NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults

Novartis Pharmaceuticals UK Ltd

Submitted according to the specification for manufacturer/sponsor submission of evidence

Revised in line with ERG responses, and updated indication, in line with CHMP opinion: Submitted 18 March 2011

Confidential information redacted 6th June 2011

Contents

List of tables

List of figures

Abbreviations

ABN	Association of British Neurologists
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal consultation document
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ARMD	Age-related macular degeneration
ARR	Annualised relapse rate
AV	Atrioventricular
BNF	British National Formulary
BSC	Best supportive care
CE	Cost-effectiveness
CC	Complications
CHMP	Committee on Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CSR	Case study report
DMG	Direct governmental medical costs
DMOP	Direct medical out-of-pocket costs
DMT	Disease-modifying treatment
DNMG	Direct governmental non-medical costs
DNMOP	Direct non-medical out-of-pocket costs
DSMB	Data and Safety Monitoring Board
DSS	Disability Status Scale
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EED	Economic Evaluation Database
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-dimension survey
FAD	Final appraisal determination
FS	Functional system
GA	Glatiramer acetate
GGT	Gamma-glutamyl transferase
HIV	Human immunodeficiency virus
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HS	Health state
ICER	Incremental cost-effectiveness ratio

ID	Identification
IFN	Interferon
IFNB	Interferon-beta
IFU	Information for use
IOP	Indirect costs
ITT	Intent-to-treat
KDSS	Kurtzke Disability Status Scale
KFS	Kurtzke functional scale
LY	Life-year
LYG	Life-year gained
MCT	Mixed-treatment comparison
MeSH	Medical Subject Heading
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC z	Multiple Sclerosis Functional Composite
MTC	Mixed treatment comparison
N/A	Not applicable
Nab	Natalizumab
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NR	Not recorded
PAS	Patient access scheme
PbR	Payment by results
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRIMUS-Activities	Patient-Reported Indices for Multiple Sclerosis – Activities
PRIMUS-QoL	Patient-Reported Indices for Multiple Sclerosis – Quality of Life
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMS	Prospective Assessment of Changing From Placebo to IFN beta-1a in Relapsing MS
PRMS	Progressive-relapsing multiple sclerosis
PSA	Probability sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life-year
QOD	Once daily
RCT	Randomised controlled trial
RES	Rapidly evolving severe
RR	Relative risk or relative rate
RRMS	Relapsing-remitting multiple sclerosis
RSS	Risk-Sharing Scheme
S1P	Sphingosine 1-phosphate
SAE	Serious adverse event

SD	Standard deviation
SE	Standard error
SIENA	Structural Image Evaluation Using Normalisation of Atrophy
SNRS	Scripps Neurological Rating Scale
SPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
STA	Single technology appraisal
TA	Technology appraisal
UFIS	Unidimensional Fatigue Impact Scale
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale
VZV	Varicella-Zoster virus

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of Appendices 1 to 13 (Sections **Error! Reference source not found.**-**Error! Reference source not found.**) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document *Guide to the Methods of Technology Appraisal* (www.nice.org.uk), particularly with regard to the "reference case". Users should see NICE's *Guide to the Single Technology Appraisal (STA) Process* (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission.

Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, Appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Table 1 Base-case cost-effectiveness results

	Intervention	**Comparator 1**	**Comparator 2**	**Etc.**
Technology acquisition cost				
Other costs				
Total costs				
Difference in total costs	N/A	Intervention minus comparator 1	Intervention minus comparator 2	
LYG				
LYG difference	N/A	Intervention minus comparator 1	Intervention minus comparator 2	
QALYs				
QALY difference	N/A	Intervention minus comparator 1	Intervention minus comparator 2	
ICER	N/A			

ICER, incremental cost-effectiveness ratio; LYG, life-years gained; N/A, not applicable; QALY, quality-adjusted life-year.

- When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance. For example:

Table 2 Incremental cost-effectiveness results

Technology (and comparators)	**Total cost**	**Total QALY**	**Incre-mental cost**	**Incre-mental QALY**	**ICERs versus baseline (A)**	**Incre-mental analysis**
A	100	3	0	0	N/A	N/A
B	200	6	100	3	33.33333	33.33333
C	300	4	200	1	200	Dominated
D	400	8	300	5	60	Extended dominance
E	500	11	400	8	50	60

ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life-year.

- Subgroup analyses considered and clinical- and cost-effectiveness results.

United Kingdom-approved name: Fingolimod

Brand name: Gilenya™

Marketing status: Fingolimod does not currently have a United Kingdom (UK) marketing authorisation for the indication detailed in this submission. Novartis submitted an application for marketing authorisation for fingolimod to the European Medicines Agency (EMA) on 21 December 2009. On 20 January 2011, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for fingolimod 0.5 mg for the treatment of adult patients with relapsing-remitting MS with high disease activity. It is estimated that full marketing authorisation in the European Union will follow 67 days after this opinion. Thus, an estimated earliest date for final UK authorisation is 30 March 2011.

Principal pharmacological action:

Fingolimod is a sphingosine 1-phosphate (S1P)-receptor modulator with a unique mechanism of action. There are five known S1P receptors, expressed in lymphocytes and neural cells, which are involved in leukocyte recirculation, neurogenesis, neural cell function, endothelial cell function, vasoregulation, and cardiovascular development.

Fingolimod acts by preventing lymphocyte exit from the lymph nodes and by reducing the infiltration of autoaggressive cells into the central nervous system (CNS), where they are involved in inflammation and tissue damage. Only lymphocytes that regularly traffic through lymphoid organs are retained, including the pro-inflammatory T-helper 17 cells that are implicated in the pathogenesis of multiple sclerosis (MS). Fingolimod does not affect peripheral effector memory T lymphocytes because they do not recirculate through the lymph nodes. Unlike classic immunosuppressants, fingolimod does not affect the activation, expansion, or proliferation of T or B lymphocytes in response to infection.

Furthermore, fingolimod is able to cross the blood-brain barrier into the CNS and is able to modulate receptors on neural cells in the CNS, potentially reducing neurodegeneration and gliosis and promoting neuroprotection and repair.

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment, and acquisition cost:

Fingolimod is formulated as a hard capsule containing 0.5 mg of active ingredient. Fingolimod will be available in blister packs containing 7 or 28 hard capsules.

Fingolimod is administered orally once daily.

The acquisition cost is £1,470 for one 28-day pack of capsules.

Fingolimod is anticipated to be prescribed by a physician experienced in the treatment of MS.

Indication(s):

Gilenya is indicated as a single disease-modifying therapy in highly-active relapsing-remitting multiple sclerosis (MS) for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion. A “non-responder” also could be defined as a patient with an unchanged or increased relapse rate or with ongoing severe relapses, as compared with the previous year.
- Patients with rapidly evolving, severe, relapsing-remitting MS defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.

The base case for the submission will focus on the first part of the license, non-responder patients with high disease activity despite treatment with a beta-interferon. The justification for selecting this population as the base case is described in Section A, Section 5, and Section 6 of the dossier.

Restriction(s):

It is not anticipated that the marketing authorisation will be subject to any special conditions or restrictions.

Recommended course of treatment:

Continuous treatment; administered orally once daily. Patients can be switched directly to treatment with fingolimod from previous treatment with the disease-modifying treatments (DMT) glatiramer acetate or beta-interferon. When switching from a DMT, there is no need for a wash-out period, assuming any treatment-related immune effects (i.e., cytopenia) of such therapies have resolved. Patients who wish to stop treatment with fingolimod, such as those who wish to start a family, should allow for a washout period of 2 months, the maximum washout period for fingolimod.

The main comparator(s):

Fingolimod is expected to be used as a single, disease-modifying therapy in highly active, relapsing-remitting multiple sclerosis in non-responder patients with high disease activity despite treatment with a beta-interferon. Patients with high disease activity despite treatment with a beta-interferon are defined as those with an unchanged or increased relapse rate or ongoing severe relapses, as compared with the previous year. The main comparators for fingolimod are interferon-beta (interferon-beta-1a [Avonex and Rebif] and interferon-beta-1b [Betaferon and Extavia]), and glatiramer acetate (Copaxone).

