£1,184.57	2 Neurology visits 2 full blood counts 2 liver function tests	£589.83	1 Neurology visit
Natalizumab	£1,334.07	2 Neurology visits 2 full blood counts 2 liver function tests 1 MRI scan	£1,179.66	2 Neurology visits

Abbreviations: IFN, interferon; IM, intramuscular; SC, subcutaneous.

Table 68: Unit costs associated with monitoring

Resource	Unit cost (£)	Source
Neurology visit	£589.83	NHS Reference costs 2011-12: weighted average cost per day of AA30A and AA30B (day case) (31)
Full blood count	£1.23	NHS Reference costs 2011-12: pathology services (Biochemistry - DAP841) (31)
Liver function	£1.23	NHS Reference costs 2011-12: pathology services (Biochemistry - DAP841) (31)
Basic metabolism	£1.23	NHS Reference costs 2011-12: weighted average cost per day of RA01A, RA01B and RA01C (31)
Renal function test	£1.23	NHS Reference costs 2011-12: pathology services (Biochemistry - DAP841) (31)
MRI scan	£149.49	NHS Reference costs 2011-12: pathology services (Biochemistry - DAP841) (31)
Patient observation after first admin	£538.00	2012-13 tariff - outpatient attendances [WF01B First Attendance - Single Professional] (32)
Ophthalmology visit	£115.00	2012-13 tariff - admitted patient care & outpatient procedures (AA30Z) [Combined day case/ordinary elective tariff] (32)

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in Section 7.2.4.

Resource use was taken from the UK MS survey, which included 115 different resources (128), with associated costs determined as described in Table 69. The quantity of each resource used per patient was estimated based on a number of relevant covariates including type of MS, EDSS state, sex, and presence of relapse. These quantities were multiplied by the 2011 unit costs for each resource to find the mean cost of each resource per person. As most data were collected for less than a year, resource use per person was adjusted to a 12 months basis consistent with the cycle of the Markov model.

Table 69: Resource costs associated with MS

Type	Description	Period	Reference	Cost used in regression
Inpatient admission	Neurology	per day	NHS Reference costs 2011-12: weighted average cost per day of AA30A and AA30B (inpatient) (31)	£565.87
Inpatient admission	Other	per day	NHS Reference costs 2011-12: weighted average cost per day of AA30A and AA30B (inpatient) (31)	£565.87
Nursing home	Inpatient	per day	PSSRU 2011: Residential home for younger adults with physical and sensory impairments (157)	£109.71
Nursing home	Outpatient	per day	PSSRU 2011: Rehabilitation day centre for younger adults with brain injury (157)	£92.00
Day admission	Neurology	per admission	NHS Reference costs 2011-12: weighted average cost per day of AA30A and AA30B (day case) (31)	£589.83
Day admission	Other	per admission	NHS Reference costs 2011-12: weighted average cost per day of AA30A and AA30B (day case) (31)	£589.83
REHAB	Inpatient	per session	NHS Reference costs 2011-12: weighted average of all codes under the MHCC_APC sheet (31)	£335.00
REHAB	Outpatient	per session	NHS Reference costs 2011-12: weighted average of all codes under the MHCC_APC sheet (31)	£335.00
Visit to specialist	Neurology visit	per consultation	NHS Reference costs 2011-12: Neurology (Code 400) (31)	£205.00
Visit to specialist	Junior doctor	per hour	PSSRU 2011: Foundation house office 1 (costs without qualifications) (157)	£33.00
Visit to specialist	Urologist	per consultation	NHS Reference costs 2011-12: Urologist (Code 101) (31)	£179.00
Visit to specialist	Ophthalmologist	per consultation	NHS Reference costs 2011-12: Ophthalmologist (Code 130) (31)	£106.18
Visit to specialist	Psychiatrist	per hour	PSSRU 2011: NHS community occupational therapist (costs without qualifications) (157)	£31.00
Visit to specialist	GP	per consultation	PSSRU 2011: General practitioner - unit costs (with qualification costs) [including direct care staff costs] (157)	£36.00
Visit to specialist	Nurse	per consultation	Inflated 2011 value to 2012	£9.34
Other healthcare specialist	Physiotherapist	per hour	PSSRU 2011: Community physiotherapist (157)	£31.00

Type	Description	Period	Reference	Cost used in regression
Other healthcare specialist	Social worker	per hour	PSSRU 2011: Social worker (adult services) [per hour of face-to-face contact] (157)	£152.00
Other healthcare specialist	Occupational therapist	per hour	PSSRU 2011: NHS community occupational therapist (costs without qualifications) (157)	£31.00
Other healthcare specialist	Speech therapist	per hour	PSSRU 2011: Community speech and language therapist (costs without qualifications) (157)	£31.00
Other healthcare specialist	Acupuncturist	per consultation	Inflated original value to 2012	£24.33
Other healthcare specialist	Chiropractor/Osteopath	per consultation	Inflated original value to 2012	£19.67
Other healthcare specialist	Counsellor/Psychologist	per consultation	Inflated original value to 2012	£28.56
Other healthcare specialist	Chiropodist	per consultation	Inflated original value to 2012	£11.13
Other healthcare specialist	Reflexologist	per consultation	Inflated original value to 2012	£24.33
Investigation, Test	MRI(brain)	per test	NHS Reference costs 2011-12: weighted average cost per day of RA01A, RA01B and RA01C (31)	£149.49
Investigation, Test	MRI(spine)	per test	NHS Reference costs 2011-12: weighted average cost per day of RA01A, RA01B and RA01C (31)	£149.49
Investigation, Test	CT scan	per test	NHS Reference costs 2011-12: weighted average cost per day of RA08A, RA08B and RA08C (31)	£83.94
Investigation, Test	Lumbar puncture (LP)	per test	NHS Reference costs 2011-12: Neuropathy (DAP832) (31)	£73.63
Investigation, Test	Evoked potential	per test	NHS Reference costs 2011-12: Neuropathy (DAP832) (31)	£73.63
Investigation, Test	Ultrasound	per test	NHS Reference costs 2011-12: weighted average cost per day of RA23Z and RA24Z (31)	£53.14
Investigation, Test	Electrocardiogram	per test	NHS Reference costs 2011-12: Electrocardiogram Monitoring and stress testing (DADs) [EA47Z] (31)	£60.73
Investigation, Test	Blood test	per test	NHS Reference costs 2011-12: Haematology [Excluding Anti-Coagulant Services] (DAP823) (31)	£3.09
MS drugs	AVONEX	Month	-	£0.00
MS drugs	BETAFERON	Month	BNF 64 (2012), dosage from product literature (156)	£556.92
MS drugs	GLATIRAMER	Month	BNF 64 (2012), dosage from product literature (156)	£524.44
MS drugs	IMURAN	Month	BNF 64 (2012), dosage from product literature (156)	£4.47
MS drugs	METHOTREXATE	Month	BNF 62 (2011), dosage from product literature (156)	£1.53

Type	Description	Period	Reference	Cost used in regression
MS drugs	NOVANTRONE	Month	BNF 62 (2011), dosage from product literature (156)	£20.00
MS drugs	REBIF22	Month	BNF 64 (2012), dosage from product literature (156)	£624.84
MS drugs	REBIF44	Month	BNF 64 (2012), dosage from product literature (156)	£813.24
MS drugs	STEROID	Month	BNF 62 (2011), dosage from product literature (156)	£49.29
MS drugs	NATALIZUMAB	4 weeks	BNF 64 (2012), dosage from product literature (156)	£1,130.00
Other prescription drugs	Baclofen	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.11
Other prescription drugs	Clonazepam	Daily cost	BNF 62 (2011), dosage from product literature (156)	£0.14
Other prescription drugs	Dantrolene	Daily cost	BNF 64 (2012), dosage from product literature (156)	£1.52
Other prescription drugs	Diazepam	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.09
Other prescription drugs	Gabapentin	Daily cost	BNF 64 (2012), dosage from product literature (156)	£1.28
Other prescription drugs	Tizanidine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.29
Other prescription drugs	Amitriptyline	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.09
Other prescription drugs	Citalopram	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.12
Other prescription drugs	Escitalopram	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.53
Other prescription drugs	Fluoxetine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.09
Other prescription drugs	Fluvoxamine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.40
Other prescription drugs	Imipramine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.25
Other prescription drugs	Mianserin	Daily cost	BNF 64 (2012), dosage from product literature (156)	£1.12
Other prescription drugs	Mirtazapine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.06
Other prescription drugs	Nortriptyline	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.96

Type	Description	Period	Reference	Cost used in regression
Other prescription drugs	Paroxetine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.08
Other prescription drugs	Sertaline	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.06
Other prescription drugs	Venlafaxine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.27
Other prescription drugs	Amantadine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.35
Other prescription drugs	Methylphenidate	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.36
Other prescription drugs	Modafinil	Daily cost	BNF 64 (2012), dosage from product literature (156)	£5.26
Other prescription drugs	Prochlorperazine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.47
Other prescription drugs	Bisacodyl	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.07
Other prescription drugs	Docusate	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.37
Other prescription drugs	Glycerol	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.10
Other prescription drugs	Ispaghula husk	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.21
Other prescription drugs	Lactulose	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.14
Other prescription drugs	Milk of Magnesia	Daily cost	BNF 62 (2011), dosage from product literature (156)	£0.23
Other prescription drugs	Nitrofurantoin	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.36
Other prescription drugs	Oxybutynin	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.41
Other prescription drugs	Senna	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.07
Other prescription drugs	Sildenafil	Daily cost	BNF 64 (2012), dosage from product literature (156)	£12.45
Other prescription drugs	Tolterodine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£1.09

Type	Description	Period	Reference	Cost used in regression
Other prescription drugs	Botulinum toxin A	Daily cost	BNF 64 (2012), dosage from product literature (156)	£72.00
Other prescription drugs	Carbamazepine	Daily cost	BNF 64 (2012), dosage from product literature (156)	£0.17
Other prescription drugs	Phenytoin	Daily cost	BNF 64 (2012), dosage from product literature	£0.09
Health visitor home visit	Health visitor home visit	per visit	PSSRU 2011: Health visitor (without qualifications) (157)	£44.00
Health visitor home visit	Health visitor home visit	per hour on visit	PSSRU 2011: Health visitor (without qualifications) (157)	£64.00

Abbreviations: BNF, British National Formulary; CT, computed tomography; GP, general practitioner; MRI, magnetic resonance imaging; NHS, National Health Service; ONS, Office of National Statistics; PSSRU, Personal Social Services Research Unit; SSP, statutory sick pay.

As described in Section 7.2.4, patients' health states are defined by their EDSS score. Costs associated with these states and costs associated with relapses were considered within the model. The data were modelled using a regression (SUR) to obtain all disease-related costs. The SUR accounts for correlation between costs, with the error term for each patient sampled from a multivariate normal distribution instead of the error terms in the two regression models being independent of each other (both within and between patients). In this way there is dependence in costs within a patient, but still independence between patients. The model fitting was achieved using the SUR package in R. The result of SUR was costs per EDSS state and relapse (Table 70). Utilities were applied to a mid-year estimate of the cohort distribution.

Table 70: EDSS state costs used in the model (£)

Disease type	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
RRMS	903	939	688	3,765	1,824	3,094	4,130	10,871	26,478	21,187
SPMS	1,217	1,254	1,002	4,079	2,138	3,409	4,444	11,185	26,793	21,502

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

Table 71: Average cost of relapse

Disease type	Average cost of relapse
RRMS	£2,028
SPMS	£2,028

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

7.5.7 Please summarise the costs for each adverse event listed in Section 6.9 (Adverse events). These should include the costs of therapies identified in Section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

The cost of treating each AE was calculated from the expected resource use of treating a patient with a specific adverse event, sourced from published literature and validated by clinical expert opinion, multiplied by appropriate unit costs. In some instances clinical experts provided resource use estimates. The final cost for each AE for a patient on each treatment was calculated using the proportion of AEs that were serious associated with the treatment, the cost of a serious AE, and the cost of a non-serious AE (Table 72).

Table 72: Cost of treatment for AEs used in the model

Adverse event	Cost per event (non-serious)	Source	Cost per serious event	Source
Abdominal pain	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)
Abdominal pain upper	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)
ALT increased	£0.00	Assumption: no cost	£0.00	Assumption: no cost
Arthralgia	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)
ACB	£469.63	NHS Reference costs 2011-12: Arrhythmia or Conduction Disorders, with CC (NEI short stay) (31)	£1,833.54	NHS Reference costs 2011-12: Arrhythmia or Conduction Disorders, with CC (NEI LS) (31)

Adverse event	Cost per event (non-serious)	Source	Cost per serious event	Source
Back pain	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)	£53.00	PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)
Bradycardia	£1,091.90	NHS Reference costs 2011-12: Arrhythmia or Conduction Disorders (Total HRGs) [PA22Z] (31)	£1,357.49	NHS Reference costs 2011-12: Arrhythmia or Conduction Disorders, with CC (Total HRGs) [EB07H] (31)
Chest pain	£542.03	NHS Reference costs 2011-12: Chest Pain (Total HRGs) [PA24Z] (31)	£542.03	NHS Reference costs 2011-12: Chest Pain (Total HRGs) [PA24Z] (31)
Cough	£0.00	Assumption: no cost	£0.00	Assumption: no cost
Depression	£265.00	Based on 5 GP consultations per year, with Citalopram use	£636.00	Based on 5 GP consultations per year, with Citalopram use
Diarrhoea	£0.00	Assumption: no cost	£0.00	Assumption: no cost
Fatigue	£0.00	Assumption: no cost	£0.00	Assumption: no cost
Flu-like symptoms	£50.55	Assumption: same as non-serious influenza	£251.48	Assumption: same cost
Flushing	£0.00	Assumption: no cost	£0.00	Assumption: no cost
Gastroenteritis	£642.38	NHS Reference costs 2011-12: Infectious or Non-Infectious Gastroenteritis, without CC (PA21B) [Total HRGs] (31)	£1,172.99	NHS Reference costs 2011-12: Infectious or Non-Infectious Gastroenteritis, with CC (Total - HRGs) [PA21A] (31)
Headache	£661.03	NHS Reference costs 2011-12: weighted average of AA31A and AA31B [Total HRGs] (31)	£661.03	NHS Reference costs 2011-12: weighted average of AA31A and AA31B [Total HRGs] (31)
Influenza	£50.55	Assumption: same cost	£502.97	Assumption: same cost
Leukopenia	£0.00	Assumption: no cost	£0.00	Assumption: no cost
Lower RTIs	£860.97	NHS Reference costs 2011-12: Lobar, Atypical or Viral Pneumonia, without CC (31)	£860.97	NHS Reference costs 2011-12: Lobar, Atypical or Viral Pneumonia, without CC (31)
Nausea	£0.00	Resource use assumptions: no cost	£53.00	Resource use assumptions: PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)
Pain in extremity	£125.50	NHS Reference costs 2011-12: Pain management (OPATT)	£125.50	NHS Reference costs 2011-12: Pain

Adverse event	Cost per event (non-serious)	Source	Cost per serious event	Source
		[Service code 191] (31)		management (OPATT) [Service code 191] (31)
Pruritus	£0.00	Assumption: no cost	£53.00	Resource use assumptions: PSSRU 2011: General practitioner (per clinic consultation lasting 17.2 minutes) (157)
Rash	£564.22	NHS Reference costs 2011-12: Rash or Other Non-Specific Skin Eruption (Total HRGs) [PA66Z] (31)	£564.22	NHS Reference costs 2011-12: Rash or Other Non-Specific Skin Eruption (Total HRGs) [PA66Z] (31)
UTI	£86.92	Assumption: same cost	£173.85	Assumption: same cost

Abbreviations: ACB, atrioventricular conduction block; AE, adverse event; ALT, alanine transaminase; HRG, healthcare resource group; RTI, respiratory tract infection; UTI, urinary tract infection.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

NA

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

To evaluate the effect of changing various model inputs, a number of scenarios were considered:

- Varying the price of fingolimod from 20–50% less than its list price in increments of 5%. This was performed as fingolimod is provided through a PAS, for which the price is not available in the public domain.
- No treatment waning effect
- Discount rates
    - Costs and benefits at 0%
    - Costs and benefits at 6%
    - Costs at 0%, benefits at 6%
    - Costs at 6% and benefits at 0%
    - Costs at 1.5% and benefits at 3.5%
    - Costs at 3.5% and benefits at 1.5%
- No caregiver disutility
- Time horizons

    - 1 year
    - 5 years
    - 10 years
    - 20 years
    - 50 years
- Mortality set to general population level
- Annualised relapse rate relative to placebo set to upper or lower 95% CI
- Disability progression rate relative to placebo set to upper or lower 95% CI
- London Ontario transition matrix used instead of combined dimethyl fumarate and London Ontario matrix (Table 73)

Table 73: Annual transition matrix for RRMS-RRMS used in sensitivity analysis *(Academic in confidence information removed)*

EDSS from/to†	0	1	2	3	4	5	6	7	8	9
0										
1										
2										
3										
4										
5										
6										
7										
8										
9										

Values not reported in the London Ontario dataset were replaced with values from the base case.

- Cost of fingolimod reduced by 35%, as a PAS scheme has been provided for fingolimod for which the actual cost was not available.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Univariate sensitivity analysis

Univariate sensitivity analysis was conducted in order to identify variables to which the cost effectiveness analysis was most sensitive and to explore the impact of those drivers on the outcomes of the analyses. In order to test the robustness of the ICERS and to explore areas of key variability the following variables within the model were adjusted individually by ±20%:

- EDSS state costs
- Relapse costs
- Patient utilities

- Natural history relapse rates
- Relapse rate on treatment
- Disability progression rate on treatment
- Dropout rate

Two-way sensitivity analysis

The effect of varying the treatment efficacy inputs and drop-out rates used was examined in two-way sensitivity analysis. Efficacy inputs were varied simultaneously using the upper and lower CIs from the MTC results for dimethyl fumarate and each comparator (Table 50), while drop-out rates were varied ±20% as 95% CIs were not available from the MTC.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in Section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

In probabilistic sensitivity analysis (PSA) all model parameters were varied concurrently within their assigned statistical distributions and ranges in order to assess the overall effect of parameter uncertainty on the model outcomes. Key model parameters were assigned to statistical distributions based on the parameter type and the expected uncertainty around the default parameter values. Each parameter is sampled at the same time during each of the PSA iterations, which allows the underlying uncertainty in the cost per QALY to be explored. The following distributions were used:

- Cost data were varied using a gamma distribution with an assumed standard error (SE) of 10%.
- Utility data were varied using a beta distribution with an assumed SE of 10%.
- Relative relapse rates and hazard ratios for disability progression were varied using the CIs calculated in the MTC.
- Natural history relapse rates (i.e. relapse rates under no treatment) were distributed according to a log-normal distribution, with an assumed standard error of 10% due to lack of data.
- Natural transition rates between RRMS states were sampled using a Dirichlet distribution, since the rates are co-dependent and mutually exhaustive. The natural history transitions were varied according to the sample size observed for each transition in the relevant population. The PSA allows for small variations in possible transitions, even if the observed sample size was zero. The sample sizes used in the PSA are shown in Table 74.

Table 74: Sample size for transition matrix within RRMS patients (Data from dimethyl fumarate clinical trials was based on placebo arms only) *(Academic in confidence information removed)*

EDSS from/to†	0	1	2	3	4	5	6	7	8	9
0										
1										
2										
3										
4										
5										
6										
7										
8										
9										

†Rows indicate initial EDSS state, columns indicate new EDSS state
Abbreviations: EDSS, Expanded Disability Status Scale.

- Natural transition rates from RRMS to SPMS states were varied using a beta distribution. The PSA allows for small variations in possible transitions, even if the observed sample size was zero. The sample sizes used in the PSA are shown in Table 75.