Key clinical evidence:

The key clinical evidence for fingolimod in the submission comes from Study D2301 (FREEDOMS), in which fingolimod was compared with placebo (Kappos et al., 2010), and Study D2302 (TRANSFORMS), in which fingolimod was compared with interferon-beta-1a (Cohen et al., 2010a). Further data also was provided from an indirect comparison of DMTs, using a common comparator (placebo). Safety data are available from Phase II and Phase III studies, representing 5,000 patient-years of exposure to fingolimod.

The main clinical results of the RCTs and any relevant non-RCT evidence:

In Study D2302 (TRANSFORMS), fingolimod 0.5 mg significantly reduced the primary endpoint, annualised relapse rate (ARR), when compared with interferon-beta-1a, after 12 months of treatment in patients with relapsing forms of MS (0.16 vs. 0.33; $P < 0.001$). Patients were either treatment-naïve or had been previously treated with another DMT. In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with fingolimod 0.5 mg resulted in a significantly lower ARR compared with interferon-beta-1a (ARR ratio of 0.50; $P < 0.001$). Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower ARR compared with interferon-beta-1a (ARR ratio of 0.48; $P < 0.001$). Treatment with fingolimod 0.5 mg for 12 months also was associated with a greater proportion of patients with no confirmed relapse, when compared with interferon-beta-1a (82.6% vs. 69.3%; $P < 0.001$). Compared with interferon-beta-1a, fingolimod also reduced brain atrophy and improved measures of inflammatory disease activity measured by magnetic resonance imaging (MRI).

In Study D2301 (FREEDOMS), fingolimod 0.5 mg administered daily for 24 months was associated with a significant reduction in the ARR, when compared with placebo (0.18 vs. 0.40; $P < 0.001$). In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with

fingolimod 0.5 mg resulted in a significantly lower ARR compared with placebo (ARR ratio of 0.38; *P* < 0.001). Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower ARR compared with placebo (ARR ratio of 0.52; *P* = 0.005). The proportion of patients with an absence of disability progression, confirmed after 3 months, was significantly greater in patients treated with fingolimod 0.5 mg compared with placebo (82.3% vs. 75.9%; *P* = 0.03). In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with fingolimod 0.5 mg resulted in a lower rate of disability progression compared with placebo ([redacted]). Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower rate of disability progression compared with placebo [redacted].Treatment with fingolimod 0.5 mg for 24 months also increased the proportion of patients with an absence of relapse, when compared with placebo (70.4% vs. 45.6%; *P* < 0.001). When compared with placebo, treatment with fingolimod 0.5 mg also led to significant improvements in MRI outcomes, disability progression, and brain volume.

Data from indirect comparisons:

Indirect treatment comparisons, using mixed-treatment comparison (MTC) methodology, were performed to compare fingolimod with the important comparators not otherwise studied in head-to-head trials against fingolimod in full patient population with RRMS. A separate MTC model was used for each of the endpoints of interest; these endpoints were confirmed disability progression, annualised relapse rate, and treatment discontinuations due to adverse events (AEs).

From studies totalling more than 5,000 years of patient exposure, fingolimod has been found to be generally safe and well tolerated, with a similar incidence of AEs, when compared with interferon-beta-1a. A similar rate of infection was reported with fingolimod 0.5 mg and interferon-beta-1a, with most infections reported being mild to moderate in severity. Fingolimod is not associated with injection-site reactions, which are associated with all currently approved, parenterally administered treatments. The overall incidence of infections was similar between treatment groups in both Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS), and infections were mostly mild or moderate in severity. The incidence of serious infection was low in Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS) and comparable to beta-interferon or placebo. The incidence of serious AEs was low across Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS). In both studies, the most serious AEs in patients receiving fingolimod 0.5 mg were infections, macular oedema, and transient atrioventricular block at treatment initiation (Novartis, 2010). Long-term treatment with fingolimod at a higher dose of 1.25 mg once daily for 5 years was well tolerated, with most AEs being mild or moderate in severity, and the incidence of serious AEs reported for more than one patient in any treatment group was low.

Type of economic evaluation and justification for the approach used:

The economic model was designed to capture health service costs and health consequences arising from disease progression and disease activity over time. The model was based on a Markov cohort approach previously used to estimate the cost-effectiveness of interventions used in the treatment of MS. The model used a transition matrix to estimate progression through the disability states defined by the EDSS scores. The model structure captured both the disability associated with MS and the relapsing nature of MS. In addition, it encapsulated the probability of change from relapsing remitting to secondary progressive MS (SPMS) and to mortality.

Pivotal assumptions underlying the model/analysis:

The analysis considers non-responder patients with high disease activity despite treatment with a beta-interferon; non-responder patients are defined as those with an unchanged or increased relapse rate or ongoing severe relapses, as compared with the previous year, in line with one of the subgroups of the approved indication.

The economic analysis makes the following key assumptions:

- Average age of cohort at start of treatment is 37.3 years, the female-to-male ratio is 2.3:1, and the time since diagnosis is 6.25 years, as reflected in the pooled analysis of non-responder subgroups from FREEDOMS and TRANSFORMS.
- The initial distribution of patients across the EDSS states is based upon the pooled analysis of non-responder subgroups from FREEDOMS and TRANSFORMS.
- Transitions within the model are assumed to be progressive only.
- The model assumes that only RRMS patients with an EDSS score of 6 or less may receive a DMT. Prior to reaching an EDSS score of 7 or greater, patients may continue on DMTs until they discontinue due to AEs or until death. All SPMS and RRMS patients with an EDSS score of 7 or greater receive best supportive care (BSC). The guidelines of the Association of British Neurologists (2009) recommend DMTs for patients who can walk independently, i.e., those with an EDSS score of 6 or less.
- The model assumes that the relative risks associated with progression and relapses are maintained for the time horizon of 50 years.
- Utility decrements attributable to AEs are applied over the total treatment duration period. Previous models have assumed that these disutilities do not persist for the whole duration of the treatment period. However, since those studies were conducted, substantial evidence has been published to suggest that disutilities actually do persist over the long term (Herndon et al., 2005; Gold et al., 2005; Rio et al., 2005). We therefore apply these disutility rates each year to treated patients in the model.

- Mortality multipliers linked to EDSS are applied to both RRMS and SPMS populations; the multipliers are not differentiated between treatments.
- The treatment effects are assumed to be fixed, i.e., relative risks associated with disease progression or relapses will not increase or decrease over time.

Base-case results:

The undiscounted and discounted incremental results, comparing fingolimod to Avonex over a 50-year time horizon, are presented in Table 3 and Table 4.

The cost per QALY was £43,197 (undiscounted) £55,634 (discounted).

The cost-effectiveness analysis was calculated from the perspective of the NHS and PSS, as per the NICE reference case. This means that costs such as loss of income and informal care provided by friends and family are not considered. If these were included in the cost-effectiveness analysis the ICER would be substantially lower.

It is worth noting that the level of ICER values that we see for fingolimod, in the £43,000 to £56,000 range, are similar to those reported for beta interferons and glatiramer acetate in the previous NICE technology appraisal, with ICER estimates for a 20-year time horizon ranging from £40,000 to £90,000 (NICE, 2002).

Table 3 Base-case results (undiscounted)

Tech-nologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incre-mental (QALYs)
Avonex	486,460	31.34	3.99	-	-	-	-	-
Fingolimod	544,122	31.62	5.33	57,662	0.28	1.33	43,197	43,197

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year.

Table 4 Base-case results (discounted)

Tech-nologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incre-mental (QALYs)
Avonex	271,647	N/A	3.98	-	-	-	-	-
Fingolimod	321,721	N/A	4.88	50,084	N/A	0.90	55,634	55,634

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; N/A, not applicable; QALY, quality-adjusted life-year.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, Appendix 1).

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.

Brand name: Gilenya™

Approved name: Fingolimod

Therapeutic class: Selective immunosuppressants ATC code: L04AA27

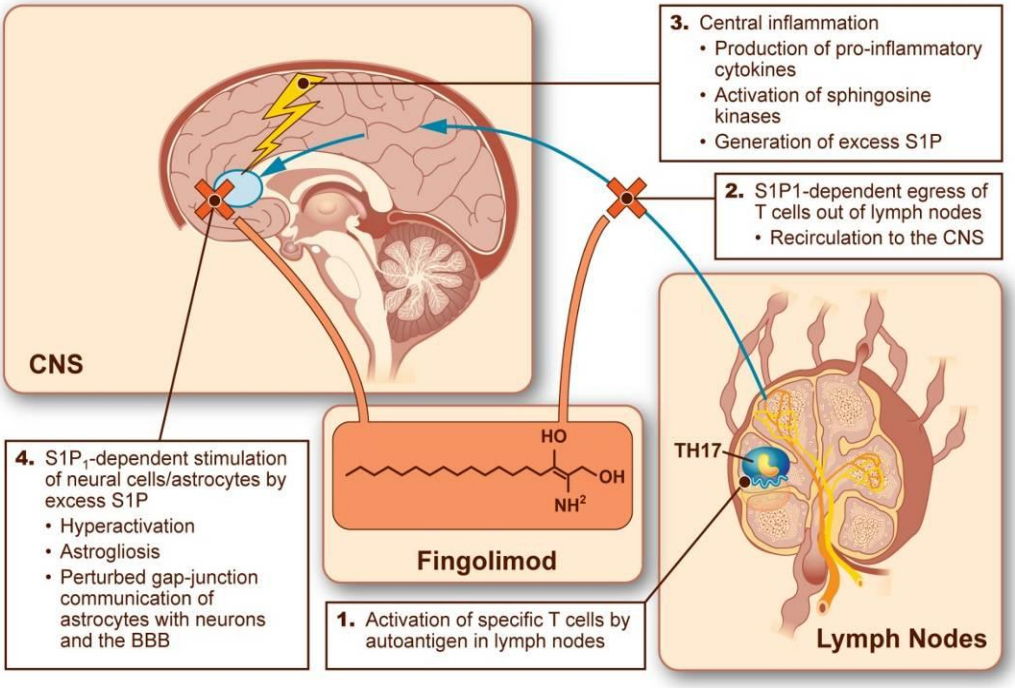
1.2 What is the principal mechanism of action of the technology?

Oral fingolimod is a structural analogue of natural sphingosine (Brinkmann et al., 2002; Nofer et al., 2007). Fingolimod is phosphorylated by sphingosine kinase-2 (SphK2) to yield the biologically active compound fingolimod-phosphate, a close structural analogue of sphingosine 1-phosphate (S1P) (Brinkmann et al., 2002; Zemann et al., 2006; Albert et al., 2005). S1P is a naturally occurring bioactive sphingolipid that plays a key role in the processes relevant to multiple sclerosis (MS), including inflammation and repair (Dev et al., 2008; Chun and Hartung, 2010). S1P has five known receptors, expressed in lymphocytes and neural cells, which are involved in leukocyte recirculation, neurogenesis, neural cell function,

endothelial cell function, vasoregulation and cardiovascular development (Chun and Hartung, 2010; Massberg and von Andrian, 2006).

Modulation of S1P1 receptors by oral fingolimod prevents lymphocyte egress from the lymph nodes and thereby reduces the infiltration of autoaggressive cells into the central nervous system (CNS), where they are involved in inflammation and tissue damage (Figure A1) (Matloubian et al., 2004; Mandala et al., 2002; Pinschewer et al., 2000; Massberg and von Andrian, 2006).

Figure A1 Oral fingolimod modulates sphingosine 1-phosphate receptors on lymphocytes and neural cells

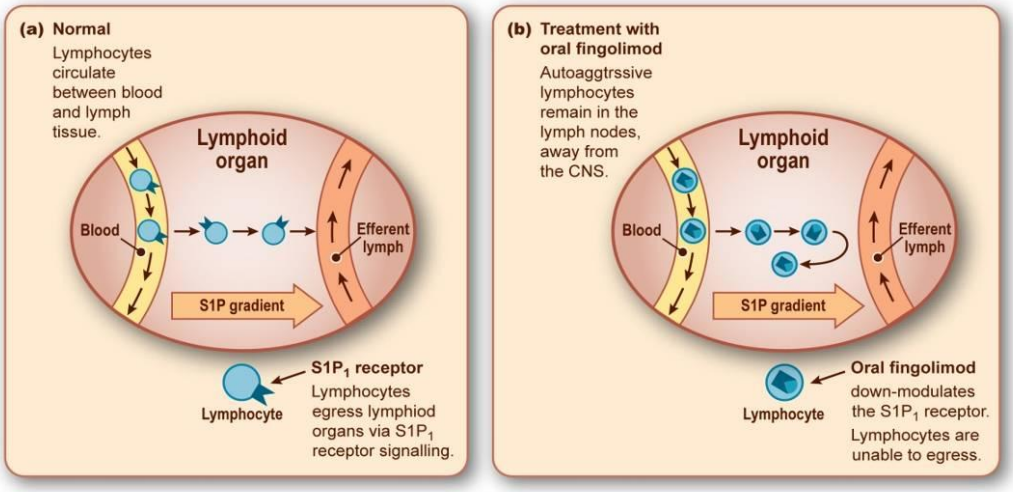


CNS, central nervous system; S1P, sphingosine 1-phosphate; S1P1, sphingosine 1-phosphate receptor 1.

Oral fingolimod prevents lymphocyte egress from lymph nodes. Only lymphocytes that regularly circulate through lymphoid organs are retained, including the pro-inflammatory T helper 17 cells that are implicated in MS pathogenesis (Figure A2) (Chun and Hartung, 2010; Mehling et al., 2008). Fingolimod does not affect peripheral effector memory T lymphocytes because they do not recirculate through the lymph nodes (Mehling et al., 2008; Hofmann et al., 2006). Unlike classic immunosuppressants, fingolimod does not affect the

activation, expansion, or proliferation of T or B lymphocytes in response to infection (Pinschewer et al., 2000).

Figure A2 Modulation of sphingosine 1-phosphate receptors by oral fingolimod prevents lymphocyte egress from the lymph nodes



CNS, central nervous system; S1P, sphingosine 1-phosphate.

Fingolimod is able to cross the blood-brain barrier into the CNS and modulates receptors on neural cells in the CNS, including astrocytes, oligodendrocytes, neurons, and microglia (Dev et al., 2008; Brinkmann, 2007). Modulation of S1P receptors on neural cells by fingolimod may reduce neurodegeneration and gliosis, and promote neuroprotection and repair (Dev et al., 2008; Miron et al., 2008).

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).

Fingolimod does not currently have a United Kingdom (UK) marketing authorisation. An application for marketing authorisation was made by Novartis to the European Medicines Agency (EMA) on 21 December 2009. On 20 January 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for

fingolimod for the treatment of adult patients with relapsing-remitting MS with high disease activity (EMA, 2011a). It is estimated that the earliest date for final UK authorisation is 30 March 2011.

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).

The main EMA Scientific Advisory Group conclusions were as follows:

- In general, fingolimod is an efficacious drug and potentially a valuable addition to the existing disease-modifying treatments in MS. However, there was concern about the safety profile of fingolimod such that fingolimod cannot be recommended for first-line treatment.
- The efficacy of fingolimod in the treatment of MS could be regarded as broadly similar to that of natalizumab. However, the efficacy and safety of fingolimod in relation to drugs other than Avonex that are used for treatment of MS could only be assessed by head-to head comparisons.
- The group recognised that the oral route of administration of fingolimod is advantageous.
- Having considered that consistent treatment effects were demonstrated in highly active subgroups, the EMA Scientific Advisory Group recommended an expert group to define criteria describing subpopulations eligible for second-line treatment.
- The group considered fingolimod as a potential therapeutic option for patients with clinically aggressive disease (high disease activity) causing disabling relapses or accumulating disability at a stage before they have serious impairment. The group did not *a priori* see any reason to apply different indications for second-line therapy drugs in MS.

There were no 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 following indication has been granted by the EMA (EMA, 2011a):

Gilenya is indicated as a single, disease-modifying therapy in highly active, relapsing-remitting multiple sclerosis (MS) adult patients who have the following indications:

- With high disease activity despite treatment with a beta-interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy and have had at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion. A non-responder also could be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year.
- With rapidly evolving, severe, relapsing remitting MS defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.

The base-case population will be non-responder patients with high disease activity despite prior treatment with a beta-interferon (i.e., Part 1b: patients with an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year).

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.

Randomised, controlled trials (RCTs) and extension studies investigating fingolimod in relapsing MS that have been reported are summarised in Table A1; those that are expected to report before November 2011 are summarised in Table A2.