Table 75: Sample sizes for probability of conversion RRMS to SPMS *(Academic in confidence information removed)*

EDSS from/to†	EDSS + 1 in SPMS
1	
2	
3	
4	
5	
6	
7	
8	
9	

SOURCE: London Ontario (academic in confidence). †Rows indicate initial RRMS EDSS state, columns indicate new state
Abbreviations: EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

- Natural transition rates between SPMS states were varied using a Dirichlet distribution. The natural history transitions are varied according to the sample size observed for each transition in the SPMS patients in the London Ontario dataset. The PSA allows for small variations in possible transitions, even if the observed sample size was zero. The sample sizes used in the PSA are shown in Table 76.

Table 76: Sample size for transition matrix within SPMS patients, from London Ontario *(Academic in confidence information removed)*

EDSS from/to†	0	1	2	3	4	5	6	7	8	9
0										
1										
2										
3										
4										
5										
6										
7										
8										
9										

SOURCE: London Ontario (academic in confidence). †Rows indicate initial EDSS state, columns indicate new EDSS state Abbreviations: EDSS, Expanded Disability Status Scale.

- Risk of discontinuation was varied using a beta distribution, with an assumed SE of 10%.

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The EDSS distributions observed in DEFINE and CONFIRM are compared with those predicted in the model in Table 77 (no treatment) and Table 78 (dimethyl fumarate treatment). The model predicts a similar EDSS distribution after 2 years in both cases. The placebo patient population after two years is slightly larger in the model compared to week 96 of the clinical trial (615 vs 592), while the dimethyl fumarate population is lower (494 vs 600). The discrepancy in the placebo population may be due to the fact that the withdrawals allowed for the no treatment population in the model included mortality for which the rates were obtained from real-world patients with MS. Therefore, mortality rates used in the model could be higher than the mortality rates compared with observed rates in the clinical trial setting. The discrepancy in the dimethyl fumarate population may be mainly due to transfer to SPMS which was a discontinuation criterion in the model. Whereas, SPMS was not followed in the clinical trials, thus was not used as a treatment stopping criteria. Also, the rate of transfer to SPMS is based on rates from the London Ontario data set, not rates seen in the clinical trial. An analysis with transition to SPMS was therefore performed for the dimethyl fumarate population, which showed very similar predicted patient populations (Table 79).

Table 77: Actual and predicted baseline, year 1, and year 2 EDSS distributions for the placebo population

RRMS EDSS state	Baseline	Year 1 comparison		Year 2 comparison	
	Baseline, n (%)	DEFINE and CONFIRM week 48, n (%)	Model year 1, n (%)	DEFINE and CONFIRM week 96, n (%)	Model year 2, n (%)
0	34 (4.4)	31 (4.7)	41 (5.9)	37 (6.3)	41 (6.7)
1	63 (8.2)	62 (9.5)	69 (10.0)	46 (7.8)	66 (10.7)
2	265 (34.4)	219 (33.5)	228 (33.3)	179 (30.2)	204 (33.2)
3	181 (23.5)	141 (21.6)	153 (22.3)	139 (23.5)	131 (21.3)
4	161 (20.9)	128 (19.6)	128 (18.6)	127 (21.5)	106 (17.2)
5	66 (8.6)	48 (7.3)	39 (5.7)	27 (4.6)	34 (5.5)
6	1 (0.1)	20 (3.1)	19 (2.7)	24 (4.1)	19 (3.1)
7	0 (0.0)	4 (0.6)	6 (0.9)	11 (1.9)	8 (1.3)
8	0 (0.0)	1 (0.2)	3 (0.4)	1 (0.2)	6 (1.0)
9	0 (0.0)	31 (4.7)	0 (0.0)	1 (0.2)	0 (0.0)
Total RRMS	771	654	686	592	615

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis.

Table 78: Actual and predicted baseline, year 1, and year 2 EDSS distributions for the dimethyl fumarate population

RRMS EDSS state	Baseline	Year 1 comparison		Year 2 comparison	
	Baseline, n (%)	DEFINE and CONFIRM week 48, n (%)	Model year 1, n (%)	DEFINE and CONFIRM week 96, n (%)	Model year 2, n (%)
0	44 (5.7)	43 (6.7)	49 (8.1)	43 (7.2)	49 (10.0)
1	69 (9.0)	73 (11.4)	73 (11.9)	67 (11.2)	68 (13.7)
2	260 (33.9)	207 (32.3)	218 (35.6)	208 (34.7)	181 (36.6)
3	172 (22.4)	119 (18.6)	127 (20.8)	110 (18.3)	95 (19.3)
4	155 (20.2)	140 (21.8)	98 (16.0)	114 (19.0)	66 (13.4)
5	66 (8.6)	38 (5.9)	31 (5.0)	29 (4.8)	19 (3.9)
6	1 (0.1)	17 (2.7)	10 (1.7)	22 (3.7)	9 (1.9)
7	1 (0.1)	3 (0.5)	4 (0.6)	5 (0.8)	3 (0.7)
8	0 (0.0)	1 (0.2)	2 (0.2)	0 (0.0)	3 (0.0)
9	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Total RRMS	768	641	611	600	494

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis.

Table 79: Actual and predicted baseline, year 1, and year 2 EDSS distributions for the dimethyl fumarate population with transfer to SPMS turned off

RRMS EDSS state	Baseline	Year 1 comparison		Year 2 comparison	
	Baseline, n (%)	DEFINE and CONFIRM week 48, n (%)	Model year 1, n (%)	DEFINE and CONFIRM week 96, n (%)	Model year 2, n (%)
0	44 (5.7)	43 (6.7)	50 (7.4)	43 (7.2)	52 (8.7)
1	69 (9.0)	73 (11.4)	75 (11)	67 (11.2)	74 (12.3)
2	260 (33.9)	207 (32.3)	232 (33.9)	208 (34.7)	207 (34.5)
3	172 (22.4)	119 (18.6)	145 (21.2)	110 (18.3)	122 (20.3)
4	155 (20.2)	140 (21.8)	119 (17.5)	114 (19.0)	95 (15.8)
5	66 (8.6)	38 (5.9)	41 (6)	29 (4.8)	32 (5.3)
6	1 (0.1)	17 (2.7)	14 (2.1)	22 (3.7)	16 (2.7)
7	1 (0.1)	3 (0.5)	5 (0.7)	5 (0.8)	6 (1)
8	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)	4 (0.7)
9	0 (0.0)	0 (0.0)	0 (0)	2 (0.3)	0.5 (0.1)
Total RRMS	768	641	683	600	608

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces were not available from the model. However, data on the proportion of patients in each state over the first 2 years are provided in Sections 7.7.1 and 7.8.1.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Total patient quality adjusted life years (QALYs) accrued in each cycle were calculated by multiplying QoL (utility) values derived for each EDSS state by the proportion of patients alive in each EDSS state in each cycle. Total QALYs in each cycle were calculated by subtracting the reduction in QALYs associated with treatment/adverse events and the reduction in QALYs associated with caregivers from the total cohort QALYs (summed across all EDSS states). The QALYs accrued in each year for the EDSS states only are shown in Table 80 and Table 82 for dimethyl fumarate and IM IFNβ-1a 30 µg (Avonex®), respectively. The total QALYs accrued in each year of the model are detailed in Table 81 and Table 83 for dimethyl fumarate and IM IFNβ-1a 30 µg (Avonex®), respectively.

Table 80: QALYs accrued per year in EDSS states (dimethyl fumarate) (cohort of 1,000 patients)

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total undiscounted QALYs (EDSS states)
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	
1	50.1	77.0	253.2	144.3	110.0	35.7	4.1	1.0	0.0	0.0	0.0	0.0	0.1	3.5	7.6	10.6	5.2	0.0	0.0	0.0	702.4
2	59.1	84.2	232.8	120.9	82.4	21.9	7.8	2.1	0.0	0.0	0.0	0.0	0.3	8.9	18.5	27.4	15.5	1.6	-0.1	-0.1	683.0
3	60.5	82.2	212.5	104.6	67.7	17.5	7.7	2.2	-0.1	0.0	0.0	0.0	0.4	11.8	22.7	37.1	25.8	5.0	-0.4	-0.3	656.9
4	57.1	76.3	193.3	93.7	59.7	15.3	7.1	2.2	-0.1	0.0	0.0	0.0	0.5	13.1	23.8	42.2	35.6	9.4	-0.9	-0.7	627.6
5	52.5	69.8	175.7	84.9	53.8	13.8	6.5	2.0	-0.1	0.0	0.0	0.0	0.5	13.4	23.7	44.5	44.1	14.2	-1.5	-1.4	596.3
6	46.7	62.7	159.1	77.7	49.5	12.7	6.0	1.9	-0.1	0.0	0.0	0.0	0.5	13.2	22.8	44.9	50.8	19.2	-2.3	-2.5	562.8
7	40.9	55.9	143.8	71.4	45.9	11.8	5.7	1.8	-0.1	0.0	0.0	0.0	0.5	12.6	21.6	44.2	55.7	24.0	-3.3	-3.8	528.5
8	36.1	49.8	129.7	65.2	42.4	11.0	5.3	1.7	-0.1	0.0	0.0	0.0	0.5	11.8	20.3	42.8	58.8	28.4	-4.3	-5.5	493.8
9	32.0	44.5	116.8	59.3	38.9	10.2	4.9	1.6	-0.1	0.0	0.0	0.0	0.4	11.0	18.9	40.8	60.5	32.3	-5.4	-7.5	459.0
10	28.4	39.8	105.1	53.7	35.5	9.4	4.6	1.5	-0.1	0.0	0.0	0.0	0.4	10.1	17.4	38.5	60.9	35.6	-6.5	-10.0	424.3
11	25.3	35.6	94.5	48.6	32.3	8.6	4.2	1.4	-0.1	0.0	0.0	0.0	0.3	9.2	15.9	36.0	60.3	38.1	-7.6	-12.7	389.9
12	22.5	31.8	84.9	43.9	29.3	7.8	3.9	1.3	-0.1	0.0	0.0	0.0	0.3	8.3	14.5	33.4	58.8	40.0	-8.6	-15.8	356.2
13	20.1	28.5	76.2	39.6	26.6	7.1	3.5	1.2	-0.1	0.0	0.0	0.0	0.3	7.5	13.2	30.8	56.6	41.1	-9.6	-19.2	323.3
14	17.9	25.5	68.4	35.7	24.0	6.5	3.2	1.1	-0.1	0.0	0.0	0.0	0.3	6.8	12.0	28.2	53.9	41.6	-10.6	-22.9	291.4
15	16.0	22.8	61.3	32.1	21.7	5.9	2.9	1.0	-0.1	0.0	0.0	0.0	0.2	6.1	10.8	25.7	50.9	41.5	-11.4	-26.7	260.7
16	14.2	20.4	54.9	28.9	19.5	5.3	2.7	0.9	-0.1	0.0	0.0	0.0	0.2	5.5	9.7	23.4	47.7	40.9	-12.1	-30.7	231.3
17	12.7	18.2	49.2	25.9	17.6	4.8	2.4	0.8	-0.1	0.0	0.0	0.0	0.2	4.9	8.8	21.2	44.4	39.8	-12.7	-34.8	203.2
18	11.3	16.3	44.0	23.3	15.8	4.3	2.2	0.7	-0.1	0.0	0.0	0.0	0.2	4.4	7.9	19.1	41.1	38.4	-13.1	-39.0	176.7
19	10.1	14.5	39.4	20.8	14.2	3.9	1.9	0.7	-0.1	0.0	0.0	0.0	0.1	4.0	7.1	17.3	37.8	36.7	-13.5	-43.0	151.8
20	9.0	12.9	35.2	18.6	12.7	3.5	1.8	0.6	-0.1	0.0	0.0	0.0	0.1	3.6	6.3	15.5	34.6	34.8	-13.7	-47.0	128.5
21	8.0	11.5	31.4	16.7	11.4	3.1	1.6	0.5	-0.1	0.0	0.0	0.0	0.1	3.2	5.7	13.9	31.6	32.8	-13.7	-50.8	106.9
22	7.1	10.3	28.0	14.9	10.2	2.8	1.4	0.5	-0.1	0.0	0.0	0.0	0.1	2.8	5.1	12.5	28.7	30.7	-13.7	-54.4	86.9
23	6.3	9.2	25.0	13.3	9.1	2.5	1.3	0.4	-0.1	0.0	0.0	0.0	0.1	2.5	4.5	11.2	25.9	28.5	-13.5	-57.7	68.6
24	5.6	8.2	22.3	11.9	8.1	2.2	1.1	0.4	0.0	0.0	0.0	0.0	0.1	2.3	4.0	10.0	23.4	26.3	-13.2	-60.6	51.9
25	5.0	7.3	19.8	10.6	7.2	2.0	1.0	0.3	0.0	0.0	0.0	0.0	0.1	2.0	3.6	8.9	21.1	24.2	-12.9	-63.2	36.9
26	4.4	6.4	17.6	9.4	6.4	1.8	0.9	0.3	0.0	0.0	0.0	0.0	0.1	1.8	3.2	7.9	18.9	22.1	-12.5	-65.3	23.5
27	3.9	5.7	15.6	8.4	5.7	1.6	0.8	0.3	0.0	0.0	0.0	0.0	0.1	1.6	2.8	7.1	16.9	20.1	-12.0	-67.0	11.7
28	3.5	5.1	13.9	7.4	5.1	1.4	0.7	0.2	0.0	0.0	0.0	0.0	0.1	1.4	2.5	6.3	15.1	18.2	-11.4	-68.0	1.4

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
29	3.1	4.5	12.3	6.6	4.5	1.2	0.6	0.2	0.0	0.0	0.0	0.0	0.0	1.2	2.2	5.6	13.4	16.4	-10.8	-68.5	-7.4
30	2.7	4.0	10.9	5.8	4.0	1.1	0.6	0.2	0.0	0.0	0.0	0.0	0.0	1.1	2.0	4.9	11.9	14.7	-10.1	-68.4	-14.7
31	2.4	3.5	9.6	5.1	3.5	1.0	0.5	0.2	0.0	0.0	0.0	0.0	0.0	1.0	1.7	4.4	10.5	13.1	-9.4	-67.7	-20.7
32	2.1	3.1	8.5	4.5	3.1	0.9	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.9	1.5	3.8	9.3	11.6	-8.7	-66.4	-25.3
33	1.9	2.7	7.4	4.0	2.7	0.8	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.8	1.4	3.4	8.1	10.2	-8.0	-64.4	-28.5
34	1.6	2.4	6.5	3.5	2.4	0.7	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.7	1.2	3.0	7.1	9.0	-7.3	-61.8	-30.6
35	1.4	2.1	5.7	3.1	2.1	0.6	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.6	1.0	2.6	6.2	7.8	-6.5	-58.6	-31.6
36	1.3	1.8	5.0	2.7	1.8	0.5	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.5	0.9	2.3	5.4	6.8	-5.8	-55.0	-31.6
37	1.1	1.6	4.3	2.3	1.6	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.8	2.0	4.6	5.8	-5.1	-50.8	-30.6
38	0.9	1.4	3.8	2.0	1.4	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.7	1.7	4.0	5.0	-4.5	-46.2	-28.9
39	0.8	1.2	3.3	1.7	1.2	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.3	0.6	1.5	3.4	4.2	-3.8	-41.4	-26.5
40	0.7	1.0	2.8	1.5	1.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.5	1.3	2.9	3.5	-3.3	-36.3	-23.6
41	0.6	0.9	2.4	1.3	0.9	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	1.1	2.4	2.9	-2.7	-31.1	-20.3
42	0.5	0.7	2.0	1.1	0.7	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	0.9	2.0	2.4	-2.2	-26.0	-16.9
43	0.4	0.6	1.7	0.9	0.6	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.8	1.7	1.9	-1.8	-21.1	-13.5
44	0.4	0.5	1.4	0.8	0.5	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.6	1.4	1.5	-1.4	-16.5	-10.1
45	0.3	0.4	1.2	0.6	0.4	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.5	1.1	1.2	-1.0	-12.4	-7.1
46	0.2	0.4	1.0	0.5	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.9	0.9	-0.7	-8.9	-4.6
47	0.2	0.3	0.8	0.4	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.7	0.7	-0.5	-6.1	-2.6
48	0.2	0.2	0.6	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.5	0.5	-0.3	-3.9	-1.1
49	0.1	0.2	0.5	0.3	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.3	-0.2	-2.3	-0.1
50	0.1	0.1	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.2	-0.1	-1.3	0.4

Abbreviations: EDSS, expanded disability status scale; QALY, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 81: Total and per patient QALYs accrued per year (dimethyl fumarate) (cohort of 1,000 patients)

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
1	702.4	3.3	7.5	691.7	668.3	668	0.668
2	683.0	2.5	9.1	671.4	626.7	1295	1.295
3	656.9	2.0	11.3	643.5	580.4	1875	1.875
4	627.6	1.6	14.1	611.9	533.2	2409	2.409
5	596.3	1.3	17.3	577.7	486.4	2895	2.895
6	562.8	1.0	20.9	540.9	440.0	3335	3.335
7	528.5	0.8	24.7	503.0	395.4	3730	3.730
8	493.8	0.7	28.7	464.5	352.7	4083	4.083
9	459.0	0.5	32.8	425.6	312.3	4395	4.395
10	424.3	0.4	37.0	386.8	274.2	4670	4.670
11	389.9	0.3	41.2	348.4	238.6	4908	4.908
12	356.2	0.3	45.4	310.6	205.5	5114	5.114
13	323.3	0.2	49.4	273.7	175.0	5289	5.289
14	291.4	0.2	53.3	238.0	147.0	5436	5.436
15	260.7	0.1	57.0	203.6	121.5	5557	5.557
16	231.3	0.1	60.4	170.8	98.5	5656	5.656
17	203.2	0.1	63.5	139.6	77.8	5734	5.734
18	176.7	0.1	66.3	110.3	59.4	5793	5.793
19	151.8	0.1	68.8	83.0	43.2	5836	5.836
20	128.5	0.0	70.9	57.6	28.9	5865	5.865
21	106.9	0.0	72.6	34.2	16.6	5882	5.882
22	86.9	0.0	74.0	12.9	6.1	5888	5.888
23	68.6	0.0	74.9	-6.3	-2.9	5885	5.885
24	51.9	0.0	75.4	-23.5	-10.3	5875	5.875
25	36.9	0.0	75.5	-38.6	-16.3	5858	5.858
26	23.5	0.0	75.3	-51.8	-21.2	5837	5.837
27	11.7	0.0	74.6	-62.9	-24.9	5812	5.812
28	1.4	0.0	73.4	-72.0	-27.5	5785	5.785
29	-7.4	0.0	71.8	-79.2	-29.2	5756	5.756
30	-14.7	0.0	69.8	-84.5	-30.1	5725	5.725

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
31	-20.7	0.0	67.3	-88.0	-30.3	5695	5.695
32	-25.3	0.0	64.5	-89.7	-29.8	5665	5.665
33	-28.5	0.0	61.2	-89.7	-28.8	5636	5.636
34	-30.6	0.0	57.6	-88.1	-27.4	5609	5.609
35	-31.6	0.0	53.7	-85.2	-25.6	5584	5.584
36	-31.6	0.0	49.5	-81.1	-23.5	5560	5.560
37	-30.6	0.0	45.1	-75.7	-21.2	5539	5.539
38	-28.9	0.0	40.5	-69.4	-18.8	5520	5.520
39	-26.5	0.0	35.8	-62.4	-16.3	5504	5.504
40	-23.6	0.0	31.1	-54.7	-13.8	5490	5.490
41	-20.3	0.0	26.5	-46.8	-11.4	5479	5.479
42	-16.9	0.0	22.0	-38.9	-9.2	5469	5.469
43	-13.5	0.0	17.8	-31.2	-7.1	5462	5.462
44	-10.1	0.0	13.9	-24.0	-5.3	5457	5.457
45	-7.1	0.0	10.5	-17.6	-3.7	5453	5.453
46	-4.6	0.0	7.6	-12.2	-2.5	5451	5.451
47	-2.6	0.0	5.2	-7.8	-1.6	5449	5.449
48	-1.1	0.0	3.4	-4.5	-0.9	5448	5.448
49	-0.1	0.0	2.1	-2.2	-0.4	5448	5.448
50	0.4	0.0	1.2	-0.8	-0.1	5448	5.448