Table A1 List of reported RCTs and extension studies

Trial number (acronym) Phase	Interventions	Population	Primary outcome measure	Primary reference
D2302 (TRANSFORMS) Phase 3 core trial	• Oral fingolimod (0.5 mg) once daily • Oral fingolimod (1.25 mg) once daily • Intramuscular interferon-beta-1a (30 µg) once weekly For 12 months	1,292 patients with RRMS, aged 18-55 years, with a recent history of relapse (≥ 1 in previous year, or ≥ 2 in previous 2 years), and EDSS score of 0-5.5	ARR (number of confirmed relapses during 12-month period)	Cohen et al., 2010a
D2301 (FREEDOMS) Phase 3 core trial	• Oral fingolimod (0.5 mg) once daily • Oral fingolimod (1.25 mg) once daily • Placebo once daily For 24 months	1,272 patients with RRMS, aged 18-55 years, with a recent history of relapse (≥ 1 in previous year, or ≥ 2 in previous 2 years), and EDSS score of 0-5.5	ARR (number of confirmed relapses during 12-month period)	Kappos et al., 2010
D2201 Phase 2 core trial	• Oral fingolimod (1.25 mg) once daily • Oral fingolimod (5 mg) once daily • Placebo once daily For 6 months	281 patients with relapsing MS, aged 18-60 years, with at least one of the following: ≥ 1 relapse in year before enrolment; ≥ 2 relapses in previous 2 years before enrolment; or ≥ 1 gadolinium-enhanced lesions detected on MRI at screening. In addition, patients were required to have an EDSS score of 0-6, a neurologically stable condition, with no evidence of relapse for at least 30 days before screening and during the screening and baseline phases.	Total number of gadolinium-enhanced lesions recorded on T_1-weighted MRI every month for 6 months	Kappos et al., 2006

Trial number (acronym) Phase	Interventions	Population	Primary outcome measure	Primary reference
D2201E Extension of Phase 2 trial (3-year data)	• Patients who had received oral fingolimod remained on same dose, while those who had received placebo were randomly assigned in a dose-blinded manner to fingolimod 1.25 mg or 5.0 mg once daily. During months 15-24, all patients receiving fingolimod 1.25 mg switched to fingolimod 5.0 mg	250 patients completing the 6-month visit of the core study 2201 173 patients received 3 years of treatment in extension study	Long-term safety and tolerability	Comi et al., 2010

ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis.

Table A2 List of RCTs and extension studies expected to report new data in the next 12 months

Trial number (acronym) Phase	Interventions	Population	Primary outcome measure	Secondary outcome measures	Date expected to report
2301E1 Extension of FREEDOMS Phase 3	• Oral fingolimod (0.5 mg) once daily • Blanket, long-term safety and tolerability extension study from September 2010 until available under reimbursement	920 patients with RRMS that completed FREEDOMS	Long-term safety and tolerability	Relapses, MRI, disability progression, and QoL	Annually Full report expected end of 2011
2309 FREEDOMS II Phase 3	• Oral fingolimod (0.5 mg) once daily • Oral fingolimod (1.25 mg) once daily • Placebo once daily For 24 months	1,083 patients with RRMS	ARR	Proportion of relapse-free patients, safety and tolerability, MRI lesion parameters, disability progression, and QoL	September 2011 (study completion March 2011)

Trial number (acronym) **Phase**	**Interventions**	**Population**	**Primary outcome measure**	**Secondary outcome measures**	**Date expected to report**
2309E1 Extension of FREEDOMS II Phase 3	• Oral fingolimod (0.5 mg) once daily, until available under reimbursement	Patients with RRMS who completed the 24-month core study with or without 24 months on study drug 300 patients entered extension phase since end of 2009	Long-term safety and tolerability (using vital signs, PFTs, CXR, or HRCT findings, bradycardia events, dermatologic and ophthalmic exams, and ECG data)	Long-term efficacy: ARR, disability progression (EDSS scores), MSFC scores, number of MRI gadolinium-enhanced T_1-weighted lesions, and QoL	2013
2302E1 Extension of 2302 (TRANSFORMS) Phase 3	• Oral fingolimod (0.5 mg) once daily, until available under reimbursement	1,030 patients with RRMS completing TRANSFORMS	Long-term safety and tolerability	Relapses, MRI, disability progression, and QoL	Annually (only 24-month data are currently available)
2201E1 Extension of study 2201 (5-year data) Phase 2	• Oral fingolimod (1.25 mg) once daily, recently reduced to 0.5 mg • Long-term extension study until fingolimod on the market	250 patients completing the 6-month visit of study 2201 136 patients completing 5 years in extension study	Long-term safety and tolerability	Relapses, MRI, disability progression and QoL	Annually (5-year data submitted)

Trial number (acronym) **Phase**	**Interventions**	**Population**	**Primary outcome measure**	**Secondary outcome measures**	**Date expected to report**
1201 Japan study Phase 2	• Oral fingolimod (0.5 mg) once daily • Oral fingolimod (1.25 mg) once daily • Placebo once daily For 6 months	[redacted] patients with relapsing MS	MRI lesion parameters	Proportion of patients free of relapse at 6 months, safety and tolerability of 2 doses at 6 months	2011 (primary completion: May 2010 [final data collection date for primary outcome measure])
1201E Extension of Japan study Phase 2	• Oral fingolimod (0.5 mg) once daily • Oral fingolimod (1.25 mg) once daily	171 patients with relapsing MS entered extension phase	Long-term efficacy on MRI lesion parameters at 3 and 6 months	Long-term efficacy on proportion of patients free of relapse at 3 and 6 months, long-term safety and tolerability at 3 and 6 months	Unknown (study completion July 2012)

ARR, annualised relapse rate; CXR, chest x-ray; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; PFT, pulmonary function test; QoL, quality of life; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis.

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

Fingolimod is expected to be available for purchase in the UK in the second quarter of 2011.

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

Fingolimod gained regulatory approval to treat relapsing forms of multiple sclerosis from the Russian health authority, the Federal Service on Surveillance in Healthcare and Social Development, in September 2010; from the Food and Drug Administration (FDA) in the United States (US) in September 2010; from Swissmedic, the Swiss Agency for Therapeutic Products in Switzerland, in January 2011; and from the Australian Therapeutic Goods Administration in February 2011.

Fingolimod was submitted for regulatory approval to the EMA in Europe (application submitted 21 December 2009). On 20 January 2011, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for fingolimod 0.5 mg for the treatment of adult patients with relapsing-remitting MS with high disease activity (EMA, 2011a). It is estimated that full marketing authorisation in the European Union will follow 67 days after this opinion. Thus, an estimated earliest date for final UK authorisation is 30 March 2011.

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

Fingolimod currently is not subject to any other health technology assessments in the UK. [redacted].

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 A3 Unit costs of technology being appraised

Pharmaceutical formulation	0.5 mg hard capsule
Acquisition cost (excluding value-added tax)	The proposed UK list price is £1,470 per 28-day pack, but this needs to be confirmed by the Department of Health
Method of administration	Oral
Doses	0.5 mg
Dosing frequency	Once daily
Average length of a course of treatment	Continuous
Average cost of a course of treatment	The UK price is still to be confirmed by the Department of Health The price for 12 months therapy is £19,169
Anticipated average interval between courses of treatments	24 hours
Anticipated number of repeat courses of treatments	The medium length of time on fingolimod therapy in the follow-up period of the clinical trials was approximately 5 years.
Dose adjustments	None

UK, United Kingdom.

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.

Not applicable.

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

The draft SPC describes additional tests or investigations in addition to those used currently in routine clinical practice for RRMS that are needed for the selection of patients for fingolimod treatment (Novartis, draft SPC, 2011):

- Patients who are intending to switch directly from treatment with beta interferon or glatiramer acetate to treatment with fingolimod should be checked for signs of relevant treatment-related abnormalities as a result of their previous treatment (e.g., cytopenia).

- Patients with diabetes mellitus or a history of uveitis should undergo an ophthalmological evaluation, to detect macular oedema, prior to initiating therapy.
- Patients without a history of chickenpox or those without vaccination against VZV should be tested for antibodies to VZV before initiating therapy with fingolimod. Vaccination against VZV in antibody-negative patients should be considered before starting treatment with fingolimod.
- All patients should have a recent complete blood count (CBC) (i.e., within 6 months) available, to ensure that the absolute lymphocyte count is $\geq 0.2 \times 10^9$/l, before initiating fingolimod therapy.
- In women of childbearing potential, a negative pregnancy test result must be available.

Fingolimod is administered orally. There are no particular administration requirements.

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

The draft SPC states that certain groups of patients receiving fingolimod will need to be monitored over and above usual clinical practice (Novartis, draft SPC, 2011).

Please note that Novartis are looking into ways it could provide some or all of this monitoring on behalf of the NHS.

- Due to the potential for heart rate and rhythm disturbances, all patients should have their heart rate and blood pressure observed for the first 6 hours of treatment initiation. A baseline electrocardiogram prior to treatment initiation may be useful in patients with a history of cardiac problems.

- Patients should undergo an ophthalmological evaluation 3 to 4 months after treatment initiation because of the risk of macular oedema. Patients with concomitant diabetes mellitus should have regular ophthalmological examinations. If a patient reports visual disturbance, evaluation of the fundus, including the macula, should be carried out. As with any immunomodulatory agent, patients receiving fingolimod should be instructed to report symptoms of infection to their physician, during and up to 2 months after treatment. Assessments of CBC are recommended periodically during treatment and in cases of any infection. If absolute lymphocyte count is found to be $< 0.2 \times 10^9$/l, treatment should be interrupted until recovery. Blood pressure should be regularly monitored during treatment with fingolimod.
- Patients with pre-existing liver abnormalities should be monitored regularly for signs of liver toxicity. In the absence of clinical symptoms, liver transaminases should be monitored at 1, 3, and 6 months on therapy and periodically thereafter. If liver transaminases rise above 5-fold of the upper limit of normal (ULN), patients should be monitored more frequently, including serum bilirubin and alkaline phosphatase. If repeated incidences of liver transaminases above 5 times the ULN are repeatedly observed, fingolimod treatment should be interrupted and restarted once liver transaminase levels have normalised. In patients who develop symptoms suggestive of hepatic dysfunction, (such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, and/or dark urine), liver enzymes should be checked and treatment discontinued if significant liver injury is confirmed (e.g., liver transaminase levels greater than 5-fold the ULN and/or serum bilirubin elevations).
- Women of child-bearing age and potential should be reminded on an ongoing basis to use adequate contraception whilst on fingolimod treatment.

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?

As with all therapies for MS, steroids may be required if patients experience a relapse.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

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.

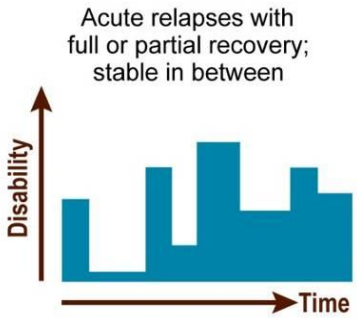
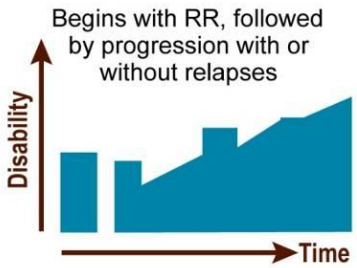
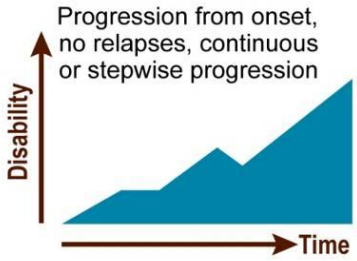
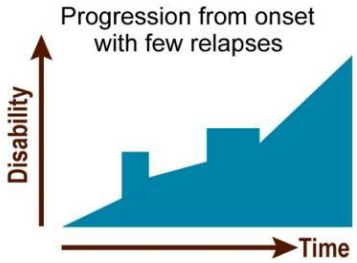
MS is a chronic autoimmune inflammatory disease of the CNS usually associated with irreversible progression of disability. It is characterised by inflammation of nervous tissue in the CNS, leading to destruction of the myelin sheaths covering nerve axons. As a consequence of this damage, nerve transmission is slowed or even blocked to and from the brain and spinal cord, subsequently resulting in functions such as movement and sensation being lost (NICE, 2002; Peterson and Fujinami, 2007).

The disease has an adverse and often highly debilitating impact on quality of life for people with MS and their families. Relapses may require admission to the hospital and be associated with a level of disability and often disrupts work, family, and social lives. MS in its early stages can undermine a patient's confidence, restrict their activity, and limit their role in society, including the inability to continue employment and take part in usual family activities. Symptoms such as weakness, chronic fatigue, unsteady gait, speech problems, and incontinence can leave people with MS feeling isolated and depressed. Patients with MS also have a reduced life expectancy, which is partially because of the increased risk of depression, which is in turn linked to the increased risk of suicide (Wallin et al., 2006; Mohr et al., 2006; Sollom and Kneebone, 2007). Moreover, the emotional and financial burdens of MS also affect primary or informal carers of patients with MS (NICE, 2002).

Although MS is a highly heterogeneous disease, four broad patterns have been identified. These four patterns are classified by the pattern and frequency of relapses and the rate of progression of the disease (Table A4). These patterns do not appear to reflect differences in underlying pathology,

and classification can change over time. However, this classification is useful for defining patients for inclusion in clinical trials and for developing treatment algorithms (Lublin and Reingold, 1996).

Table A4 Four patterns of multiple sclerosis

Type	Characteristics	Visual
RRMS	Characterised by clearly defined acute attacks (relapses), with worsening of symptoms followed by full, partial or no recovery of function. Relapses evolve over several days to weeks. Recovery from a relapse takes weeks or months. This pattern usually occurs early in the course of MS in most patients.	
Secondary progressive MS	Initially begins with a relapsing-remitting course, but later evolves into progressive disease. The progressive part of the disease may begin shortly after the onset of MS, or it may occur years or decades later.	
Primary progressive MS (PPMS)	Characterised by a gradual but steady progression of disability without any obvious relapses and remissions. This form of disease has an older average age of onset than RRMS (at around age 40 years).	
Progressive-relapsing MS (PRMS)	This is the least common form of the disease and is characterised by a steady progression in disability with acute attacks that may or may not be followed by some recovery. People with PRMS initially appear to have PPMS.	

MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Source: Lublin and Reingold, 1996.

Approximately 80% to 90% of people with MS initially experience RRMS. In this form of the disease, recurrent attacks of loss of neurological function, termed relapses, are separated by periods of complete or incomplete

recovery, described as remissions (NICE, 2002). RRMS accounts for about 45% of the total population with MS. It is estimated that in England and Wales MS affects around 61,000 people (Office of National Statistics, 2009; Koutsouraki et al., 2010).

After approximately 10 years without treatment, half of people with MS begin a continuous downward progression, which may include acute relapses. This form of MS is known as secondary progressive multiple sclerosis (SPMS) and accounts for about 45% of the total population with MS. In a third type of MS, the disease progresses inexorably from onset. This is known as primary progressive MS (PPMS), which accounts for 10% of MS cases. Lastly, the fourth and least common condition is progressive-relapsing MS (PRMS) (NICE, 2002).

MS usually begins in individuals aged between 20 and 40 years and affects almost twice as many women as men (NICE, 2002; Alonso et al., 2007). In the UK, 5.3 per 1,000 women and 2.3 per 1,000 men can expect to receive a diagnosis of MS during their lifetime (Alonso et al., 2007). This gender bias is primarily because RRMS affects more women than men (Noseworthy et al., 2000; Ascherio and Munger, 2007). Although the cause of MS is not fully understood, a number of potential risk factors have been identified for development of the disease (Table A5). In addition to gender and age, other risk factors associated with the development of MS include increased distance from the equator, diet low in vitamin D, early exposure to viral infections, genetic susceptibility, and smoking (Table A5).