Abbreviations: EDSS, expanded disability status scale; QALY, quality adjusted life years

Table 82: QALYs accrued per year in EDSS states (IM IFNβ-1a 30 µg [Avonex®]) (cohort of 1,000 patients)

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total undiscounted QALYs (EDSS states)
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	
1	48.6	75.5	250.3	144.4	110.9	35.9	4.6	1.1	0.0	0.0	0.0	0.0	0.1	3.5	7.6	10.6	5.2	0.0	0.0	0.0	698.2
2	55.1	80.5	227.4	122.2	85.4	22.8	8.8	2.4	0.0	0.0	0.0	0.0	0.3	8.8	18.5	27.7	15.6	1.6	-0.1	-0.1	676.7

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
3	55.2	77.4	206.7	106.2	71.0	18.7	8.6	2.6	-0.1	0.0	0.0	0.0	0.4	11.6	22.9	37.8	26.2	5.3	-0.4	-0.3	649.6
4	51.6	71.5	187.4	94.8	62.4	16.5	7.9	2.5	-0.1	0.0	0.0	0.0	0.4	12.8	24.1	43.2	36.4	9.8	-0.9	-0.8	619.4
5	47.2	65.1	169.7	85.4	55.9	14.8	7.2	2.3	-0.1	0.0	0.0	0.0	0.5	13.1	23.8	45.7	45.3	14.8	-1.6	-1.6	587.3
6	42.2	58.5	153.2	77.5	50.8	13.4	6.5	2.1	-0.1	0.0	0.0	0.0	0.5	12.8	22.9	46.1	52.2	19.9	-2.4	-2.7	553.5
7	37.3	52.3	138.0	70.6	46.6	12.3	6.0	2.0	-0.1	0.0	0.0	0.0	0.5	12.2	21.6	45.2	57.2	24.9	-3.4	-4.1	518.8
8	33.1	46.7	124.1	64.0	42.5	11.3	5.5	1.8	-0.1	0.0	0.0	0.0	0.4	11.4	20.1	43.4	60.3	29.4	-4.4	-5.9	483.8
9	29.4	41.8	111.6	57.9	38.6	10.3	5.1	1.7	-0.1	0.0	0.0	0.0	0.4	10.6	18.6	41.2	61.9	33.4	-5.6	-8.0	448.7
10	26.2	37.4	100.2	52.2	35.0	9.4	4.7	1.5	-0.1	0.0	0.0	0.0	0.4	9.7	17.0	38.6	62.1	36.6	-6.7	-10.6	413.7
11	23.4	33.4	90.0	47.1	31.7	8.6	4.3	1.4	-0.1	0.0	0.0	0.0	0.3	8.8	15.5	35.9	61.1	39.1	-7.8	-13.4	379.3
12	20.9	29.9	80.7	42.4	28.7	7.8	3.9	1.3	-0.1	0.0	0.0	0.0	0.3	8.0	14.1	33.1	59.3	40.9	-8.9	-16.6	345.5
13	18.6	26.8	72.4	38.1	25.9	7.0	3.5	1.2	-0.1	0.0	0.0	0.0	0.3	7.2	12.8	30.3	56.9	41.9	-9.9	-20.2	312.7
14	16.6	23.9	64.9	34.3	23.3	6.4	3.2	1.1	-0.1	0.0	0.0	0.0	0.2	6.5	11.5	27.6	54.0	42.3	-10.8	-23.9	280.9
15	14.9	21.4	58.1	30.8	21.0	5.7	2.9	1.0	-0.1	0.0	0.0	0.0	0.2	5.8	10.4	25.1	50.7	42.0	-11.7	-27.9	250.3
16	13.3	19.1	52.0	27.6	18.8	5.2	2.6	0.9	-0.1	0.0	0.0	0.0	0.2	5.2	9.3	22.7	47.3	41.2	-12.4	-32.0	221.1
17	11.8	17.1	46.6	24.7	16.9	4.6	2.3	0.8	-0.1	0.0	0.0	0.0	0.2	4.7	8.4	20.5	43.9	40.0	-12.9	-36.1	193.4
18	10.6	15.3	41.6	22.2	15.2	4.2	2.1	0.7	-0.1	0.0	0.0	0.0	0.2	4.2	7.5	18.5	40.4	38.5	-13.4	-40.3	167.2
19	9.4	13.6	37.2	19.8	13.6	3.7	1.9	0.6	-0.1	0.0	0.0	0.0	0.1	3.8	6.7	16.6	37.1	36.7	-13.7	-44.4	142.7
20	8.4	12.2	33.2	17.7	12.1	3.3	1.7	0.6	-0.1	0.0	0.0	0.0	0.1	3.4	6.0	14.9	33.8	34.7	-13.8	-48.5	119.8
21	7.5	10.8	29.7	15.8	10.9	3.0	1.5	0.5	-0.1	0.0	0.0	0.0	0.1	3.0	5.4	13.4	30.7	32.5	-13.9	-52.3	98.6
22	6.7	9.7	26.5	14.1	9.7	2.7	1.4	0.5	-0.1	0.0	0.0	0.0	0.1	2.7	4.8	12.0	27.8	30.3	-13.8	-55.9	79.1
23	5.9	8.6	23.6	12.6	8.7	2.4	1.2	0.4	-0.1	0.0	0.0	0.0	0.1	2.4	4.3	10.7	25.1	28.1	-13.6	-59.2	61.2
24	5.3	7.7	21.0	11.2	7.7	2.1	1.1	0.4	0.0	0.0	0.0	0.0	0.1	2.1	3.8	9.5	22.6	25.9	-13.3	-62.1	45.1
25	4.7	6.8	18.7	10.0	6.9	1.9	1.0	0.3	0.0	0.0	0.0	0.0	0.1	1.9	3.4	8.5	20.3	23.7	-12.9	-64.6	30.5
26	4.2	6.1	16.6	8.9	6.1	1.7	0.9	0.3	0.0	0.0	0.0	0.0	0.1	1.7	3.0	7.6	18.2	21.7	-12.5	-66.7	17.6
27	3.7	5.4	14.7	7.9	5.4	1.5	0.8	0.3	0.0	0.0	0.0	0.0	0.1	1.5	2.7	6.7	16.2	19.7	-11.9	-68.3	6.2
28	3.3	4.8	13.1	7.0	4.8	1.3	0.7	0.2	0.0	0.0	0.0	0.0	0.0	1.3	2.4	6.0	14.4	17.7	-11.4	-69.3	-3.6
29	2.9	4.2	11.6	6.2	4.3	1.2	0.6	0.2	0.0	0.0	0.0	0.0	0.0	1.2	2.1	5.3	12.8	15.9	-10.7	-69.7	-12.0
30	2.6	3.7	10.2	5.5	3.8	1.0	0.5	0.2	0.0	0.0	0.0	0.0	0.0	1.0	1.9	4.7	11.3	14.2	-10.1	-69.5	-18.9
31	2.3	3.3	9.0	4.8	3.3	0.9	0.5	0.2	0.0	0.0	0.0	0.0	0.0	0.9	1.6	4.1	10.0	12.7	-9.4	-68.7	-24.4
32	2.0	2.9	8.0	4.3	2.9	0.8	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.8	1.5	3.6	8.8	11.2	-8.6	-67.3	-28.6
33	1.8	2.6	7.0	3.8	2.6	0.7	0.4	0.1	0.0	0.0	0.0	0.0	0.0	0.7	1.3	3.2	7.7	9.9	-7.9	-65.2	-31.5
34	1.5	2.2	6.1	3.3	2.3	0.6	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.6	1.1	2.8	6.8	8.6	-7.2	-62.5	-33.2

Year	RRMS, by EDSS state										SPMS, by EDSS state										Total
35	1.3	2.0	5.4	2.9	2.0	0.5	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.5	1.0	2.4	5.9	7.5	-6.4	-59.2	-33.9
36	1.2	1.7	4.7	2.5	1.7	0.5	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.5	0.9	2.1	5.1	6.5	-5.7	-55.5	-33.6
37	1.0	1.5	4.1	2.2	1.5	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.7	1.8	4.4	5.6	-5.1	-51.3	-32.4
38	0.9	1.3	3.5	1.9	1.3	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.4	0.6	1.6	3.8	4.7	-4.4	-46.6	-30.4
39	0.8	1.1	3.1	1.6	1.1	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.3	0.6	1.4	3.2	4.0	-3.8	-41.7	-27.8
40	0.7	1.0	2.6	1.4	1.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.5	1.2	2.7	3.4	-3.2	-36.5	-24.7
41	0.6	0.8	2.2	1.2	0.8	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.4	1.0	2.3	2.8	-2.6	-31.3	-21.2
42	0.5	0.7	1.9	1.0	0.7	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.8	1.9	2.3	-2.2	-26.2	-17.6
43	0.4	0.6	1.6	0.9	0.6	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.7	1.6	1.8	-1.7	-21.2	-14.0
44	0.3	0.5	1.3	0.7	0.5	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.6	1.3	1.4	-1.3	-16.6	-10.6
45	0.3	0.4	1.1	0.6	0.4	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.5	1.0	1.1	-1.0	-12.4	-7.5
46	0.2	0.3	0.9	0.5	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.8	0.9	-0.7	-8.9	-4.9
47	0.2	0.3	0.7	0.4	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.6	0.6	-0.5	-6.1	-2.8
48	0.2	0.2	0.6	0.3	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.5	0.5	-0.3	-3.9	-1.3
49	0.1	0.2	0.5	0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.3	-0.2	-2.3	-0.3
50	0.1	0.1	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.2	-0.1	-1.3	0.3

Abbreviations: EDSS, expanded disability status scale; QALY, quality adjusted life years; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 83: Total and per patient QALYs accrued per year (IM IFNβ-1a 30 µg [Avonex®]) (cohort of 1,000 patients)

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
1	698.2	16.2	7.6	674.4	651.6	652	0.652
2	676.7	12.5	9.4	654.8	611.3	1263	1.263
3	649.6	9.8	11.8	628.0	566.4	1829	1.829
4	619.4	7.7	14.7	597.0	520.2	2350	2.350
5	587.3	6.0	18.1	563.2	474.2	2824	2.824
6	553.5	4.8	21.7	527.0	428.7	3252	3.252
7	518.8	3.8	25.7	489.4	384.7	3637	3.637
8	483.8	3.0	29.8	451.1	342.5	3980	3.980
9	448.7	2.3	34.0	412.3	302.5	4282	4.282
10	413.7	1.8	38.2	373.6	264.9	4547	4.547
11	379.3	1.4	42.5	335.3	229.7	4777	4.777
12	345.5	1.1	46.7	297.7	197.0	4974	4.974
13	312.7	0.9	50.8	261.0	166.9	5141	5.141
14	280.9	0.7	54.6	225.5	139.3	5280	5.280
15	250.3	0.6	58.3	191.4	114.3	5394	5.394
16	221.1	0.4	61.7	159.0	91.7	5486	5.486
17	193.4	0.3	64.8	128.3	71.5	5557	5.557
18	167.2	0.3	67.6	99.4	53.5	5611	5.611
19	142.7	0.2	70.0	72.5	37.7	5649	5.649
20	119.8	0.2	72.0	47.6	23.9	5672	5.672
21	98.6	0.1	73.7	24.8	12.0	5684	5.684
22	79.1	0.1	75.0	4.0	1.9	5686	5.686
23	61.2	0.1	75.8	-14.7	-6.6	5680	5.680
24	45.1	0.1	76.3	-31.3	-13.7	5666	5.666
25	30.5	0.0	76.3	-45.8	-19.4	5647	5.647
26	17.6	0.0	76.0	-58.4	-23.9	5623	5.623
27	6.2	0.0	75.2	-69.0	-27.3	5595	5.595
28	-3.6	0.0	73.9	-77.6	-29.6	5566	5.566
29	-12.0	0.0	72.2	-84.2	-31.1	5535	5.535
30	-18.9	0.0	70.2	-89.0	-31.7	5503	5.503

Year	Total undiscounted QALYs (EDSS states)	Total QALY loss associated with treatment	Total QALY loss associated with caregivers	Total undiscounted QALYs by year	Total discounted QALYs by year	Total cumulative discounted QALYs by year	Cumulative discounted QALYs per patient
31	-24.4	0.0	67.7	-92.1	-31.7	5471	5.471
32	-28.6	0.0	64.7	-93.3	-31.0	5440	5.440
33	-31.5	0.0	61.4	-92.9	-29.9	5411	5.411
34	-33.2	0.0	57.7	-90.9	-28.2	5382	5.382
35	-33.9	0.0	53.8	-87.6	-26.3	5356	5.356
36	-33.6	0.0	49.6	-83.1	-24.1	5332	5.332
37	-32.4	0.0	45.1	-77.5	-21.7	5310	5.310
38	-30.4	0.0	40.5	-70.9	-19.2	5291	5.291
39	-27.8	0.0	35.8	-63.6	-16.6	5274	5.274
40	-24.7	0.0	31.1	-55.7	-14.1	5260	5.260
41	-21.2	0.0	26.4	-47.6	-11.6	5249	5.249
42	-17.6	0.0	21.9	-39.6	-9.3	5239	5.239
43	-14.0	0.0	17.7	-31.7	-7.2	5232	5.232
44	-10.6	0.0	13.8	-24.4	-5.4	5227	5.227
45	-7.5	0.0	10.4	-17.9	-3.8	5223	5.223
46	-4.9	0.0	7.5	-12.4	-2.5	5220	5.220
47	-2.8	0.0	5.2	-8.0	-1.6	5219	5.219
48	-1.3	0.0	3.4	-4.7	-0.9	5218	5.218
49	-0.3	0.0	2.1	-2.3	-0.4	5218	5.218
50	0.3	0.0	1.2	-0.9	-0.2	5217	5.217

Abbreviations: EDSS, expanded disability status scale; QALY, quality adjusted life years

7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.*

Life years and QALYs accrued for each comparator are provided in Table 84.

Table 84: Model outputs by comparator *(Commerical in confidence information removed)*

Comparator	LY	QALY	Cost (£)
Dimethyl fumarate (Tecfidera®)			List: £269,751 PAS:
SC IFNβ-1a 22 µg (Rebif® 22 µg)	17.00	5.47	£234,103
Glatiramer acetate (Copaxone®)	17.00	5.50	£234,547
IM IFNβ-1a 30 µg (Avonex®)	17.01	5.50	£239,460
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)	17.00	5.45	£240,159
SC IFNβ-1a 44 µg (Rebif® 44 µg)	17.01	5.50	£242,290
Natalizumab (Tysabri®)	17.03	5.79	£281,697
Fingolimod (Gilenya®)	17.00	5.50	£282,065

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

7.7.5 *Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.*

A breakdown of incremental QALYs for dimethyl fumarate vs IM IFNβ-1a 30 µg (Avonex®) can be found in Table 85. Table 86 and Table 87 show a breakdown of the incremental costs for dimethyl fumarate vs IM IFNβ-1a 30 µg (Avonex®) with the dimethyl fumarate PAS price, and the list price, respectively.

Table 88 and Table 89 show the total cost breakdown by category for dimethyl fumarate vs IM IFNβ-1a 30 µg (Avonex®) with the dimethyl fumarate PAS price, and the list price, respectively.

Table 85: Summary of QALY gain per patient by comparator

Health state	QALY (dimethyl fumarate)	QALY ((IM IFNβ-1a 30 µg (Avonex®))	Increment	Absolute increment	% absolute increment
EDSS health states:	**6.54**	**6.39**	**0.16**	**0.16**	**69.7%**
RRMS, EDSS 0	*0.51*	*0.47*	*0.04*	*0.04*	*17.9%*
RRMS, EDSS 1	*0.71*	*0.67*	*0.04*	*0.04*	*18.0%*
RRMS, EDSS 2	*1.93*	*1.86*	*0.07*	*0.07*	*30.4%*
RRMS, EDSS 3	*0.99*	*0.98*	*0.01*	*0.01*	*4.4%*
RRMS, EDSS 4	*0.66*	*0.67*	*-0.01*	*0.01*	*2.9%*
RRMS, EDSS 5	*0.18*	*0.19*	*0.00*	*0.00*	*1.9%*
RRMS, EDSS 6	*0.07*	*0.08*	*0.00*	*0.00*	*1.8%*
RRMS, EDSS 7	*0.02*	*0.02*	*0.00*	*0.00*	*0.7%*
RRMS, EDSS 8	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
RRMS, EDSS 9	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
SPMS, EDSS 0	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
SPMS, EDSS 1	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
SPMS, EDSS 2	*0.00*	*0.00*	*0.00*	*0.00*	*0.1%*
SPMS, EDSS 3	*0.13*	*0.13*	*0.00*	*0.00*	*1.9%*
SPMS, EDSS 4	*0.24*	*0.24*	*0.00*	*0.00*	*1.4%*
SPMS, EDSS 5	*0.49*	*0.49*	*0.00*	*0.00*	*0.3%*
SPMS, EDSS 6	*0.71*	*0.71*	*0.00*	*0.00*	*1.7%*
SPMS, EDSS 7	*0.46*	*0.47*	*-0.01*	*0.01*	*2.5%*
SPMS, EDSS 8	*-0.14*	*-0.14*	*0.00*	*0.00*	*1.0%*
SPMS, EDSS 9	*-0.45*	*-0.46*	*0.01*	*0.01*	*6.2%*
Treatment-related adverse events:	**-0.01**	**-0.06**	**0.05**	**0.05**	**22.8%**
Abdominal pain	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Abdominal pain upper	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
ALT increased	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Arthralgia	*-0.0001*	*0.00*	*0.00*	*0.00*	*0.1%*
Atrioventricular conduction block	*0.000*	*0.000*	*0.00*	*0.00*	*0.0%*
Back pain	*0.00*	*0.00*	*0.00*	*0.00*	*0.3%*
Bradycardia	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Chest pain	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Cough	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Depression	*-0.01*	*-0.01*	*0.01*	*0.01*	*4.0%*
Diarrhoea	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Fatigue	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Flu-like symptoms	*0.00*	*-0.03*	*0.03*	*0.03*	*14.2%*
Flushing	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Gastroenteritis	*0.00*	*0.00*	*0.00*	*0.00*	*0.1%*
Headache	*0.00*	*0.00*	*0.00*	*0.00*	*0.8%*
Influenza	*0.00*	*-0.01*	*0.01*	*0.01*	*4.2%*
Leucopoenia	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Lower respiratory tract infection	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Nausea	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*

Health state	QALY (dimethyl fumarate)	QALY ((IM IFNβ-1a 30 µg (Avonex®))	Increment	Absolute increment	% absolute increment
Pain in extremity	*0.00*	*0.00*	*0.00*	*0.00*	*0.2%*
Pruritus	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Rash	*0.00*	*0.00*	*0.00*	*0.00*	*0.0%*
Urinary tract infection	*0.00*	*0.00*	*0.00*	*0.00*	*0.1%*
Caregiver	**-0.80**	**-0.82**	**0.02**	**0.02**	**7.5%**
Total:	**5.725**	**5.503**	**0.222**	**0.222**	**100.00%**

Abbreviations: ALT, alanine transaminase; EDSS, expanded disability status scale; PAS, patient access scheme; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 86: Summary of costs per patient by health state (PAS price)

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS health states	**£200,712**	**£205,616**	**-£4,905**	**£4,905**	**12.0%**
RRMS, EDSS 0	*£1,744*	*£1,763*	*-£19*	*£19*	*0.0%*
RRMS, EDSS 1	*£2,685*	*£2,770*	*-£86*	*£86*	*0.2%*
RRMS, EDSS 2	*£7,098*	*£7,543*	*-£445*	*£445*	*1.1%*
RRMS, EDSS 3	*£8,626*	*£8,958*	*-£332*	*£332*	*0.8%*
RRMS, EDSS 4	*£4,375*	*£4,733*	*-£358*	*£358*	*0.9%*
RRMS, EDSS 5	*£1,844*	*£1,995*	*-£151*	*£151*	*0.4%*
RRMS, EDSS 6	*£1,004*	*£1,087*	*-£83*	*£83*	*0.2%*
RRMS, EDSS 7	*£891*	*£955*	*-£64*	*£64*	*0.2%*
RRMS, EDSS 8	*£4,514*	*£4,830*	*-£316*	*£316*	*0.8%*
RRMS, EDSS 9	*£27*	*£28*	*-£2*	*£2*	*0.0%*
SPMS, EDSS 0	*£0*	*£0*	*£0*	*£0*	*0.0%*
SPMS, EDSS 1	*£0*	*£0*	*£0*	*£0*	*0.0%*
SPMS, EDSS 2	*£19*	*£18*	*£1*	*£1*	*0.0%*
SPMS, EDSS 3	*£1,572*	*£1,522*	*£50*	*£50*	*0.1%*
SPMS, EDSS 4	*£1,812*	*£1,789*	*£23*	*£23*	*0.1%*
SPMS, EDSS 5	*£6,045*	*£6,053*	*-£7*	*£7*	*0.0%*
SPMS, EDSS 6	*£11,765*	*£11,827*	*-£62*	*£62*	*0.2%*
SPMS, EDSS 7	*£20,383*	*£20,632*	*-£249*	*£249*	*0.6%*
SPMS, EDSS 8	*£79,401*	*£80,754*	*-£1,352*	*£1,352*	*3.3%*
SPMS, EDSS 9	*£46,906*	*£48,358*	*-£1,452*	*£1,452*	*3.6%*
Treatment acquisition costs	**£34,317**	**£29,790**	**£4,527**	**£4,527**	**87.0%**
Treatment administration costs	**£0**	**£84**	**-£84**	**£84**	**0.2%**
Treatment monitoring costs	**£3,192**	**£3,086**	**£107**	**£107**	**0.2%**

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
Treatment-related adverse events	**£543**	**£884**	**-£341**	**£341**	**0.8%**
Abdominal pain	*£10*	*£0*	*£10*	*£10*	*0.0%*
Abdominal pain upper	*£10*	*£0*	*£10*	*£10*	*0.0%*
ALT increased	*£0*	*£0*	*£0*	*£0*	*0.0%*
Arthralgia	*£9*	*£10*	*-£1*	*£1*	*0.0%*
Atrioventricular conduction block	*£6*	*£15*	*-£9*	*£9*	*0.0%*
Back pain	*£13*	*£10*	*£3*	*£3*	*0.0%*
Bradycardia	*£0*	*£0*	*£0*	*£0*	*0.0%*
Chest pain	*£12*	*£0*	*£12*	*£12*	*0.0%*
Cough	*£0*	*£0*	*£0*	*£0*	*0.0%*
Depression	*£37*	*£116*	*-£79*	*£79*	*0.2%*
Diarrhoea	*£0*	*£0*	*£0*	*£0*	*0.0%*
Fatigue	*£0*	*£0*	*£0*	*£0*	*0.0%*
Flu-like symptoms	*£1*	*£73*	*-£72*	*£72*	*0.2%*
Flushing	*£0*	*£0*	*£0*	*£0*	*0.0%*
Gastroenteritis	*£77*	*£0*	*£77*	*£77*	*0.2%*
Headache	*£231*	*£533*	*-£302*	*£302*	*0.7%*
Influenza	*£7*	*£38*	*-£31*	*£31*	*0.1%*
Leucopoenia	*£0*	*£0*	*£0*	*£0*	*0.0%*
Lower respiratory tract infection	*£4*	*£0*	*£4*	*£4*	*0.0%*
Nausea	*£0*	*£0*	*£0*	*£0*	*0.0%*
Pain in extremity	*£19*	*£28*	*-£10*	*£10*	*0.0%*
Pruritus	*£0*	*£0*	*£0*	*£0*	*0.0%*
Rash	*£84*	*£48*	*£36*	*£36*	*0.1%*
Urinary tract infection	*£24*	*£14*	*£11*	*£11*	*0.0%*
Total:	**£238,764**	**£239,460**	**-£696**	**£9,964**	**100.00%**

Abbreviations: ALT, alanine transaminase; EDSS, expanded disability status scale; PAS, patient access scheme; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 87: Summary of costs per patient by health state (List price)

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS health states:	**£200,712**	**£205,616**	**-£4,905**	**£4,905**	**12.0%**
RRMS, EDSS 0	*£1,744*	*£1,763*	*-£19*	*£19*	*0.0%*
RRMS, EDSS 1	*£2,685*	*£2,770*	*-£86*	*£86*	*0.2%*
RRMS, EDSS 2	*£7,098*	*£7,543*	*-£445*	*£445*	*1.1%*
RRMS, EDSS 3	*£8,626*	*£8,958*	*-£332*	*£332*	*0.8%*
RRMS, EDSS 4	*£4,375*	*£4,733*	*-£358*	*£358*	*0.9%*
RRMS, EDSS 5	*£1,844*	*£1,995*	*-£151*	*£151*	*0.4%*
RRMS, EDSS 6	*£1,004*	*£1,087*	*-£83*	*£83*	*0.2%*
RRMS, EDSS 7	*£891*	*£955*	*-£64*	*£64*	*0.2%*
RRMS, EDSS 8	*£4,514*	*£4,830*	*-£316*	*£316*	*0.8%*
RRMS, EDSS 9	*£27*	*£28*	*-£2*	*£2*	*0.0%*
SPMS, EDSS 0	*£0*	*£0*	*£0*	*£0*	*0.0%*
SPMS, EDSS 1	*£0*	*£0*	*£0*	*£0*	*0.0%*
SPMS, EDSS 2	*£19*	*£18*	*£1*	*£1*	*0.0%*
SPMS, EDSS 3	*£1,572*	*£1,522*	*£50*	*£50*	*0.1%*
SPMS, EDSS 4	*£1,812*	*£1,789*	*£23*	*£23*	*0.1%*
SPMS, EDSS 5	*£6,045*	*£6,053*	*-£7*	*£7*	*0.0%*
SPMS, EDSS 6	*£11,765*	*£11,827*	*-£62*	*£62*	*0.2%*
SPMS, EDSS 7	*£20,383*	*£20,632*	*-£249*	*£249*	*0.6%*
SPMS, EDSS 8	*£79,401*	*£80,754*	*-£1,352*	*£1,352*	*3.3%*
SPMS, EDSS 9	*£46,906*	*£48,358*	*-£1,452*	*£1,452*	*3.5%*
Treatment acquisition costs	**£65,350**	**£29,790**	**£35,560**	**£35,560**	**86.7%**
Treatment administration costs	**£0**	**£84**	**-£84**	**£84**	**0.2%**
Treatment monitoring costs	**£3,192**	**£3,086**	**£107**	**£107**	**0.3%**
Treatment-related adverse events:	**£543**	**£884**	**-£341**	**£341**	**0.8%**
Abdominal pain	*£10*	*£0*	*£10*	*£10*	*0.0%*
Abdominal pain upper	*£10*	*£0*	*£10*	*£10*	*0.0%*
ALT increased	*£0*	*£0*	*£0*	*£0*	*0.0%*
Arthralgia	*£9*	*£10*	*-£1*	*£1*	*0.0%*
Atrioventricular conduction block	*£6*	*£15*	*-£9*	*£9*	*0.0%*
Back pain	*£13*	*£10*	*£3*	*£3*	*0.0%*
Bradycardia	*£0*	*£0*	*£0*	*£0*	*0.0%*
Chest pain	*£12*	*£0*	*£12*	*£12*	*0.0%*
Cough	*£0*	*£0*	*£0*	*£0*	*0.0%*

Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
Depression	*£37*	*£116*	*-£79*	*£79*	*0.2%*
Diarrhoea	*£0*	*£0*	*£0*	*£0*	*0.0%*
Fatigue	*£0*	*£0*	*£0*	*£0*	*0.0%*
Flu-like symptoms	*£1*	*£73*	*-£72*	*£72*	*0.2%*
Flushing	*£0*	*£0*	*£0*	*£0*	*0.0%*
Gastroenteritis	*£77*	*£0*	*£77*	*£77*	*0.2%*
Headache	*£231*	*£533*	*-£302*	*£302*	*0.7%*
Influenza	*£7*	*£38*	*-£31*	*£31*	*0.1%*
Leucopoenia	*£0*	*£0*	*£0*	*£0*	*0.0%*
Lower respiratory tract infection	*£4*	*£0*	*£4*	*£4*	*0.0%*
Nausea	*£0*	*£0*	*£0*	*£0*	*0.0%*
Pain in extremity	*£19*	*£28*	*-£10*	*£10*	*0.0%*
Pruritus	*£0*	*£0*	*£0*	*£0*	*0.0%*
Rash	*£84*	*£48*	*£36*	*£36*	*0.1%*
Urinary tract infection	*£24*	*£14*	*£11*	*£11*	*0.0%*
Total:	**£269,798**	**£239,460**	**£30,337**	**£40,997**	**100.00%**

Abbreviations: AE, adverse event; ALT, alanine transaminase; EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 88: Summary of predicted resource use per patient by category of cost (PAS price)

EDSS Health state	Cost of dimethyl fumarate	Cost of IM IFNβ-1a 30 µg (Avonex®)	Increment	Absolute increment	% absolute increment
EDSS state costs	200,712	205,616	-4,905	4,905	49.2246%
Treatment cost	34,317	29,790	4,527	4,527	45.4345%
Administration cost	0	84	-84	84	0.8479%
Monitoring cost	3,192	3,086	107	107	1.0731%
Adverse events	543	884	-341	341	3.4199%
Total:	**238,764**	**239,460**	**-696**	**9,964**	**100.00%**

Abbreviations: EDSS, expanded disability status scale

Table 89: Summary of predicted resource use per patient by category of cost, per patient (list price)

EDSS Health state	Cost intervention (Dimethyl fumarate)	Cost comparator (Avonex)	Increment	Absolute increment	% absolute increment
EDSS state costs	200,712	205,616	-4,905	4,905	11.9632%
Treatment cost	65,350	29,790	35,560	35,560	86.7387%
Administration cost	0	84	-84	84	0.2061%
Monitoring cost	3,192	3,086	107	107	0.2608%
Adverse events	543	884	-341	341	0.8311%
Total:	**269,798**	**239,460**	**30,337**	**40,997**	**100.00%**

Abbreviations: EDSS, expanded disability status scale

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Base case results using the list price are presented in Table 90. Dimethyl fumarate resulted in a greater number of life years and QALYs than all comparators, with the exception of natalizumab.

Table 90: Base-case results (list price)

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Dimethyl fumarate (Tecfidera®)	£269,798	17.02	5.73	-	-	-	-
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£234,103	17.00	5.47	£35,695	0.02	0.26	£142,283
Glatiramer acetate (Copaxone®)	£234,547	17.00	5.50	£35,250	0.02	0.23	£159,295
IM IFNβ-1a 30 µg (Avonex®)	£239,460	17.01	5.50	£30,337	0.01	0.23	£136,452
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)	£240,159	17.00	5.45	£29,639	0.02	0.28	£106,127
SC IFNβ-1a 44 µg (Rebif® 44 µg)	£242,290	17.01	5.50	£27,507	0.01	0.23	£122,105
Fingolimod (Gilenya®)	£282,065	17.00	5.50	-£12,267	0.02	0.23	**Dominant**
Natalizumab (Tysabri®)	£284,763	17.03	5.81	-£14,965	-0.08	-0.06	£173,745

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

Base case results using the PAS price are shown in Table 91. Dimethyl fumarate resulted in a greater number of life years and QALYs than all comparators, with the exception of natalizumab. Dimethyl fumarate dominated fingolimod, IM IFNβ-1a 30 µg, SC IFNβ-1b 250 µg, and SC IFNβ-1a 44 µg, and produced ICERs below £20,000/QALY against GA and SC IFNβ-1a 22 µg. Dimethyl fumarate gave a lower number of QALYs

(0.08 fewer) than natalizumab, but was less expensive (£ *(Academic in confidence information removed)* less), resulting in an ICER of £534,037 in the south-west quadrant of the cost-effectiveness plane.

Table 91: Base-case results (PAS price) *(Commerical in confidence information removed)*

Technologies	Total			Incremental (dimethyl fumarate vs comparator)			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SC IFNβ-1a 22 µg (Rebif® 22 µg)							£18,581
Glatiramer acetate (Copaxone®)							£19,057
Dimethyl fumarate (Tecfidera®)							-
IM IFNβ-1a 30 µg (Avonex®)							**Dominant**
SC IFNβ-1b 250 µg (Betaferon®/ Extavia®)							**Dominant**
SC IFNβ-1a 44 µg (Rebif® 44 µg)							**Dominant**
Fingolimod (Gilenya®)							**Dominant**
Natalizumab (Tysabri®)							£534,047

Abbreviations: ICER, incremental cost-effectiveness ratio; IM, intramuscular; QALYs, quality adjusted life years; SC, subcutaneous.

In addition to these analyses, incremental analyses were also performed using the list and PAS prices (Table 92 and Table 93, respectively). These demonstrated that, using the PAS price, dimethyl fumarate is the most cost effective treatment option at a willingness to pay threshold of £20,000 per QALY (Table 93). SC IFNβ-1a 44 µg (Rebif®), SC IFNβ-1b 250 µg (Betaferon®/ Extavia®), IM IFNβ-1a 30 µg (Avonex®), and Fingolimod (Gilenya®) were all either dominated or extendedly dominated.

Table 92: Incremental cost-effectiveness analysis (list price)

Treatment	Total cost	Total QALYs	Inc. costs	Inc. QALYs	ICER
SC IFNβ-1a 22 µg (Rebif® 22 µg)	£234,103	5.47	-	-	
Glatiramer acetate (Copaxone®)	£234,547	5.50	£445	0.03	£15,026
Dimethyl fumarate (Tecfidera®)	£269,798	5.73	£35,250	0.22	£159,295
Natalizumab (Tysabri®)	£284,763	5.81	£14,965	0.09	£173,745

SC IFNβ-1a 44 µg (Rebif®), SC IFNβ-1b 250 µg (Betaferon®/ Extavia®), IM IFNβ-1a 30 µg (Avonex®), and Fingolimod (Gilenya®) were all either dominated or extendedly dominated; the results for these treatments are therefore not shown.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Table 93: Incremental cost-effectiveness analysis (PAS price) ***(Commercial in confidence information removed)***

Treatment	Total cost	Total QALYs	Inc. costs	Inc. QALYs	ICER
SC IFNβ-1a 22 µg (Rebif® 22 µg)					-
Glatiramer acetate (Copaxone®)					£15,026
Dimethyl fumarate (Tecfidera®)					£19,057
Natalizumab (Tysabri®)					£534,047

SC IFNβ-1a 44 µg (Rebif®), SC IFNβ-1b 250 µg (Betaferon®/ Extavia®), IM IFNβ-1a 30 µg (Avonex®), and Fingolimod (Gilenya®) were all either dominated or extendedly dominated; the results for these treatments are therefore not shown.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Univariate sensitivity analysis

The results of univariate sensitivity analysis using the list price are shown in Table 94 and Table 95. The results of univariate sensitivity analysis using the PAS price are shown in Table 96 and Table 97.

Table 94: List price univariate sensitivity analysis results part 1

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-	-£12,267	0.222	**Dominant**	£35,250	0.221	£159,295	£30,337	0.222	£136,452	£29,639	0.279	£106,127
EDSS state costs	+ 20%	-£13,109	0.222	**Dominant**	£34,459	0.221	£155,721	£29,720	0.222	£133,674	£28,749	0.279	£102,942
	- 20%	-£11,426	0.222	**Dominant**	£36,041	0.221	£162,869	£30,955	0.222	£139,229	£30,528	0.279	£109,312
Relapse costs	+ 20%	-£12,062	0.222	**Dominant**	£35,126	0.221	£158,735	£29,974	0.222	£134,817	£29,525	0.279	£105,719
	- 20%	-£12,473	0.222	**Dominant**	£35,374	0.221	£159,855	£30,701	0.222	£138,086	£29,753	0.279	£106,536
Patient utilities	+ 20%	-£12,267	0.259	**Dominant**	£35,250	0.257	£137,279	£30,337	0.251	£121,046	£29,639	0.319	£92,875
	- 20%	-£12,267	0.183	**Dominant**	£35,250	0.183	£192,425	£30,337	0.191	£158,561	£29,639	0.237	£125,276
Natural history relapse rates	+ 20%	-£12,658	0.224	**Dominant**	£35,278	0.221	£159,511	£30,691	0.221	£139,040	£29,639	0.279	£106,128
	- 20%	-£12,539	0.224	**Dominant**	£35,391	0.221	£160,394	£30,780	0.220	£139,701	£29,766	0.279	£106,802
Dimethyl fumarate relapse rate†	+ 20%	-£11,448	0.219	**Dominant**	£36,070	0.218	£165,772	£31,157	0.219	£142,512	£30,458	0.276	£110,527
	- 20%	-£13,087	0.226	**Dominant**	£34,431	0.225	£153,030	£29,518	0.226	£130,590	£28,819	0.283	£101,842
Comparator relapse rate†	+ 20%	-£12,992	0.226	**Dominant**	£34,212	0.226	£151,391	£29,170	0.228	£128,162	£28,494	0.284	£100,175
	- 20%	-£11,542	0.219	**Dominant**	£36,289	0.217	£167,541	£31,504	0.217	£145,144	£30,783	0.274	£112,304
Dimethyl fumarate disability progression rate†	+ 20%	-£10,487	0.038	**Dominant**	£37,031	0.037	£998,178	£32,118	0.038	£842,130	£31,419	0.095	£330,435
	- 20%	-£14,112	0.417	**Dominant**	£33,406	0.415	£80,417	£28,493	0.416	£68,418	£27,794	0.473	£58,712
Comparator disability progression rate†	+ 20%	-£14,205	0.455	**Dominant**	£31,929	0.449	£71,180	£27,517	0.422	£65,247	£26,139	0.530	£49,314
	- 20%	-£10,250	-0.026	**Dominant**	£38,749	-0.021	Dominated	£33,292	0.011	£3,049,522	£33,339	0.010	£3,367,977
Dimethyl fumarate dropouts	+ 20%	-£17,921	0.178	**Dominant**	£29,597	0.177	£166,974	£24,684	0.178	£138,444	£23,985	0.235	£101,960
	- 20%	-£5,380	0.273	**Dominant**	£42,138	0.272	£154,921	£37,225	0.273	£136,337	£36,526	0.330	£110,692
Comparator dropouts	+ 20%	-£6,288	0.243	**Dominant**	£37,187	0.243	£153,174	£32,919	0.247	£133,415	£31,740	0.293	£108,205
	- 20%	-£19,346	0.199	**Dominant**	£32,934	0.197	£167,174	£27,183	0.195	£139,738	£27,190	0.264	£103,085

† Change applied to reduction in relapse rate relative to placebo (Table 50). Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 95: List price univariate sensitivity analysis results part 2

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-	£35,695	0.251	£142,283	£27,507	0.225	£122,105	-£14,965	-0.086	Negative
EDSS state costs	+ 20%	£34,866	0.251	£138,979	£26,785	0.225	£118,897	-£14,630	-0.086	Negative
	- 20%	£36,524	0.251	£145,587	£28,230	0.225	£125,313	-£15,300	-0.086	Negative
Relapse costs	+ 20%	£35,379	0.251	£141,025	£27,270	0.225	£121,052	-£14,639	-0.086	Negative
	- 20%	£36,010	0.251	£143,541	£27,744	0.225	£123,157	-£15,291	-0.086	Negative
Patient utilities	+ 20%	£35,695	0.289	£123,720	£27,507	0.258	£106,617	-£14,965	-0.102	Negative
	- 20%	£35,695	0.210	£169,929	£27,507	0.190	£144,892	-£14,965	-0.069	Negative
Natural history relapse rates	+ 20%	£35,955	0.250	£143,995	£27,687	0.224	£123,345	-£15,316	-0.085	Negative
	- 20%	£36,074	0.249	£144,786	£27,791	0.224	£124,068	-£15,365	-0.084	Negative
Dimethyl fumarate relapse rate†	+ 20%	£36,514	0.247	£147,730	£28,327	0.222	£127,844	-£14,145	-0.090	Negative
	- 20%	£34,875	0.255	£136,994	£26,688	0.229	£116,551	-£15,784	-0.082	Negative
Comparator relapse rate†	+ 20%	£34,755	0.255	£136,232	£26,594	0.229	£115,929	-£14,145	-0.090	£157,460
	- 20%	£36,635	0.247	£148,542	£28,420	0.221	£128,511	-£15,784	-0.082	£191,494
Dimethyl fumarate disability progression rate†	+ 20%	£37,475	0.067	£562,011	£29,288	0.041	£712,871	-£13,184	-0.270	Negative
	- 20%	£33,850	0.445	£76,069	£25,663	0.419	£61,190	-£16,809	0.108	**Dominant**
Comparator disability progression rate†	+ 20%	£33,109	0.422	£78,450	£25,022	0.403	£62,023	-£13,184	-0.270	£48,773
	- 20%	£38,394	0.070	£544,827	£30,103	0.037	£807,215	-£16,809	0.108	**Dominant**
Dimethyl fumarate dropouts	+ 20%	£30,041	0.207	£145,242	£21,854	0.181	£120,579	-£20,618	-0.130	Negative
	- 20%	£42,583	0.302	£141,198	£34,395	0.276	£124,627	-£8,077	-0.035	Negative
Comparator dropouts	+ 20%	£38,041	0.278	£136,626	£30,687	0.254	£120,927	-£8,036	-0.038	£210,640
	- 20%	£32,728	0.219	£149,726	£23,534	0.192	£122,493	-£23,320	-0.141	£165,465

† Change applied to reduction in relapse rate relative to placebo (Table 50).