Table A5 Several potential risk factors for the development of MS

Risk factor	Comments
Female sex	Prevalence of RRMS (but not PPMS) is higher in women than in men
Age 20-40 years	Onset of disease is most common during this age range
Increased distance from the equator	Prevalence tends to increase as distance from the equator increases or exposure to ultraviolet light decreases
Diet low in vitamin D	Vitamin D in the diet may protect against development of MS (vitamin D can also be synthesised in the skin if there is sufficient exposure to ultraviolet light)

Risk factor	Comments
Early exposure to viral infections	Childhood exposure to Epstein-Barr virus and other viruses may increase the risk of developing MS
Genetic susceptibility	Studies of monozygotic and dizygotic twins indicate that genetic factors play some role in increasing risk; possible involvement of genes encoding the receptors for interleukin 2 and 7
Smoking	Heavy smoking is associated with increased risk of developing MS

MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Sources: Keegan and Noseworthy, 2002; Noseworthy et al., 2000; Compston and Coles, 2002; Alonso et al., 2007; Duquette et al., 1992.

2.2 How many patients are assumed to be eligible? How is this figure derived?

In line with data from the budget-impact model, 3,529 patients are assumed to be eligible for treatment with fingolimod each year, based on a steady prevalence population; these patients are the specific part of the licensed population this submission is focussed on.

The current RRMS population in England and Wales is estimated by:

(Total population of England and Wales [55,319,249]) x (prevalence of MS [0.110%]) x (proportion of patients with RRMS [35.5%]) = 21,602 patients.

The sources for these data are as follows:

- Total population of England and Wales (Office of National Statistics, 2009),
- Prevalence of MS (Koutsouraki et al., 2010),
- Proportion of patients in the UK with RRMS (Kobelt et al., 2006)

The current RRMS population previously treated with a DMT = 21,602 × 31% = 6,697 patients (Zajicek et al., 2010).

The current RRMS population previously treated with a DMT and eligible for fingolimod (i.e., 1 or more relapses in the last 12 months and the relapse

frequency unchanged or increased) = 6,697 × 53% (Synovate, 2010). This is calculated based on Synovate prescribing data for fourth quarter 2010 (assuming that Synovate data set is representative of England and Wales), as follows:

- The number of DMT-treated RRMS patients in UK = 222 patients
- The number of DMT-treated RRMS patients in the UK who are eligible (1 or more relapses in last 12 months and relapse frequency unchanged or increased) = 117 patients
- The proportion of DMT-treated RRMS patients who are eligible = 117/222 = 53%

2.3 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.

A NICE clinical guideline was issued in 2003 (Clinical Guideline 8, Multiple sclerosis: management of multiple sclerosis in primary and secondary care [NICE, 2003]).

Two technology appraisals (TAs) have been published:

- *Beta interferon and glatiramer acetate for the treatment of multiple sclerosis* (TA32 [NICE, 2002]),
- *Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis* (TA127 [NICE, 2007]).

A single technology appraisal (TA) is also currently in preparation for cladribine: *Cladribine for the Treatment of Relapsing-Remitting Multiple Sclerosis* (NICE, 2010). The first NICE appraisal committee meeting, which was scheduled for 25 November 2010, has now been cancelled in the event of a negative CHMP opinion. NICE are currently monitoring the situation and will provide an update in due course.

Subgroups that were addressed are summarised in Table A6.

Table A6 Specific subgroups addressed in NICE guidelines and TAs

Guideline/TA	Subgroups Considered
Clinical Guideline 8 (November 2003) Multiple sclerosis: management of multiple sclerosis in primary and secondary care	RRMS SPMS
TA32 (January 2002) Beta interferon and glatiramer acetate for the treatment of multiple sclerosis	Subgroups not considered
TA127 (August 2007) Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis	Patients with RES MS (defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing lesions on brain Magnetic Resonance Image (MRI) or a significant increase in T_2-lesion load as compared to a previous MRI). Patients with "suboptimal therapy" (defined as patients who have had at least 1 relapse in the previous year while on therapy, and have at least 9 T_2-hyperintense lesions in brain MRI or at least 1 Gadolinium-enhancing lesion.)

MS, multiple sclerosis; NICE, National Institute for Health and Clinical Excellence; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal.

2.4 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.

The licence for fingolimod can be considered to be formed of two parts. The first part is "patients with high disease activity despite treatment with a beta-interferon". The second part of the indication is "patients with rapidly evolving severe relapsing-remitting MS" (EMA, 2011a).

To facilitate analysis, Novartis suggest that the licence should be considered as separate populations. Table A7 shows that a greater extent of clinical data

is available for the first part (Part 1) of the licence (non-responder patients with high disease activity despite treatment with a beta-interferon), so this has been selected as the base case for this STA. Part 1 itself is composed of two definitions of high disease activity despite treatment. Within the two pivotal trials, there is a large overlap between these definitions; and 72% to 84% of subjects in Part 1 qualify for either definition of high disease activity despite treatment.

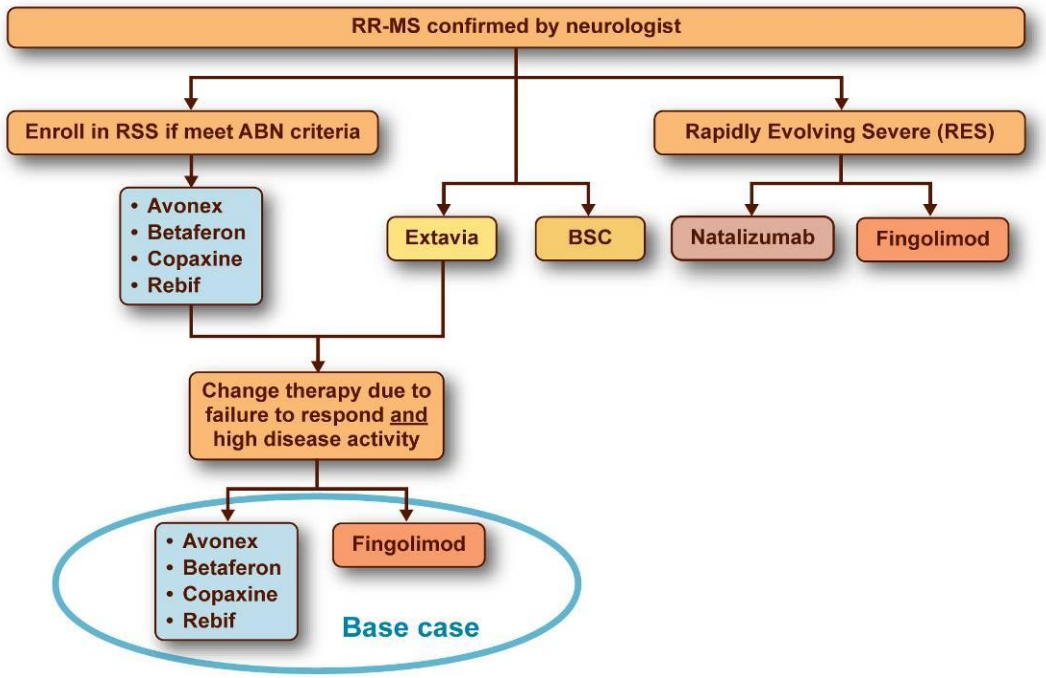
Table A7 Summary of the breakdown of the ITT population from the two pivotal Phase III trials TRANSFORMS and FREEDOMS

Trial; treatment arm	N	Label Part 1		Label Part 2	
		n	%	n	%
FREEDOMS					
Fingolimod 0.5 mg	425	96	23%	77	18%
Placebo	418	97	23%	63	15%
TRANSFORMS					
Fingolimod 0.5 mg	431	207	48%	56	13%
Interferon	435	203	47%	65	15%

ITT, intent-to-treat.

The current clinical pathway of care for patients with RRMS, as recommended in NICE Clinical Guideline 8 is presented in Figure A3, along with the proposed place in the treatment pathway for fingolimod.

Figure A3 Current clinical pathway of care for patients with RRMS



ABN, Association of British Neurologists; BSC, best supportive care; RRMS, relapsing-remitting multiple sclerosis; RSS, Risk-Sharing Scheme.

Copaxone = glatiramer acetate; Rebif = interferon-beta-1a; Avonex = interferon-beta-1a; Betaferon = interferon-beta-1b; Extavia = interferon-beta-1b.

Within the proposed UK licence for fingolimod, RES could be considered a sub-population. As such, Novartis investigated whether it would be feasible to carry out a comparison of fingolimod and natalizumab within a RES population and this is described briefly below. However, Novartis concluded that on balance there are too many limitations to carry out a comparison in a RES population.