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 96: PAS price Univariate sensitivity analysis results part 1 *(Commercial in confidence information removed)*

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-			**Dominant**			£19,057			**Dominant**			**Dominant**
EDSS state costs	+ 20%			**Dominant**			£15,482			**Dominant**			**Dominant**
	- 20%			**Dominant**			£22,631			**Dominant**			**Dominant**
Relapse costs	+ 20%			**Dominant**			£18,497			**Dominant**			**Dominant**
	- 20%			**Dominant**			£19,616			**Dominant**			**Dominant**
Patient utilities	+ 20%			**Dominant**			£16,423			**Dominant**			**Dominant**
	- 20%			**Dominant**			£23,020			**Dominant**			**Dominant**
Natural history relapse rates	+ 20%			**Dominant**			£19,193			**Dominant**			**Dominant**
	- 20%			**Dominant**			£19,751			**Dominant**			**Dominant**
Dimethyl fumarate relapse rate†	+ 20%			**Dominant**			£23,148			£566			**Dominant**
	- 20%			**Dominant**			£15,100			**Dominant**			**Dominant**
Comparator relapse rate†	+ 20%			**Dominant**			£14,065			**Dominant**			**Dominant**
	- 20%			**Dominant**			£24,265			£2,171			**Dominant**
Dimethyl fumarate disability progression rate†	+ 20%			**Dominant**			£181,145			£47,385			£11,659
	- 20%			**Dominant**			£3,876			**Dominant**			**Dominant**
Comparator disability progression rate†	+ 20%			**Dominant**			£1,997			**Dominant**			**Dominant**
	- 20%			£1,612,298			Dominated			£206,886			£232,917
Dimethyl fumarate dropouts	+ 20%			**Dominant**			£9,160			**Dominant**			**Dominant**
	- 20%			**Dominant**			£27,226			£9,128			£5,436
Comparator dropouts	+ 20%			**Dominant**			£25,346			£7,642			£2,409
	- 20%			**Dominant**			£9,646			**Dominant**			**Dominant**

† Change applied to reduction in relapse rate relative to placebo (Table 50).

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 97: Univariate sensitivity analysis results part 2 (PAS price) ***(Commercial in confidence information removed)***

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
Baseline results	-			**£18,581**			**Dominant**			**£534,047**
EDSS state costs	+ 20%			£15,277			**Dominant**			Negative
	- 20%			£21,886			**Dominant**			Negative
Relapse costs	+ 20%			£17,324			**Dominant**			Negative
	- 20%			£19,839			**Dominant**			Negative
Patient utilities	+ 20%			£16,157			**Dominant**			Negative
	- 20%			£22,192			**Dominant**			Negative
Natural history relapse rates	+ 20%			£19,711			**Dominant**			Negative
	- 20%			£20,233			**Dominant**			Negative
Dimethyl fumarate relapse rate†	+ 20%			£22,176			**Dominant**			Negative
	- 20%			£15,092			**Dominant**			Negative
Comparator relapse rate†	+ 20%			£14,589			**Dominant**			
	- 20%			£22,711			**Dominant**			
Dimethyl fumarate disability progression rate†	+ 20%			£107,448			**Dominant**			Negative
	- 20%			£4,617			**Dominant**			Dominant
Comparator disability progression rate†	+ 20%			£4,919			**Dominant**			
	- 20%			£104,456			**Dominant**			
Dimethyl fumarate dropouts	+ 20%			£9,999			**Dominant**			Negative
	- 20%			£26,029			**Dominant**			Negative
Comparator dropouts	+ 20%			£25,170			**Dominant**			
	- 20%			£7,752			**Dominant**			

† Change applied to reduction in relapse rate relative to placebo (Table 50).

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Two-way sensitivity analysis

The results of the two-way sensitivity analysis (PAS price) are shown in Table 98.

Table 98: Two-way sensitivity analysis results *(Commercial in confidence information removed)*

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
vs fingolimod	**Base case**				-£12,267	0.222	**Dominant**			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.360	-£12,161	0.222	**Dominant**			**Dominant**
		Upper confidence interval	0.620	0.500	-£11,974	0.221	**Dominant**			**Dominant**
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.630	-£12,505	0.208	**Dominant**			**Dominant**
		Upper confidence interval	0.890	1.040	-£11,604	0.200	**Dominant**			**Dominant**
	Drop outs	+ 20%	0.151	12.82%	-£11,941	0.199	**Dominant**			**Dominant**
		- 20%	10.04%	8.54%	-£12,459	0.250	**Dominant**			**Dominant**
vs GA	**Base case**				£35,250	0.221	£159,295			£19,057
	Treatment effect on relapse rate	Lower confidence interval	0.45	0.69	£35,111	0.222	£158,216			£18,375
		Upper confidence interval	0.62	0.88	£35,387	0.221	£160,360			£19,729
	Treatment effect on disability progression rate	Lower confidence interval	0.47	0.49	£37,596	0.147	£255,760			£37,695
		Upper confidence interval	0.89	1.16	£32,498	0.290	£111,991			£9,795
	Drop outs	+ 20%	15.10%	15.80%	£31,533	0.199	£158,667			£17,913
		- 20%	10.00%	10.50%	£39,821	0.248	£160,759			£20,542
vs IM IFNβ-1a 30 µg	**Base case**				£30,337	0.222	£136,452			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.690	£30,392	0.222	£136,850			**Dominant**
		Upper confidence interval	0.620	0.880	£30,285	0.223	£136,072			**Dominant**

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.490	£33,051	0.110	£300,127			£9,046
		Upper confidence interval	0.890	1.160	£26,274	0.395	£66,446			**Dominant**
	Drop outs	+ 20%	0.151	0.158	£27,265	0.203	£134,508			**Dominant**
		- 20%	10.04%	10.50%	£34,071	0.245	£138,930			**Dominant**
vs SC IFNβ-1b 250 µg	**Base case**				£29,639	0.279	£106,127			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.600	£29,618	0.279	£106,017			**Dominant**
		Upper confidence interval	0.620	0.760	£29,566	0.280	£105,742			**Dominant**
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.550	£33,510	0.075	£444,510			£19,293
		Upper confidence interval	0.890	1.260	£24,311	0.548	£44,348			**Dominant**
	Drop outs	+ 20%	0.151	10.73%	£26,086	0.249	£104,640			**Dominant**
		- 20%	10.04%	7.15%	£34,078	0.314	£108,365			**Dominant**
vs SC IFNβ-1a 22 µg	**Base case**				£35,695	0.251	£142,283			£18,581
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.620	£35,076	0.254	£138,277			£18,728
		Upper confidence interval	0.620	0.830	£36,391	0.248	£146,898			£18,487
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.490	£33,231	0.511	£65,029			£31,515
		Upper confidence interval	0.890	1.160	£39,115	-0.100	Dominated			£7,908
	Drop outs	+ 20%	0.151	0.211	£32,388	0.234	£138,174			£18,834
		- 20%	10.04%	14.08%	£39,615	0.269	£147,110			£18,132

Comparison	Analysis	Change	Dimethyl fumarate	Comparator	List price			PAS price		
					Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
vs SC IFNβ-1a 44 µg	**Base case**				£27,507	0.225	£122,105			**Dominant**
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.600	£27,366	0.226	£121,132			**Dominant**
		Upper confidence interval	0.620	0.740	£27,726	0.224	£123,619			**Dominant**
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.480	£29,705	0.146	£203,088			**Dominant**
		Upper confidence interval	0.890	1.150	£24,338	0.343	£71,024			**Dominant**
	Drop outs	+ 20%	15.06%	19.39%	£25,033	0.210	£119,361			**Dominant**
		- 20%	10.04%	12.93%	£30,421	0.243	£125,278			**Dominant**
vs natalizumab	**Base case**				-£14,965	-0.086	£173,745			£534,047
	Treatment effect on relapse rate	Lower confidence interval	0.450	0.290	-£15,178	-0.085	£178,202			£542,568
		Upper confidence interval	0.620	0.400	-£14,756	-0.087	£169,465			£525,864
	Treatment effect on disability progression rate	Lower confidence interval	0.470	0.430	-£15,479	-0.103	£150,150			£461,103
		Upper confidence interval	0.890	0.840	-£14,203	-0.075	£188,462			£581,969
	Drop outs	+ 20%	15.06%	13.56%	-£13,690	-0.082	£166,569			£506,925
		- 20%	10.04%	9.04%	-£16,432	-0.090	£182,118			£567,056

Abbreviations: ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; SC, subcutaneous; QALY, quality adjusted life year.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

List price

Probabilistic sensitivity analysis using the list price produced the incremental cost and QALY ranges shown in Table 100. The cost-effectiveness planes for the probabilistic sensitivity analyses of dimethyl fumarate, versus each comparator, are shown in Figure 39 and Figure 40. From these results cost-effectiveness acceptability curves were generated (Figure 41 and Figure 42).

Table 99: Incremental cost and QALY range from PSA (list price) *(Commercial in confidence information removed)*

Comparison	Incremental cost range			Incremental QALY range		
Dimethyl fumarate vs fingolimod		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs GA		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs IM IFNβ-1a 30 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs SC IFNβ-1b 250 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs SC IFNβ-1a 22 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs SC		**Mean**	**SD**		**Mean**	**SD**

Comparison	Incremental cost range			Incremental QALY range		
IFNβ-1a 44 µg	**Absolute**	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs natalizumab		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**

Abbreviations: CI, confidence interval; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SD, standard deviation.

Figure 35: List price cost-effectiveness planes: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®)

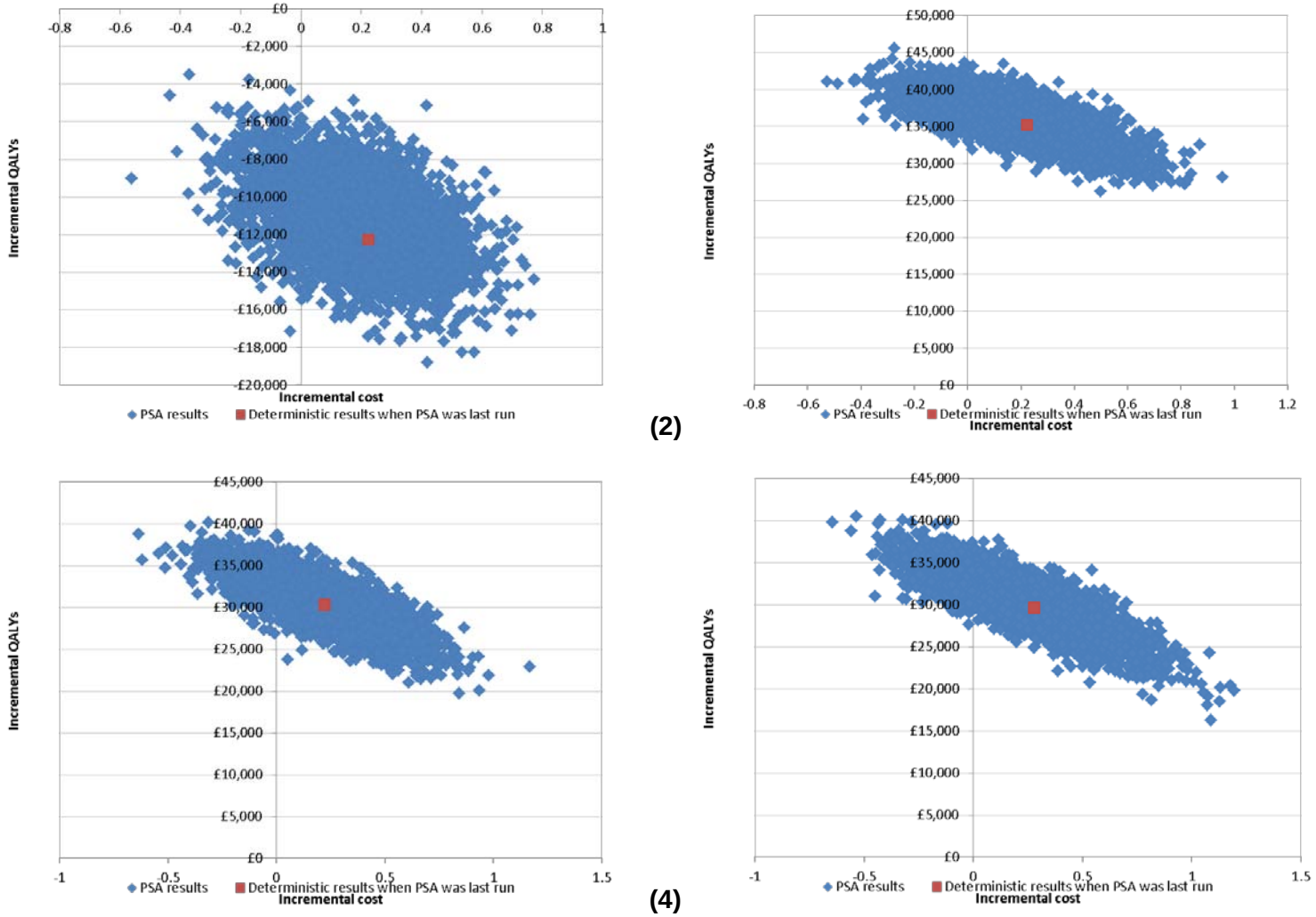
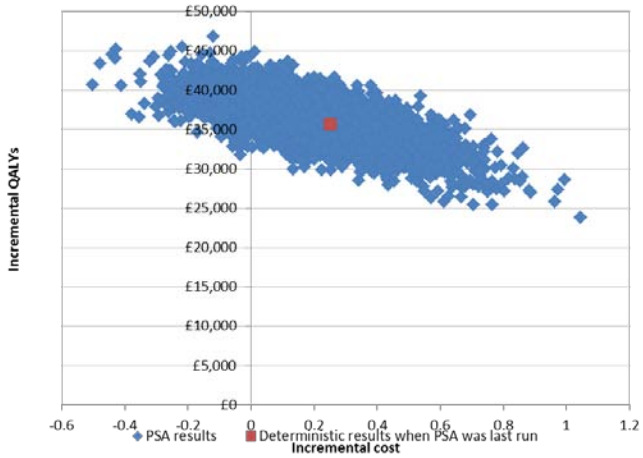
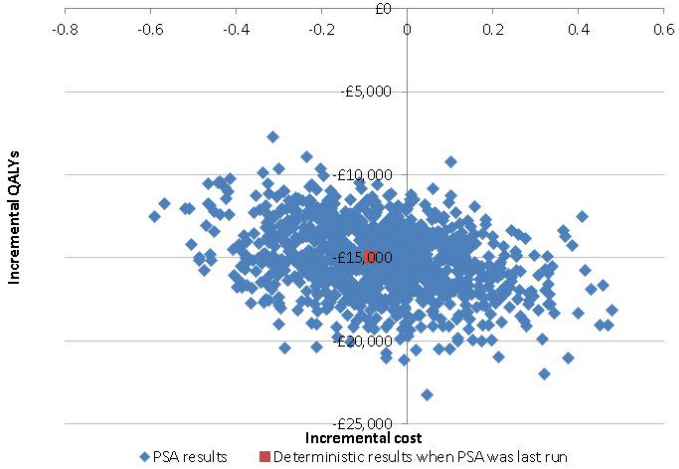


Figure 36: List price cost-effectiveness planes: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



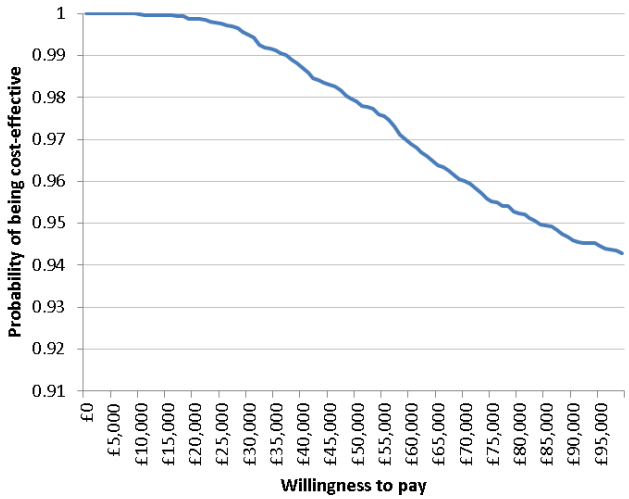
(1)

(2)

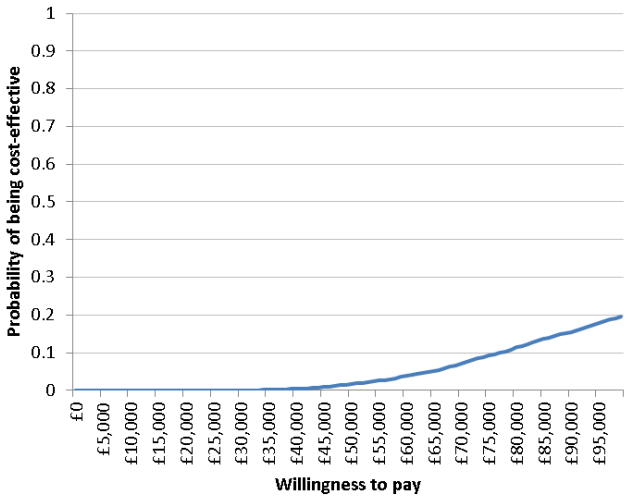


(3)

Figure 37: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®)



(1)



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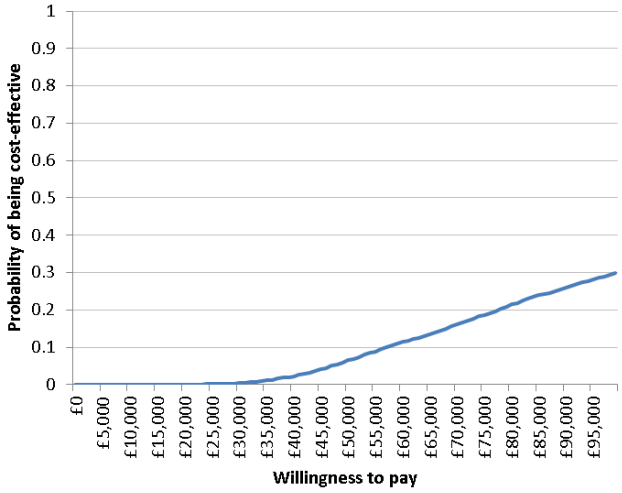

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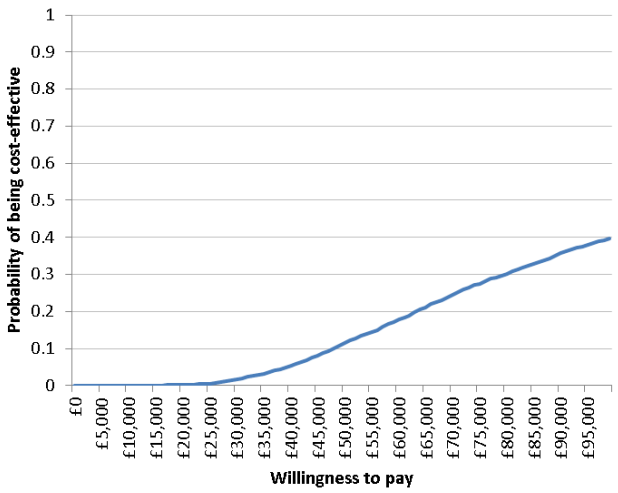
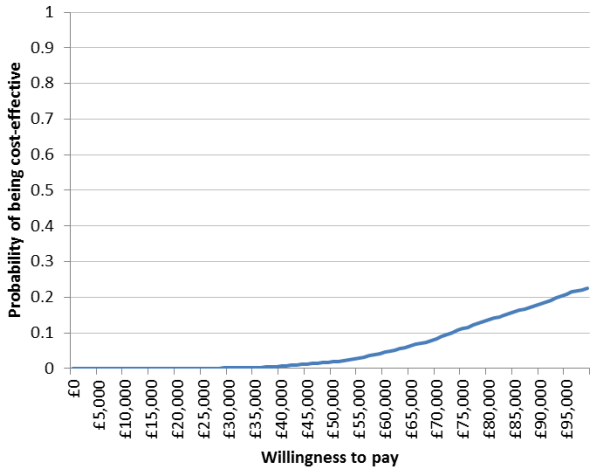
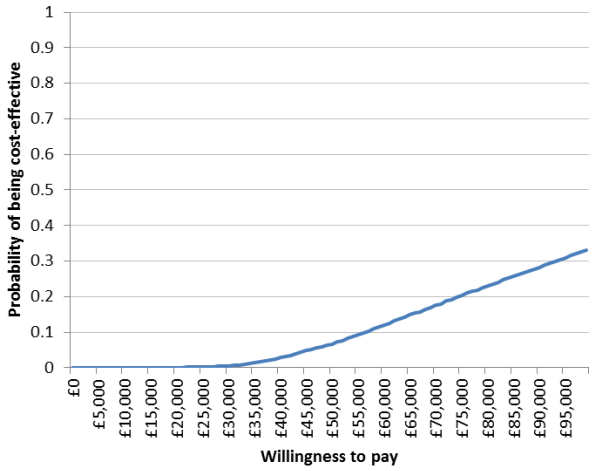


(4)

Figure 38: List price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



(1)



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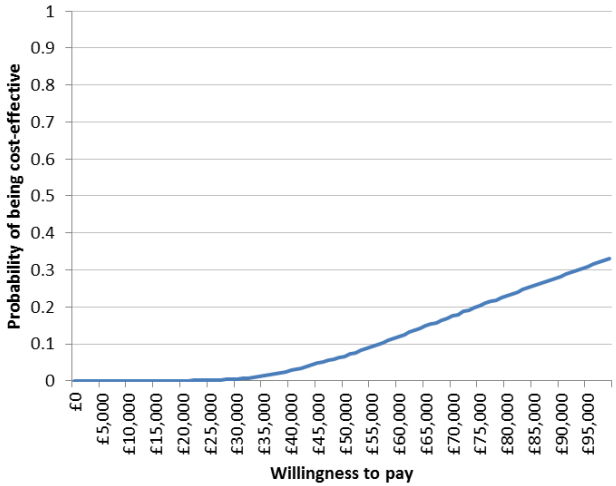


(3)

PAS price

Probabilistic sensitivity analysis using the PAS price produced the incremental cost and QALY ranges shown in Table 100. The cost-effectiveness planes for the probabilistic sensitivity analyses of dimethyl fumarate, versus each comparator, are shown in Figure 39 and Figure 40. From these results cost-effectiveness acceptability curves were generated (Figure 41 and Figure 42), demonstrating that the probability of dimethyl fumarate being cost-effective at £20,000/QALY is ≥70% for all comparators, with the exception of glatiramer acetate.

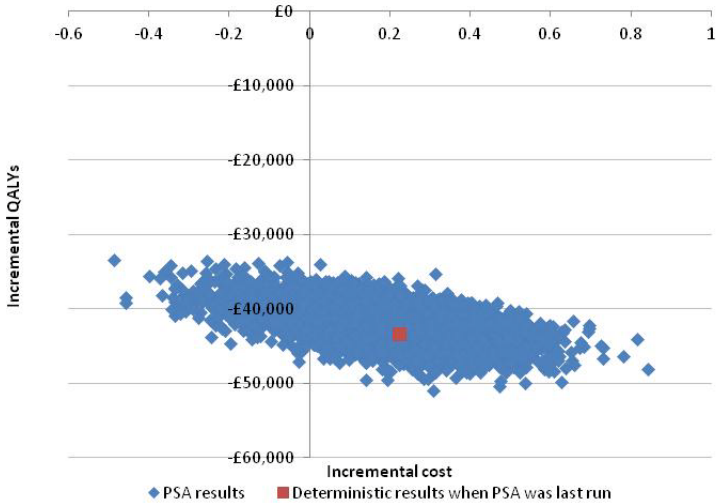
Table 100: Incremental cost and QALY range from PSA (PAS price) *(Commercial in confidence information removed)*

Comparison	Incremental cost range			Incremental QALY range		
Dimethyl fumarate vs fingolimod		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs GA		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs IM IFNβ-1a 30 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs SC IFNβ-1b 250 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs SC IFNβ-1a 22 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs SC IFNβ-1a 44 µg		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**

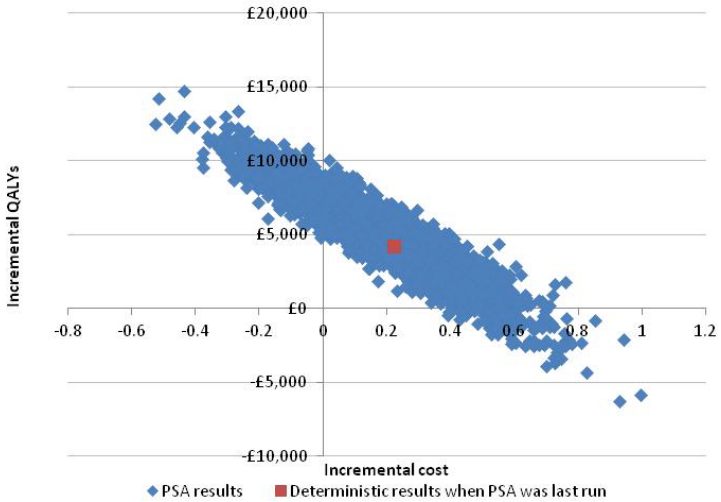
Comparison	Incremental cost range			Incremental QALY range		
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**
Dimethyl fumarate vs natalizumab		**Mean**	**SD**		**Mean**	**SD**
	Absolute	**Min**	**Max**	**Absolute**	**Min**	**Max**
	95% CI	**Lower**	**Upper**	**95% CI**	**Lower**	**Upper**

Abbreviations: CI, confidence interval; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SD, standard deviation.

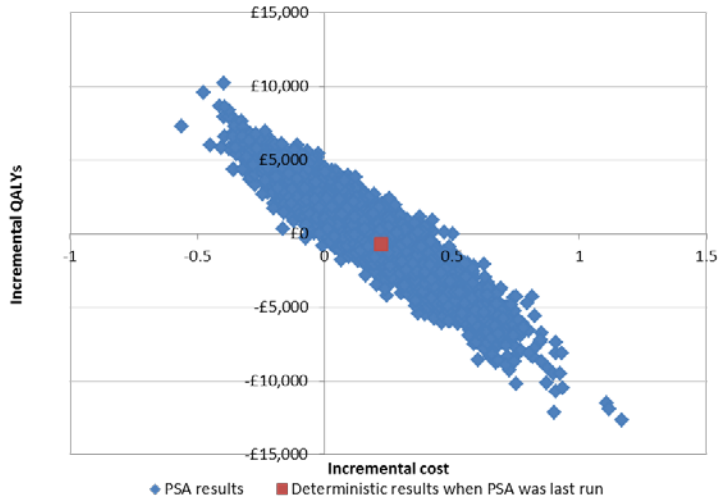
Figure 39: PAS price cost-effectiveness planes: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®)



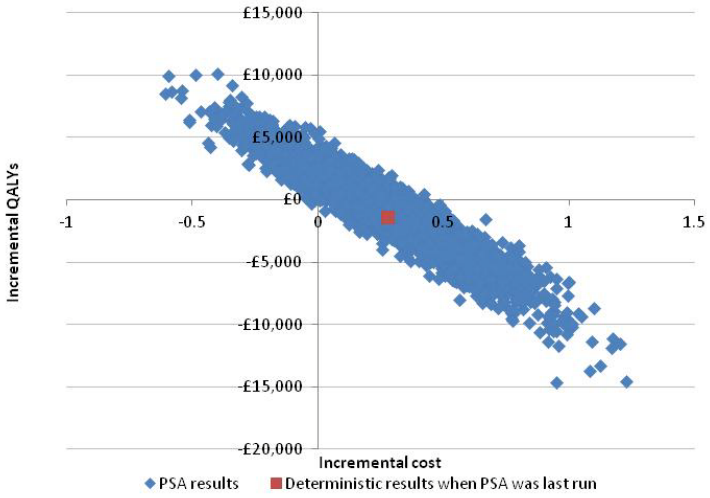
(1)



(2)

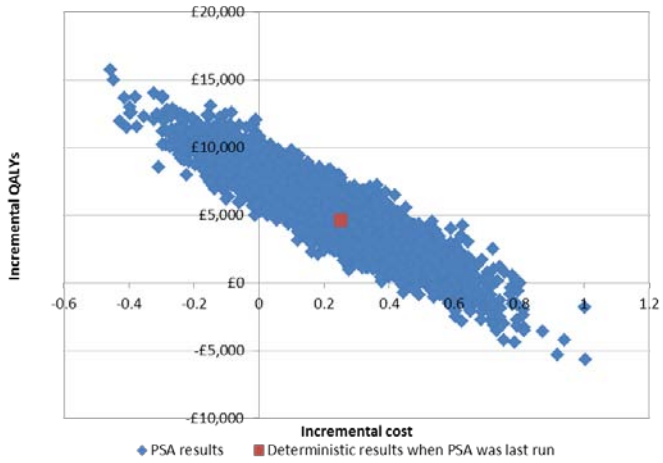


(3)

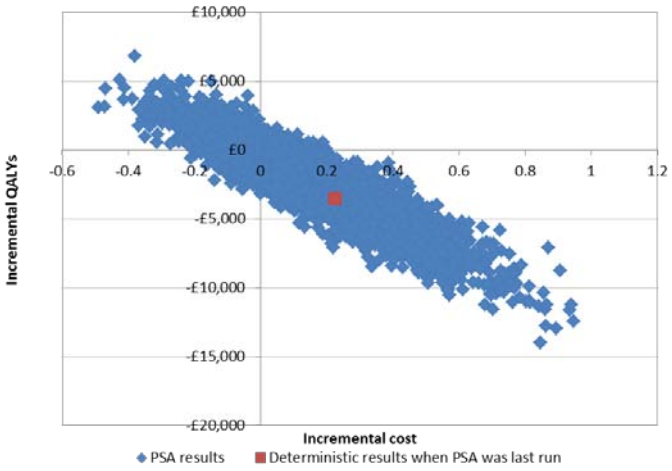


(4)

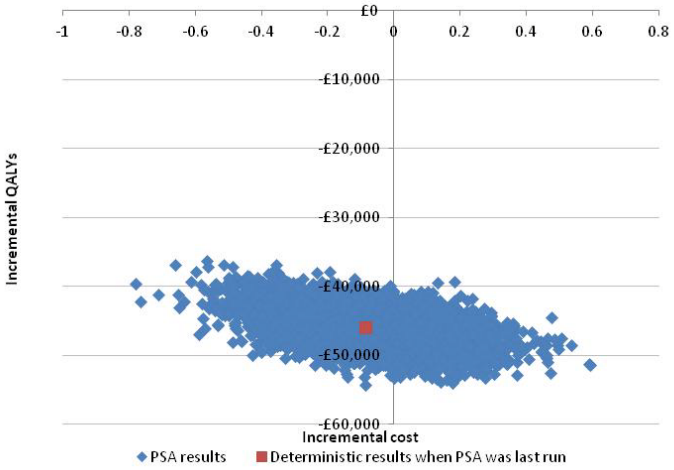
Figure 40: PAS price cost-effectiveness planes: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



(1)

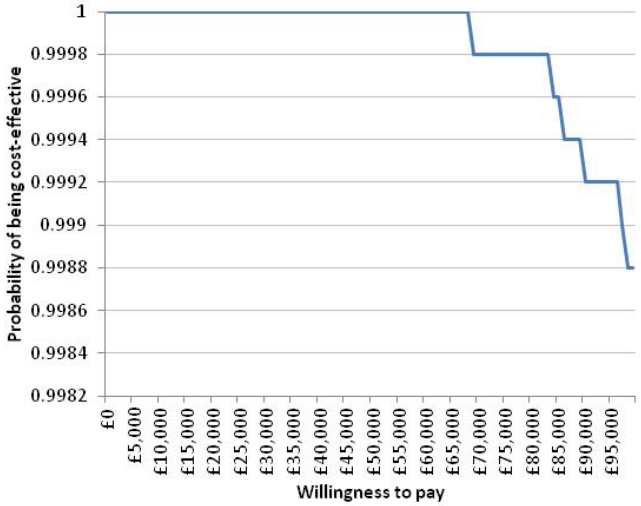


(2)

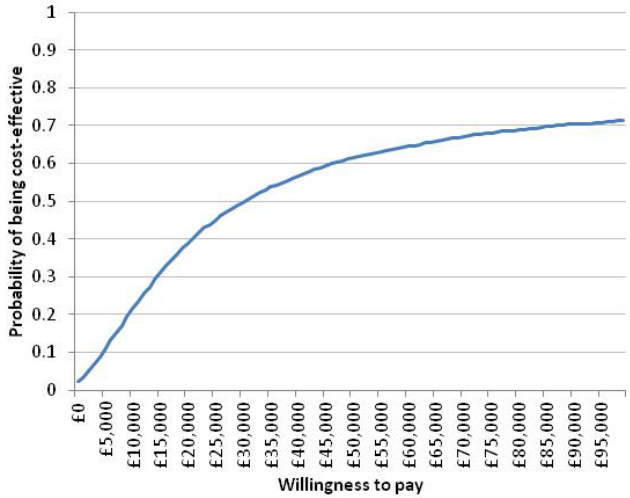


(3)

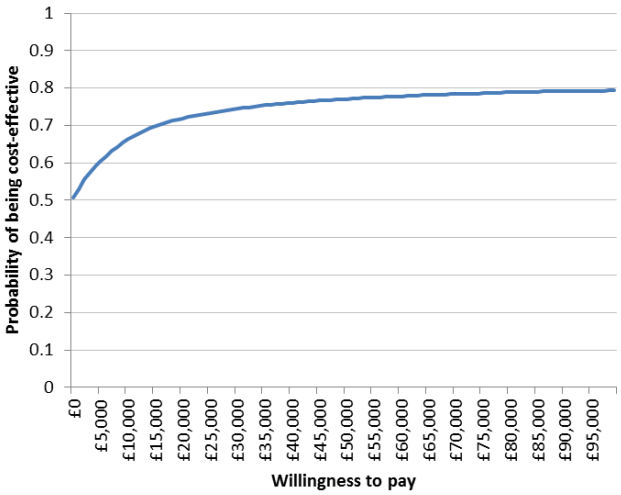
Figure 41: PAS price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) fingolimod, (2) glatiramer acetate, (3) IM IFNβ-1a 30 µg (Avonex®), and (4) SC IFNβ-1b 250 µg (Betaferon®/Extavia®)



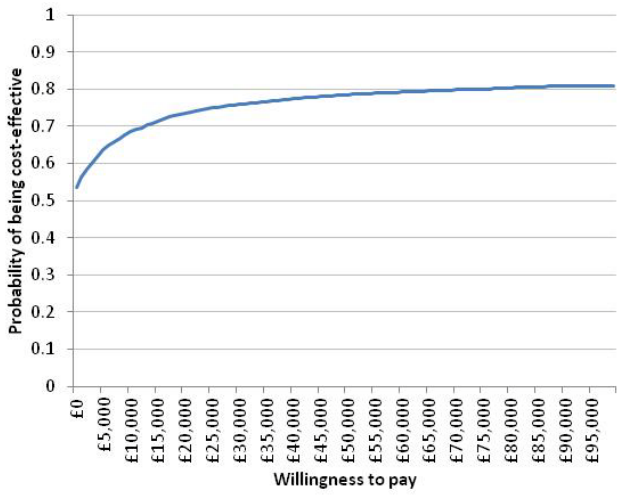
(1)



(2)

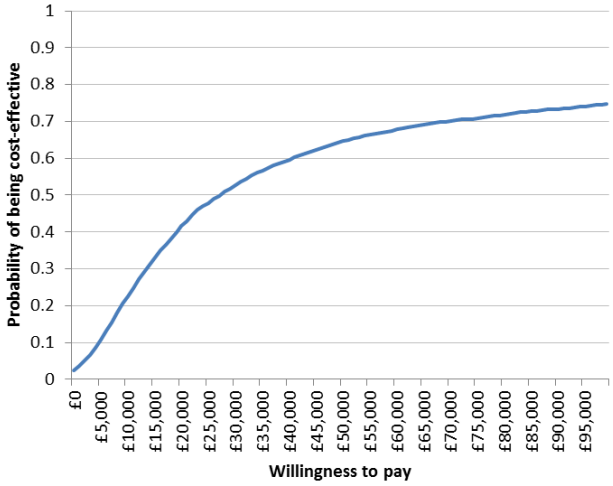


(3)

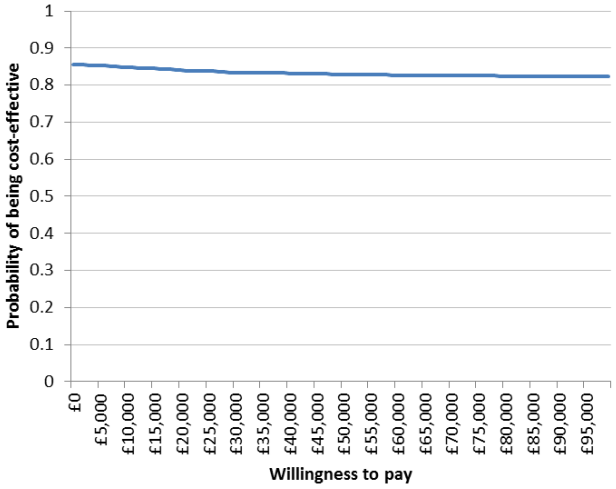


(4)

Figure 42: PAS price cost-effectiveness acceptability curves: dimethyl fumarate vs (1) SC IFNβ-1a 22 µg (Rebif® 22 µg), (2) SC IFNβ-1a 44 µg (Rebif® 44 µg), and (3) natalizumab



(1)



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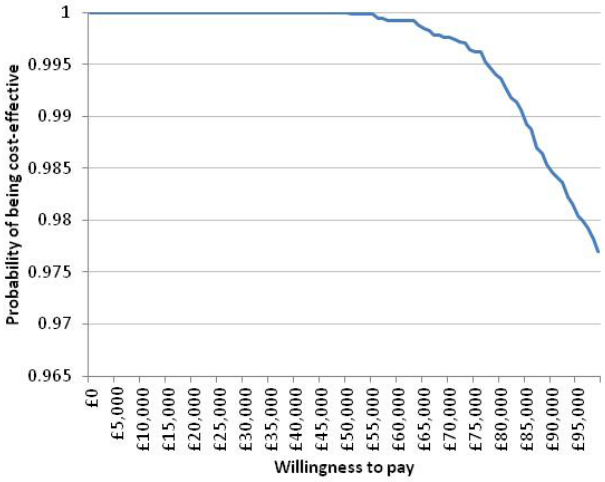


(3)

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the scenario analyses in which the price of fingolimod was varied are provided in Table 101. The results of the other scenario analyses using the list price are shown in Table 102 and Table 103. The results of the scenario analyses using the PAS price are shown in Table 104 and Table 105.