The systematic review discussed in Section 5.1 failed to identify any head-to-head studies comparing fingolimod and natalizumab. As such, an indirect comparison between the natalizumab RES population from AFFIRM and a RES population from FREEDOMS would be necessary. However, there are a number of shortcomings with the comparison which are described below. Therefore, Novartis concluded that an indirect comparison could lead to misleading results so Novartis abandoned the comparison.

AFFIRM is a placebo-controlled study so a comparison would have to be undertaken between AFFIRM and FREEDOMS. There are differences between the trials in the definition of RES.

In FREEDOMS, the definition is:

- Two or more relapses in 1 year and at least one gadolinium-enhanced lesion at baseline;

whilst in AFFIRM, the definition is:

- Two or more **disabling** relapses in 1 year and at least one gadolinium-enhanced lesion at baseline,
- Or a significant increase in T_2-lesion load compared with a previous MRI.

In addition, the sample sizes within this comparison group are small, especially within the FREEDOMS subgroup data. There were 148 patients in the natalizumab AFFIRM RES population, whereas there would only be 77 fingolimod patients from FREEDOMS. It is worth noting that the clinical efficacy data for the natalizumab AFFIRM RES population is a treatment-naive population. If a treatment-naive RES population is considered for fingolimod, then only 48 out of 425 subjects (11.3%) from FREEDOMS would fulfil this criterion.

The AFFIRM study had an exclusion criterion for patients with a relapse within 50 days prior to the administration of the first dose of the study drug. In contrast, FREEDOMS had an exclusion criterion for patients with a relapse within 30 days prior to randomisation. This means that, on average, AFFIRM patients were likely to be relapse-free for longer than FREEDOMS patients.

The median disease duration, prior to study, for patients receiving natalizumab 300 mg in AFFIRM was 5.0 years, compared with 6.6 years for patients receiving fingolimod 0.5 mg in FREEDOMS. Finally, the distribution of

baseline EDSS in the range of 1 to 2.5 differs between these subgroups in AFFIRM and FREEDOMS.

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

Although treatments exist for RRMS, namely the disease-modifying therapies (DMTs) glatiramer acetate and beta interferon, these are typically prescribed only to patients who are eligible for treatment under the Department of Health's Risk-Sharing Scheme (RSS) (Department of Health, 2005). The RSS require that patients meet the following criteria:

- Are able to walk 100 metres without assistance;
- Must have had at least two clinically significant relapses in the last 2 years;
- Are aged 18 years or older;
- Must not have the following contraindications:
    - Glatiramer acetate: pregnant women or persons hypersensitive to glatiramer acetate or mannitol;
    - Beta interferon: pregnant women, persons hypersensitive to natural or recombinant beta interferon or to any excipients, persons with severe depression and/or suicidal ideation, or persons with decompensated liver disease (for interferon-beta-1b only).

If patients do not meet these criteria, they will usually receive best supportive care. Another interferon-beta-1b treatment, Extavia, is also available to patients with RRMS but is not available through the RSS. The Department of Health has advised that primary care trusts are able to choose if they want to use interferon-beta-1b via the RSS (i.e., Betaferon) or outside the RSS (i.e., Extavia).

In patients who do receive beta interferon or glatiramer acetate, an unmet need still remains because of suboptimal efficacy and/or safety issues of the treatments themselves. Since RRMS is the result of both inflammation and

neurodegeneration in the CNS, treatments that target both components of the disease would likely possess improved efficacy (Confavreux and Vukusic, 2006). However, current DMTs primarily target the inflammatory component of the disease, resulting in suboptimal outcomes, as indicated in several studies. A previous systematic review reported that current DMTs have only partial efficacy in relapsing forms of MS, reducing relapse rates by 29% to 34% compared with placebo (Filippini et al., 2003). Current DMTs are also suboptimal in delaying progression of disability, and only Avonex is indicated specifically for slowing disability progression (Biogen, 2009). There also are substantial tolerability and safety issues with current DMTs. Both beta interferons and glatiramer acetate are frequently associated with injection-related issues, including injection-site reactions and injection anxiety, as reported in a number of systematic reviews (Filippini et al., 2003; Rice et al., 2001; Munari et al., 2004). Furthermore, beta interferons and glatiramer acetate also are associated with treatment-specific AEs. Frequent adverse events with beta interferon include influenza-like symptoms, fever, myalgia, and hair loss (Filippini et al., 2003; Rice et al., 2001), while treatment with glatiramer acetate is commonly associated with dizziness and palpitations (Munari et al., 2004). As a result of these tolerability issues, and in particular injection-site reactions, adherence with current DMTs is low. A 3-year retrospective cohort study in 1,606 patients with RRMS receiving beta interferons reported that only 27% to 41% of patients each year were considered adherent (i.e., medication possession ratio of ≥ 85%) (Steinberg et al., 2010). Lower adherence was associated with poorer clinical outcomes because patients who were considered non-adherent tended to have a greater risk of relapse over 3 years than adherent patients (Steinberg et al., 2010). An unmet need exists for a treatment with improved tolerability and, consequently, the potential for improved adherence.

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

Therapies for MS are generally delivered to the home, so national prescribing data are not readily available. Market-share data for RRMS treatments for patients with RRMS who had been previously treated and discontinued their

treatment and whose relapse rate remained stable or increased in the last 12 months, as prescribed by MS specialists in England and Wales in the fourth quarter of 2010, are provided in Table A8.

Table A8 Market share of RRMS treatments* in England and Wales, fourth quarter, 2010

Therapy†	Patient share (%)
Interferon-beta-1a (Rebif) 44	36.1
Glatiramer acetate (Copaxone)	25.8
Interferon-beta-1a (Avonex)	17.5
Interferon-beta-1b (Betaferon)	13.4
Interferon-beta-1a (Rebif) 22	6.2
Interferon-beta-1b (Extavia)	1.0

RRMS, relapsing-remitting multiple sclerosis.

* Prescribing data for treatments for patients with RRMS who had been previously treated and discontinued their treatment, and whose relapse rate remained stable or increased in the last 12 months.

† Natalizumab (Tysabri) is recommended by NICE only for RES RRMS (TA127 [NICE, 2007]). We do not believe that the introduction of fingolimod will affect the market share of Tysabri for RES RRMS.

Source: Synovate data on file, 2010.

The main comparators are the beta interferons (interferon-beta-1a [Avonex and Rebif], interferon-beta-1b [Betaferon and Extavia]), and glatiramer acetate (Copaxone). However, the beta interferons and glatiramer acetate are not recommended by NICE (NICE, 2002); rather, they are provided to the patient through an RSS (Department of Health, 2005). The Department of Health has advised that whilst Extavia is not included in the RSS, this does not preclude the use of Extavia for these patients. If patients do not qualify for the RSS, they will receive optimised standard care with no DMT. Cladribine is no longer considered as a comparator, since the CHMP recently confirmed its previous negative opinion and adopted a final negative opinion, recommending that cladribine should not be granted a marketing authorisation (EMA, 2011b). In February 2011, NICE stated that “the appraisal has now been suspended and the appraisal committee discussion that was due to take place on 6 July 2011 has been cancelled. The manufacturer of this technology has informed NICE that further clinical evidence is in development. We will continue to monitor

any development and will update this webpage if the situation changes" (NICE, 2011).

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

The management of adverse events is discussed in Section 2.8.

2.8 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.

Fingolimod will be prescribed to patients by specialists in a secondary-care setting. Fingolimod is administered orally by the patient and so is not associated with the administration costs associated with injections or infusions. The cost of a visit to a neurologist is £207 (Department of Health, 2011). It is worth noting that MS patients will already be visiting neurologists regularly even if they are not receiving a DMT.

In addition, a small proportion of patients are estimated to require hospitalisation upon treatment initiation (2% [Novartis, 2010, FREEDOMS CSR, data on file]). The cost of a hospitalisation is estimated at £2,079 (Department of Health, 2011).

In addition to those tests used currently in routine clinical practice for RRMS, the following tests also were required for selection of patients for fingolimod treatment:

- Patients with diabetes mellitus or with a history of uveitis should undergo an ophthalmological evaluation prior to initiating therapy because of an increased risk of macular oedema. It is estimated that 0.9% of patients will require this evaluation (Novartis, 2010, FREEDOMS CSR, data on file). The cost of an ophthalmological evaluation is estimated at £105 (Department of Health, 2011).