Table 101: Results of fingolimod simulated PAS price scenario analysis

Fingolimod price reduction	Annual fingolimod cost	List price			PAS price		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
-5%	£18,217	-£8,593	0.222	**Dominant**	-£39,626	0.222	**Dominant**
-10%	£17,258	-£4,919	0.222	**Dominant**	-£35,952	0.222	**Dominant**
-15%	£16,300	-£1,245	0.222	**Dominant**	-£32,278	0.222	**Dominant**
-20%	£15,341	£2,429	0.222	£10,921	-£28,604	0.222	**Dominant**
-25%	£14,382	£6,104	0.222	£27,436	-£24,930	0.222	**Dominant**
-30%	£13,423	£9,778	0.222	£43,952	-£21,256	0.222	**Dominant**
-35%	£12,464	£13,452	0.222	£60,468	-£17,581	0.222	**Dominant**
-40%	£11,506	£17,126	0.222	£76,984	-£13,907	0.222	**Dominant**
-45%	£10,547	£20,800	0.222	£93,499	-£10,233	0.222	**Dominant**
-50%	£9,588	£24,474	0.222	£110,015	-£6,559	0.222	**Dominant**
-55%	£8,629	£28,149	0.222	£126,531	-£2,885	0.222	**Dominant**
-60%	£7,670	£31,823	0.222	£143,047	£789	0.222	£3,549
-65%	£6,712	£35,497	0.222	£159,562	£4,464	0.222	£20,065
-70%	£5,753	£39,171	0.222	£176,078	£8,138	0.222	£36,580
-75%	£4,794	£42,845	0.222	£192,594	£11,812	0.222	£53,096
-80%	£3,835	£46,519	0.222	£209,110	£15,486	0.222	£69,612
-85%	£2,876	£50,194	0.222	£225,626	£19,160	0.222	£86,128
-90%	£1,918	£53,868	0.222	£242,141	£22,834	0.222	£102,643
-95%	£959	£57,542	0.222	£258,657	£26,509	0.222	£119,159

Abbreviations: ICER, incremental cost effectiveness ratio; Incr., incremental; QALY, quality adjusted life year.

Table 102: Results of scenario analysis part 1 (list price)

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)	-	-£12,654	0.285	**Dominant**	£34,948	0.283	£123,369	£29,709	0.280	£106,185	£29,320	0.343	£85,408
Discount rate costs and benefits	0%	-£16,566	0.358	**Dominant**	£39,492	0.350	£112,695	£34,558	0.333	£103,655	£32,321	0.428	£75,458
Discount rate costs and benefits	6%	-£10,252	0.166	**Dominant**	£32,607	0.167	£195,243	£27,807	0.175	£159,053	£27,769	0.216	£128,767
Discount rate costs Discount rate benefits	0% 6%	-£16,566	0.166	**Dominant**	£39,492	0.167	£236,472	£34,558	0.175	£197,672	£32,321	0.216	£149,874
Discount rate costs Discount rate benefits	6% 0%	-£10,252	0.358	**Dominant**	£32,607	0.350	£93,047	£27,807	0.333	£83,404	£27,769	0.428	£64,831
Discount rate costs and benefits	1.5%	-£14,451	0.289	**Dominant**	£37,598	0.285	£131,982	£32,645	0.277	£117,745	£31,181	0.353	£88,340
Discount rate costs Discount rate benefits	1.5% 3.5%	-£14,451	0.222	**Dominant**	£37,598	0.221	£169,905	£32,645	0.222	£146,832	£31,181	0.279	£111,651
Discount rate costs Discount rate benefits	3.5% 1.5%	-£12,267	0.289	**Dominant**	£35,250	0.285	£123,739	£30,337	0.277	£109,421	£29,639	0.353	£83,969
No caregiver utility	-	-£12,267	0.200	**Dominant**	£35,250	0.200	£176,248	£30,337	0.206	£147,453	£29,639	0.255	£116,090
Time horizon	1 year	-£1,683	0.002	**Dominant**	£9,577	0.005	£1,753,786	£7,292	0.017	£436,425	£8,506	0.012	£682,007
	5 year	-£5,562	0.038	**Dominant**	£28,295	0.045	£628,863	£23,144	0.071	£324,373	£25,318	0.072	£349,525

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
	10 year	-£8,647	0.095	**Dominant**	£34,866	0.101	£346,795	£29,399	0.123	£239,678	£30,424	0.142	£213,540
	20 year	-£11,594	0.185	**Dominant**	£35,605	0.185	£191,994	£30,578	0.193	£158,724	£30,140	0.240	£125,521
	50 year	-£12,176	0.232	**Dominant**	£35,357	0.231	£153,355	£30,421	0.230	£132,086	£29,751	0.289	£102,954
Mortality	General population	-£12,814	0.231	**Dominant**	£34,859	0.229	£152,171	£30,044	0.229	£131,460	£29,168	0.288	£101,238
Annualised relapse rate relative to placebo	Lower 95% CI	-£12,886	0.225	**Dominant**	£34,632	0.224	£154,548	£29,719	0.225	£132,010	£29,020	0.282	£102,883
	Upper 95% CI	-£11,571	0.219	**Dominant**	£35,946	0.218	£164,781	£31,033	0.219	£141,584	£30,335	0.276	£109,856
Disability progression rate relative to placebo	Lower 95% CI	-£14,731	0.483	**Dominant**	£32,786	0.481	£68,102	£27,873	0.482	£57,772	£27,175	0.539	£50,378
	Upper 95% CI	-£8,847	-0.129	£68,676	£38,671	-0.130	Dominated	£33,758	-0.129	Dominated	£33,059	-0.072	Dominated
London Ontario transition matrix for RRMS-RRMS transitions		-£11,372	0.194	**Dominant**	£32,448	0.194	£167,343	£27,655	0.196	£141,234	£27,484	0.247	£111,085

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 103: Results of scenario analysis part 2 (list price)

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)	-	£34,730	0.336	£103,511	£26,733	0.299	£89,457	-£14,519	-0.128	£113,515
Discount rate costs and benefits	0%	£40,913	0.395	£103,576	£31,582	0.352	£89,717	-£17,893	-0.144	£124,313
Discount rate costs and benefits	6%	£32,575	0.191	£170,861	£25,068	0.172	£145,610	-£13,329	-0.063	£213,065
Discount rate costs Discount rate benefits	0% 6%	£40,913	0.191	£214,594	£31,582	0.172	£183,452	-£17,893	-0.063	£286,020
Discount rate costs Discount rate benefits	6% 0%	£32,575	0.395	£82,468	£25,068	0.352	£71,211	-£13,329	-0.144	£92,604
Discount rate costs and benefits	1.5%	£38,547	0.322	£119,821	£29,736	0.288	£103,389	-£16,532	-0.114	£144,567
Discount rate costs Discount rate benefits	1.5% 3.5%	£38,547	0.251	£153,651	£29,736	0.225	£131,998	-£16,532	-0.086	£191,941
Discount rate costs Discount rate benefits	3.5% 1.5%	£35,695	0.322	£110,956	£27,507	0.288	£95,640	-£14,965	-0.114	£130,863
No caregiver utility	-	£35,695	0.229	£156,124	£27,507	0.206	£133,603	-£14,965	-0.077	£193,887
Time horizon	1 year	£7,882	0.012	£684,710	£5,879	0.011	£515,487	-£2,027	-0.001	£3,368,565
	5 year	£26,335	0.059	£445,295	£20,039	0.056	£355,974	-£9,549	-0.011	£849,040
	10 year	£34,377	0.117	£293,292	£26,452	0.108	£244,106	-£13,614	-0.031	£437,433
	20 year	£36,043	0.209	£172,244	£27,805	0.189	£147,127	-£15,012	-0.068	£220,547
	50 year	£35,803	0.262	£136,423	£27,602	0.235	£117,268	-£15,016	-0.092	£164,082
Mortality	General population	£35,294	0.259	£136,183	£27,152	0.233	£116,775	-£14,816	-0.089	£165,664
Annualised relapse rate relative to placebo	Lower 95% CI	£35,076	0.254	£138,277	£26,889	0.228	£117,896	-£15,583	-0.083	£186,994
	Upper 95% CI	£36,391	0.248	£146,898	£28,203	0.222	£126,966	-£14,269	-0.089	£159,832
Disability progression rate relative to	Lower 95% CI	£33,231	0.511	£65,029	£25,043	0.485	£51,591	-£17,429	0.174	

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
placebo	Upper 95% CI	£39,115	-0.100	Dominated	£30,928	-0.126	Dominated	-£11,545	-0.437	£26,393
London Ontario transition matrix for RRMS-RRMS transitions		£32,253	0.216	£148,986	£24,669	0.195	£126,608	-£13,016	-0.072	£181,019

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 104: Results of scenario analysis part 1 (PAS price) ***(Commercial in confidence information removed)***

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)	-			**Dominant**			£11,711			**Dominant**			**Dominant**
Discount rate costs and benefits	0%			**Dominant**			£9,007			**Dominant**			**Dominant**
Discount rate costs and benefits	6%			**Dominant**			£26,985			**Dominant**			**Dominant**
Discount rate costs Discount rate benefits	0% 6%			**Dominant**			£18,900			**Dominant**			**Dominant**
Discount rate costs Discount rate benefits	6% 0%			**Dominant**			£12,860			**Dominant**			**Dominant**
Discount rate costs and benefits	1.5%			**Dominant**			£13,129			**Dominant**			**Dominant**
Discount rate costs Discount rate benefits	1.5% 3.5%			**Dominant**			£16,901			**Dominant**			**Dominant**
Discount rate	3.5%			**Dominant**			£14,803			**Dominant**			**Dominant**

Variable	Change	Fingolimod			Glatiramer acetate			IM IFNβ-1a 30 µg			SC IFNβ-1b 250 µg		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
costs Discount rate benefits	1.5%												
No caregiver utility	-			**Dominant**			£21,085			**Dominant**			**Dominant**
Time horizon	1 year			**Dominant**			£420,018			**Dominant**			£97,977
	5 year			**Dominant**			£125,471			£512			£36,833
	10 year			**Dominant**			£60,578			£6,925			£11,568
	20 year			**Dominant**			£25,454			£5,078			**Dominant**
	50 year			**Dominant**			£18,711			**Dominant**			**Dominant**
Mortality	General population			**Dominant**			£16,371			**Dominant**			**Dominant**
Annualised relapse rate relative to placebo	Lower 95% CI			**Dominant**			£16,059			**Dominant**			**Dominant**
	Upper 95% CI			**Dominant**			£22,521			**Dominant**			**Dominant**
Disability progression rate relative to placebo	Lower 95% CI			**Dominant**			£1,518			**Dominant**			**Dominant**
	Upper 95% CI			£298,886			Dominated			**Dominant**			Dominated
London Ontario transition matrix for RRMS-RRMS transitions				**Dominant**			£19,681			**Dominant**			**Dominant**

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; IM, intramuscular; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

Table 105: Results of scenario analysis part 2 (PAS price) ***(Commercial in confidence information removed)***

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
No waning effect (all set to 100%)	-			£9,240			**Dominant**			£360,812
Discount rate costs and benefits	0%			£11,587			**Dominant**			£376,755
Discount rate costs and benefits	6%			£23,471			**Dominant**			£662,237
Discount rate costs Discount rate benefits	0% 6%			£24,007			**Dominant**			£866,841
Discount rate costs Discount rate benefits	6% 0%			£11,329			**Dominant**			£287,828
Discount rate costs and benefits	1.5%			£14,574			**Dominant**			£440,647
Discount rate costs Discount rate benefits	1.5% 3.5%			£18,689			**Dominant**			£585,043
Discount rate costs Discount rate benefits	3.5% 1.5%			£14,490			**Dominant**			£402,237
No caregiver utility	-			£20,389			**Dominant**			£360,812
Time horizon	1 year			£52,005			**Dominant**			£15,470,104
	5 year			£62,316			**Dominant**			£2,862,982
	10 year			£47,790			**Dominant**			£1,362,010
	20 year			£24,648			**Dominant**			£674,282
	50 year			£18,136			**Dominant**			£503,289
Mortality	General population			£16,150			**Dominant**			£513,509
Annualised relapse rate relative to placebo	Lower 95% CI			£15,938			**Dominant**			£559,380
	Upper 95% CI			£21,626			**Dominant**			£507,444
Disability progression rate relative to placebo	Lower 95% CI			£2,300			**Dominant**			**Dominant**
	Upper			Dominated			**Dominant**			£94,190

Variable	Change	SC IFNβ-1a 22 µg			SC IFNβ-1a 44 µg			Natalizumab		
		Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER	Incr. cost	Incr. QALY	ICER
	95% CI									
London Ontario transition matrix for RRMS-RRMS transitions				£16,727			**Dominant**			£579,201

Abbreviations: EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; IFN, interferon; Incr, incremental cost; QALYs, quality adjusted life years; SC, subcutaneous.

7.7.10 What were the main findings of each of the sensitivity analyses?

The results from univariate and two-way sensitivity analysis using the PAS price were generally consistent with those from the base case, demonstrating the robustness of the ICERs. Dimethyl fumarate was dominant in the majority of comparisons, with very few resulting in an ICER above £20,000/QALY.

The scenario analyses indicate that the model is robust to the majority of structural assumptions made, with very few analyses resulting in an ICER ≥£0. When time horizons of 1–10 years were considered the ICER first increased, then decreased, which may appear to be an erroneous result. However, this is a result of a larger accumulation of drug costs and discounting in the early period, compared with drug benefits, which become more apparent at later time points.

7.7.11 Key drivers of the cost-effectiveness results

Univariate sensitivity analysis demonstrates that the model results are robust, with very few changes resulting in an ICER ≥ £0 per QALY (from dominance in the basecase). The model is most sensitive to changes in the effect of treatment on the disability progression rate; ICERs increased most when the effect of dimethyl fumarate was reduced by 20%, or the effect of the comparator was increased by 20%

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

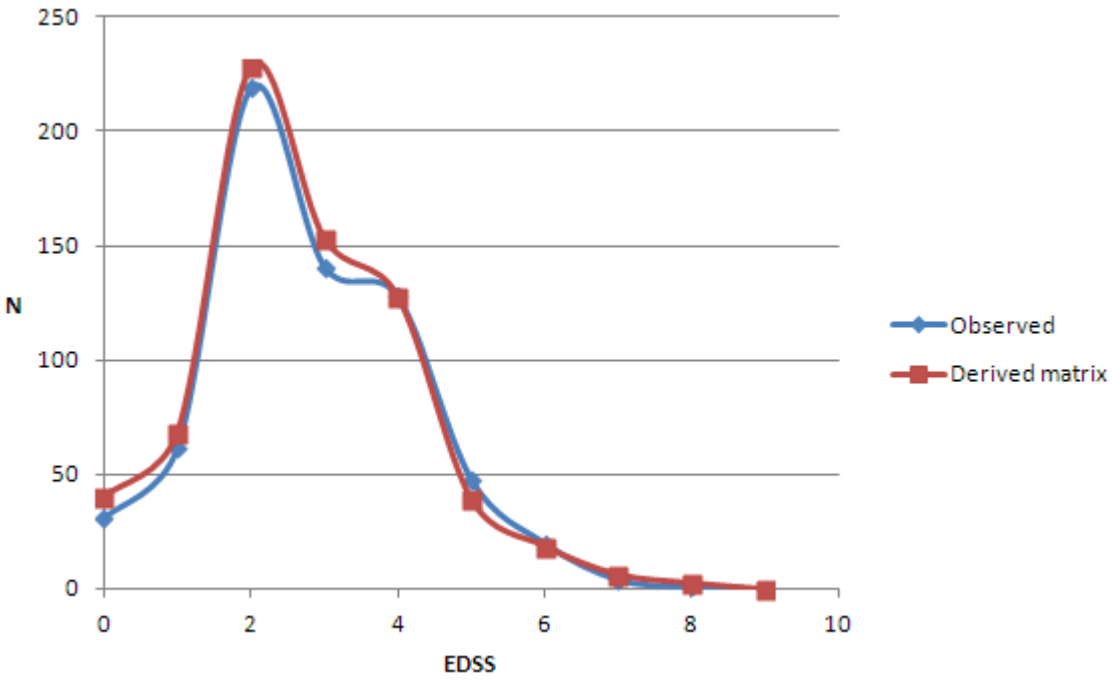
The model was validated by comparing key inputs and outputs with published data.

Validation of disease progression

A comparison of disease progression has been described in Section 7.7.1, Table 77 (placebo arm) and Table 78 (dimethyl fumarate arm). Graphs of model fit at year 1 and year 2 are provided in Figure 43–Figure 44 (placebo arm) and Figure 45–Figure 46 (dimethyl fumarate). These data demonstrate that the model predicts a similar population distribution after 2 years, compared with published data for both arms. The overall patient population after two years is slightly larger in the model compared to week 96 of the clinical trial (615 compared to 592). This discrepancy may be due to the fact that the only withdrawals allowed for the no treatment population in the model was transfer to SPMS and mortality. Patients in the trial could also have been withdrawn due to other causes. Also, the rate of transfer to SPMS is based on rates from the London Ontario data set, not rates seen in the clinical trial.

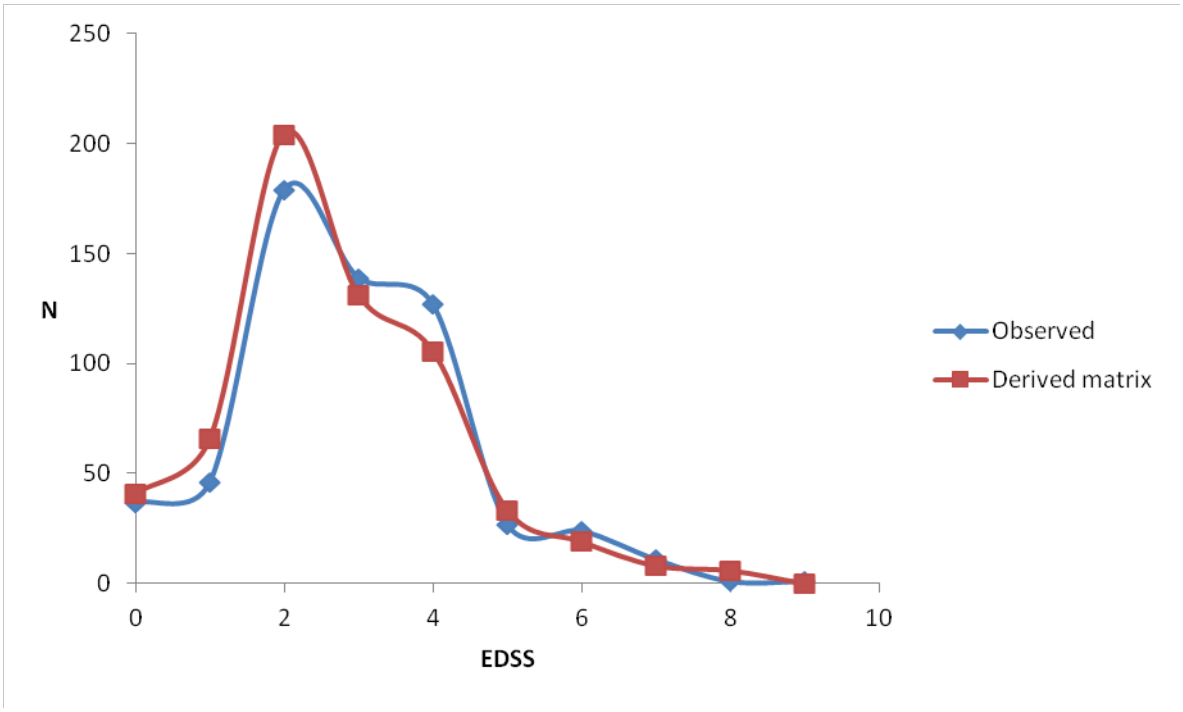
Nevertheless, the impact of underlying disease progression rates was further explored in a scenario analysis where RRMS to RRMS progression rates were replaced with the ones that were derived solely from London Ontario database (Section 7.6.1). While incremental cost and health outcome results changed from the base case with this analysis, the conclusion of the analysis did not change and dominance of dimethyl fumarate was sustained which supported the robustness of the analysis results.

Figure 43: Line graph of model EDSS state occupancy at end of year 1 (derived matrix), and observed patient distributions at week 48 in the clinical trial for the placebo population



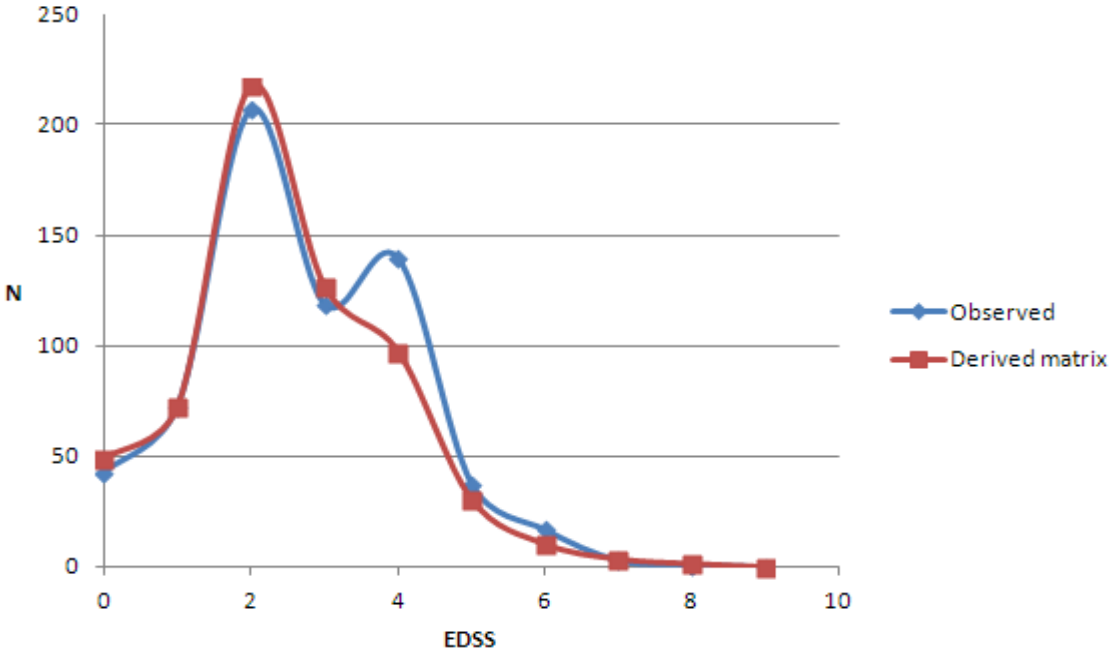
Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 46.2, Root mean square error = 6.8

Figure 44: Line graph of model EDSS state occupancy at end of year 2 (derived matrix), and observed patient distributions at week 96 in the clinical trial for the placebo population



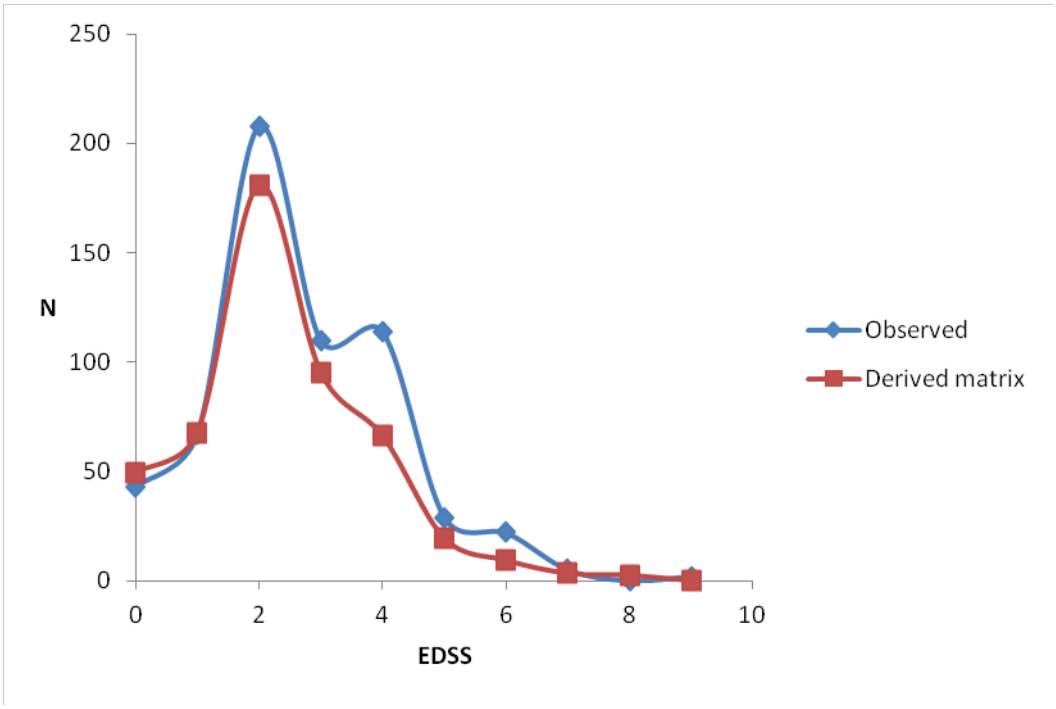
Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 166.1, Root mean square error = 12.89

Figure 45: Line graph of model EDSS state occupancy at end of year 1 (derived matrix), and observed patient distributions at week 48 in the clinical trial for the dimethyl fumarate BID population



Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 210.7, Root mean square error = 14.5

Figure 46: Line graph of model EDSS state occupancy at end of year 2 (derived matrix), and observed patient distributions at week 96 in the clinical trial for the dimethyl fumarate population



Abbreviations: EDSS, Expanded Disability Status Scale.
Mean square error = 358.41, Root mean square error = 18.93.

Validation of mortality estimates

A comparison of the number of deaths observed in the model and a recent study of mortality and survival in the British Columbia MS database (160) was conducted. Initial patient characteristics reported by Kingwell and colleagues were entered into the model (Table 64), and the simulation run over 50 years.

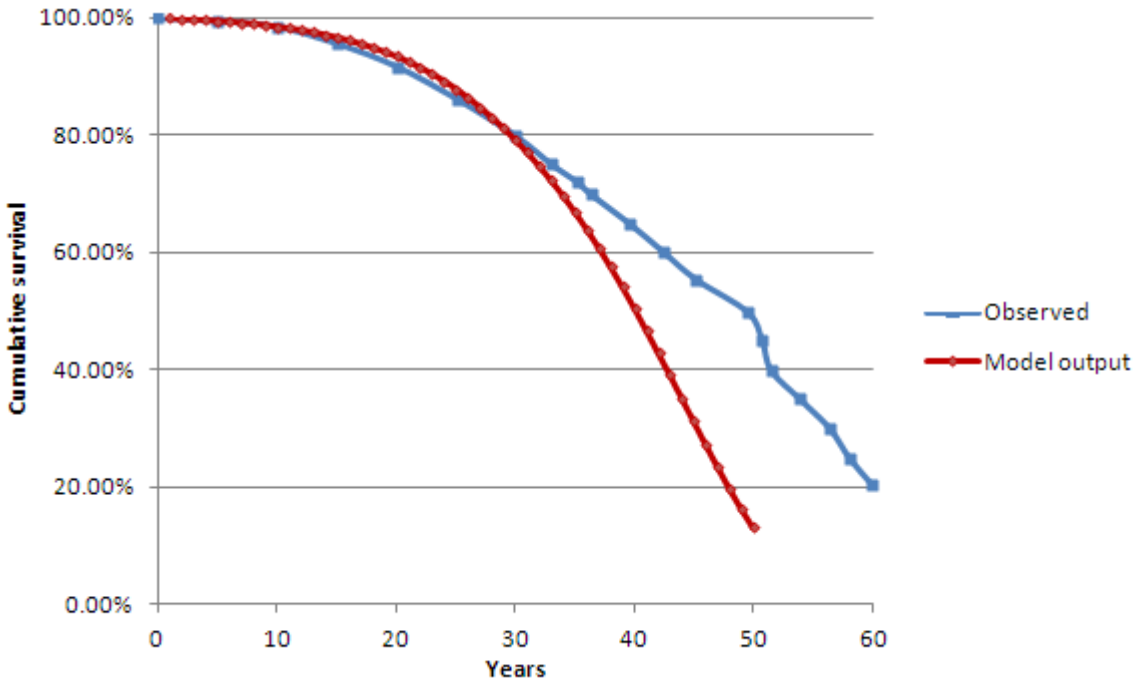
Table 106: Initial patient characteristics for the RRMS population as reported by Kingwell et al

Variable	Input value
Initial cohort size	6172
Median age at onset (starting age)	30 years
Years since diagnosis	0 years (onset at beginning of model)
Female to male ratio	2.9

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.

Cumulative survival from the model was compared with digitized graphs provided in the publication by Kingwell et al. Results are shown in Figure 47.

Figure 47: Comparison of cumulative survival in the model against observed studies



Mean square error = 2.45%, Root mean square error = 15.6%
Mean square error until 0 - 35 years: 0.05%, 35 - 50 years: 4.42%

The model shows similar rates of survival to the published observational study until about 35 years, which is longer than the time horizon employed in the base case of the economic assessment. However, after 35 years the model overestimates mortality as compared with observed data from Kingwell et al, thus results beyond this time point should be interpreted with caution.

7.9 Subgroup analysis

7.9.1 *Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to Section 6.3.7.*

Not applicable. See section 7.9.5

7.9.2 *Please clearly define the characteristics of patients in the subgroup.*

Not applicable. See section 7.9.5

7.9.3 *Please describe how the statistical analysis was undertaken.*

Not applicable. See section 7.9.5

7.9.4 *What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 7.7.6 (Base-case analysis).*

Not applicable. See section 7.9.5

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in Section 5.

Four subgroups were deemed relevant in the NICE scope:

- Patients with an inadequate response to therapy
- Patients intolerant to therapy
- Patients with highly active RRMS
- Patients with rapidly evolving severe RRMS

These subgroups have not been specifically examined in the majority of trials for the comparator treatments, and consequently there is a lack of data for each treatment to allow such subgroup comparisons. Given that data for these subgroups was not available, no subgroup analysis was performed for the MTC. However, the overall population includes patients meeting these criteria and is therefore indicative of efficacy in these groups.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature?

No economic analyses of MS treatments have previously included dimethyl fumarate as a comparator; so the results of this analysis cannot be directly compared with previous studies.

Only one study (124) used the 30 year time horizon in the current analysis, comparing IFNβ and GA against natalizumab. This study estimated costs and QALYs of (124):

- IFNβ – 5.5, £445,200
- GA – 5.1, £444,800
- Natalizumab – 7.4, £449,500

The number of QALYs estimated for IFNβ and GA are similar to those in the current analysis; however, natalizumab resulted in more QALYs than in the current analysis (5.79). This is likely to be due to the fact that Gani et al derived treatment efficacy from the pivotal trials of natalizumab and GA (124), and a Cochrane meta-analysis for IFNβ, whereas the data used in the current analysis was derived from an MTC of all treatments. NICE requests that efficacy inputs for economic models are derived from MTC or indirect comparison; the results from the current analysis are therefore likely to be more appropriate than those from the Gani et al model (124).

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5?

The economic evaluation considered all patients with RRMS, as per the indication for dimethyl fumarate (1).

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

Strengths

- All currently licensed treatments for RRMS are included in the model
- A full MTC was performed to inform the treatment efficacy inputs in the model
- The lack of a waning effect in the fingolimod STA submission model (135) was discussed as a limitation by the ERG (28); the current model therefore includes a waning effect after 2 years
- All AEs reported in the dimethyl fumarate clinical trials were included in the model
- The majority of the utilities for the EDSS health states were measured in patients directly from the dimethyl fumarate clinical trials, rather than from the literature or the use of mapping techniques
- Clinical trial data were used to model EDSS progression from EDSS 0–5, allowing for improvements in disability

Limitations and assumptions

- An inherent limitation of Markov models is that they are memory-less; i.e. all patients in a particular health state have the same probability of transitioning, regardless of any previous experience/history. This may not exactly reflect patients' experience in the real world; however, this assumption is applied to all treatments and is unlikely to bias in preference of one treatment.
- Disability progression and relapses are modelled independently, with independent treatment effects being applied to each. Although increased disability may be a result of relapses, in the absence of data quantifying this effect it was necessary to make this assumption
- Once a patient discontinues treatment, they are assumed to receive no further treatments, i.e. there is no switching between different DMTs. While patients receiving treatment are likely to switch between various therapies in clinical practice, there is no defined patient pathway, and patient/physician preference is likely to play a large role in switching therapies. As the treatment pathway is complex, this assumption was consequently necessary to simplify the comparison between treatments.
- In December 2012 a letter was issued to physicians in the UK by Novartis Pharmaceuticals stating that first dose cardiovascular monitoring should be repeated following fingolimod treatment interruptions (≥1 day during first 2 weeks; ≥7 days during weeks 3 and 4; ≥2 weeks after 1 month of treatment) (161). Given that including this in the model would have required an analysis of treatment interruptions with fingolimod, and in the absence of such data, this was not considered in the model. However, this is likely to bias the results against dimethyl fumarate, and is therefore a conservative assumption.
- The AEs included in the model are only those that were present in the dimethyl fumarate trials. This is a conservative assumption, and is likely to bias the results of the analysis against dimethyl fumarate.

- Treatments are assumed to have no direct effect on the risk of conversion to SPMS. This assumption was discussed in the response to the fingolimod NICE submission (135), and was felt to be reasonable in the absence of evidence to the contrary.
- It is assumed that a patient who receives treatment will incur the risk of disutility and cost associated with adverse events, for each year in the simulation. This may over-estimate the impact of adverse events, as patients with severe/frequent adverse events may withdraw from treatment
- In each cycle mortality is calculated based on the patient distribution at the start of the cycle. This means the models will minimally under-estimate mortality. This will have the most effect when looking at a time horizon of 1 year, and is therefore unlikely to significantly impact on the results over a 30 year time horizon (Figure 47).

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Subgroup analysis of the populations set out in the NICE scope would further enhance the completeness of the results; however, these were not performed for the following reasons:

Patients with relapsing-remitting multiple sclerosis whose disease has inadequately responded to treatment with disease modifying therapy: This subgroup has not been specifically examined in clinical trials of an RRMS treatment, meaning there is very little data for the relevant comparators. The subgroup of patients previously treated for RRMS may reflect this population in some trials; however, this group will also contain patients switching due to tolerability issues, which could bias the analysis. No MTC was therefore possible for this group.

Patients with relapsing-remitting multiple sclerosis whose disease is intolerant to treatment with disease modifying therapy: This subgroup has not been specifically examined in clinical trials of an RRMS treatment, meaning there is very little data for the relevant comparators. The subgroup of patients previously treated for RRMS may reflect this population in some trials; however, this group will also contain patients switching due to efficacy issues, which could bias the analysis. No MTC was therefore possible for this group.

Patients with highly active relapsing-remitting multiple sclerosis: This subgroup requires ≥ 1 relapse in the previous year and ≥ 9 T2-hyperintense lesions on MRI or ≥ 1 Gd+ lesion. This subgroup has not been specifically examined in clinical trials of an RRMS treatment, meaning there is very little data for the relevant comparators. No MTC was therefore possible for this group.

Patients with rapidly evolving severe relapsing-remitting multiple sclerosis: This subgroup requires ≥ 2 disabling relapses in 1 year, and with ≥1 Gd+ lesion on MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. This subgroup has not been specifically examined in clinical trials of an RRMS treatment, meaning there is very little data for the relevant comparators. No MTC was therefore possible for this group.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Prevalent population was obtained using the upper range for prevalence from Milo et al (140 per 100,000) (12), the adult population of England and Wales (43,486,200) (14), and the proportion of patients with the relapsing-remitting form of MS as their initial disease course (85%) (13). RRMS patients will generally progress to SPMS; however, no reliable data on the overall proportion of patients with RRMS and SPMS were available. The conservative assumption of 85% of patients having RRMS was consequently used, and it is likely that the true budget impact of dimethyl fumarate is significantly lower than that presented here. Incidence was calculated using data from Milo et al (7.2 per 100,000) (12).The number of incident patients in years 1–5 is shown in Table 107.

Table 107: Estimation of patients eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population, n	51,749	54,880	58,011	61,142	64,273
Incident cases, n	3,131	3,131	3,131	3,131	3,131
Eligible population	100%	100%	100%	100%	100%
Proportion expected to be treated	0.46%	1.30%	2.78%	4.30%	4.59%
Patients receiving dimethyl fumarate, n	237	714	1,615	2,632	2,951

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that 100% of the eligible population would receive treatment with IFN or GA. Uptake of dimethyl fumarate is described in Section 8.3.

8.3 What assumption(s) were made about market share (when relevant)?

Market share was calculated using sales data of all MS therapies collected on a regular basis by Biogen Idec (162). This provides data on the number of patients actually being treated for MS and is therefore indicative of the true patient population for dimethyl fumarate. Market share was estimated to be:

- Year 1: 0.46%
- Year 2: 1.30%
- Year 3: 2.78%
- Year 4: 4.30%

Table 109: Budget impact of dimethyl fumarate *(Commercial in confidence information removed)*

		Year 1	Year 2	Year 3	Year 4	Year 5
Total MS population (Table 107)		51,749	54,880	58,011	61,142	64,273
Total % uptake of dimethyl fumarate		0.46%	1.30%	2.78%	4.30%	4.59%
Patients treated with dimethyl fumarate, n		237	714	1,615	2,632	2,951
Incremental cost of dimethyl fumarate per patient	List	£10,053.94	£10,053.94	£10,053.94	£10,053.94	£10,053.94
	PAS					
Total dimethyl fumarate cost PA	List	£4,244,681	£12,787,772	£28,924,722	£47,139,238	£52,852,542
	PAS					
Total displaced medicines cost PA		£1,861,872	£5,609,255	£12,687,602	£20,677,255	£23,183,351
Incremental cost of dimethyl fumarate PA	**List**	**£2,382,809**	**£7,178,516**	**£16,237,121**	**£26,461,982**	**£29,669,191**
	PAS					

Abbreviations: MS, multiple sclerosis; PA, per annum; PAS, patient access scheme.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No additional opportunities for savings have been identified.

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