- Patients without a history of chickenpox or those without vaccination against VZV should be tested for antibodies to VZV, before initiating therapy with fingolimod. This is estimated to be necessary in approximately 10% of patients (NHS, 2010). The cost of the test for antibodies is estimated at £7 (Department of Health, 2011).
- All patients should have a recent CBC (i.e., within 6 months) available before initiating fingolimod therapy. The cost of a haematology test is £3 (Department of Health, 2011).

In addition to those tests used currently in routine clinical practice for RRMS, the following tests were also required for monitoring of patients for fingolimod treatment:

- All patients should be observed for any serious changes in heart rate for 6 hours after treatment initiation. This will need to be carried out in a hospital capable of immediate treatment should there be a severe case of bradycardia or atrioventricular block. The cost of this observation is estimated at £501 (Department of Health, 2011).
- All patients should undergo an ophthalmological evaluation 3 to 4 months after treatment initiation because of the risk of macular oedema. The cost of an ophthalmological examination is estimated at £105 (Department of Health, 2011). In those 0.9% of patients who initially received an ophthalmological evaluation prior to initiating therapy, the cost of this second ophthalmological evaluation will be considered a follow-up examination, at a cost of £74 (Department of Health, 2011).
- In patients reporting visual disturbance, evaluation of the fundus, including the macula, should be carried out. This is estimated to be necessary in approximately 3.5% of patients (Novartis, 2010, FREEDOMS CSR, data on file). The cost of this evaluation is estimated at £105 (Department of Health, 2011).

- All patients should be monitored regularly for signs of liver toxicity. This is estimated to be necessary in all patients. Monitoring would involve a simple liver enzyme check four times each year. The cost of each test to check liver enzymes is £1 (Department of Health, 2011).
- Assessments of CBC are recommended periodically during treatment and in cases of any infection. The cost of a haematology test is £3 (Department of Health, 2011).

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

There are no specific needs for storage of oral fingolimod capsules.

There will likely be a need for additional infrastructure in terms of providing closer relationships between neurology specialists and hospital departments, such as ophthalmology departments.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No issues relating to equity or equalities have been identified.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No issues relating to equity or equalities are anticipated.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

No issues relating to equity or equalities have been addressed in the clinical and cost analyses.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with RRMS	Adults with RRMS within the licensed indication for fingolimod	Not applicable
Intervention	Fingolimod	Fingolimod 0.5 mg once daily	Dose and dosing schedule not specified in scope
Comparator(s)	Beta interferon; glatiramer acetate; standard care with no DMT For people with rapidly evolving severe RRMS: natalizumab	Comparison of the clinical efficacy of fingolimod versus beta interferon; glatiramer acetate; or standard care with no DMT is considered.	The cost-effectiveness analysis does not consider a comparison with glatiramer acetate because of a lack of data. Novartis does not believe that the amount of data available justifies a comparison for the RES population when there are other comparisons available with more robust data.
Outcomes	The outcome measures to be considered include mortality, relapse rate, disability progression, disease activity, adverse effects of treatment, and health-related quality of life	The outcome measures considered include mortality, relapse rate, disability progression, disease activity, adverse effects of treatment, and health-related quality of life	Not applicable

	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 QALY. The reference case stipulates that the time horizon for estimating clinical effectiveness 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 a PSS perspective. Arrangements within the RSS, which was agreed to for the supply of DMTs for MS in the NHS (Department of Health, 2005), may be taken into consideration in the economic evaluation where these are relevant to the appraisal of fingolimod	The cost-effectiveness of fingolimod is expressed in terms of incremental costs per QALY. The time horizon for estimating clinical effectiveness and cost-effectiveness is patients' lifetimes to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and a PSS perspective. Arrangements regarding the RSS for DMTs have been considered in the economic evaluation where data exists	Not applicable
Subgroups to be considered	For people with rapidly evolving severe RRMS If evidence allows, consideration will be given to subgroups defined by prior treatment.	The subgroup rapidly evolving severe RRMS was considered. The subgroup of patients who were previously treated with DMTs is considered.	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Special considerations, including issues related to equity or equality	None identified	None identified	Not applicable

DMT, disease-modifying treatment; MS, multiple sclerosis; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services; QALY, quality-adjusted life-year; RRMS, relapsing-remitting multiple sclerosis; RSS, risk-sharing scheme.

Section B – Clinical and cost-effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document *Guide to the methods of technology appraisal* – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Table 5 Features of the reference case

Element of health technology assessment	**Reference case**	**Section(s) in *Guide to the methods of technology appraisal***
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7-5.2.10
Perspective benefits	All health effects on individuals	5.2.7-5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services; QALY, quality-adjusted life-year.

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 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 **Error! Reference source not found.**, Appendix 2.

Prior to initiating the systematic literature review, a protocol was developed to outline the methodology to be used for the searches, screening process (inclusion and exclusion criteria) and data extraction. Based on the methods defined *a priori*, the following electronic databases were selected:

- MEDLINE (using PubMed platform);
- MEDLINE In-Process (using PubMed platform);
- EMBASE (using Dialog Platform);
- The Cochrane Library, Issue 1, 2010, including the following:
  - The Cochrane Central Register of Controlled Trials;
  - The Cochrane Database of Systematic Reviews;
  - Database of Abstracts of Reviews of Effectiveness.

The search dates of interest for the above mentioned databases were from the year 1960 to 15 April 2010.

In order to identify grey literature, conference Web sites were searched for conference abstracts from January 2008 to April 2010. The following were Internet sites of interest:

- American Academy of Neurology,
- Americas Committee for Treatment and Research in Multiple Sclerosis,
- European Committee for Treatment and Research in Multiple Sclerosis,
- European Charcot Foundation.

Bibliographic reference lists of the included studies and reviews were searched for any relevant studies.

There was no limitation on the year or the language of the publication during the searches. Foreign-language sources were eliminated during the screening process.

5.2 Study selection

5.2.1 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. A suggested format is provided below.

Table 6 summarises study inclusion and exclusion criteria. Studies were first screened based on the title and abstract; those that did not match the eligibility criteria were excluded. Full-text copies of all studies then were screened. At each screening stage, the studies were assessed in parallel independently by two individual reviewers, with a third independent reviewer resolving any discrepancies.

Table 6 Eligibility criteria used in search strategy

Criteria	Clinical effectiveness
Inclusion criteria	Population • Patients with RRMS Interventions • Fingolimod • Beta-interferon (including unlicensed doses) • Glatiramer acetate • Natalizumab • Cladribine* • Best supportive care Study design • RCTs • Non-RCTs • Long-term follow-up studies (e.g., open-label follow-up studies) • Prospective observational studies (e.g., Phase IV studies) Outcomes • Relapse rate (mean annualised relapse rate, patients remaining relapse free) • Disability progression (Expanded Disability Status Scale Score, confirmed disability progression) • Disease activity (patients remaining progression free) • Mortality • MRI measures • Safety and tolerability (adverse-event outcomes, withdrawal outcomes) • Health-related quality of life Publication dates • 1960 to 15 April 2010
Exclusion criteria	Population • Patients with primary progressive MS • Patients with progressive relapsing MS Interventions • Mitoxantrone Outcomes • Immunology outcomes (e.g., Nab titres) Study design • Pre-clinical studies • Phase 1 studies • Prognostic studies • Retrospective studies

Criteria	Clinical effectiveness
	• Case reports • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews • Systematic reviews and meta-analyses[†] Language • English[‡]

MRI, magnetic resonance imaging; MS, multiple sclerosis; Nab, natalizumab; RCT, randomised controlled prospective clinical trial; RRMS, relapsing-remitting multiple sclerosis.

* Cladribine was excluded at level 2 screening.

[†] Systematic reviews and meta-analyses were reviewed to identify any additional relevant RCTs.

[‡] Language restriction was applied to English language articles only at level 2 screening.

Search terms included combinations of free text and index headings (Medical Subject Headings). Three sets of terms were used:

- Terms to search for the health condition of interest (RRMS),
- Terms to search for the types of study desired to be included (for example, RCTs, open-label studies),
- Terms of interventions included free-text terms for individual agents. This included scientific names, brand names, drug classes, and therapy terms. Medical Subject Headings were also used if it was indexed in databases.

5.2.2 A flow diagram of the numbers of studies included and excluded 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 5.2.4.

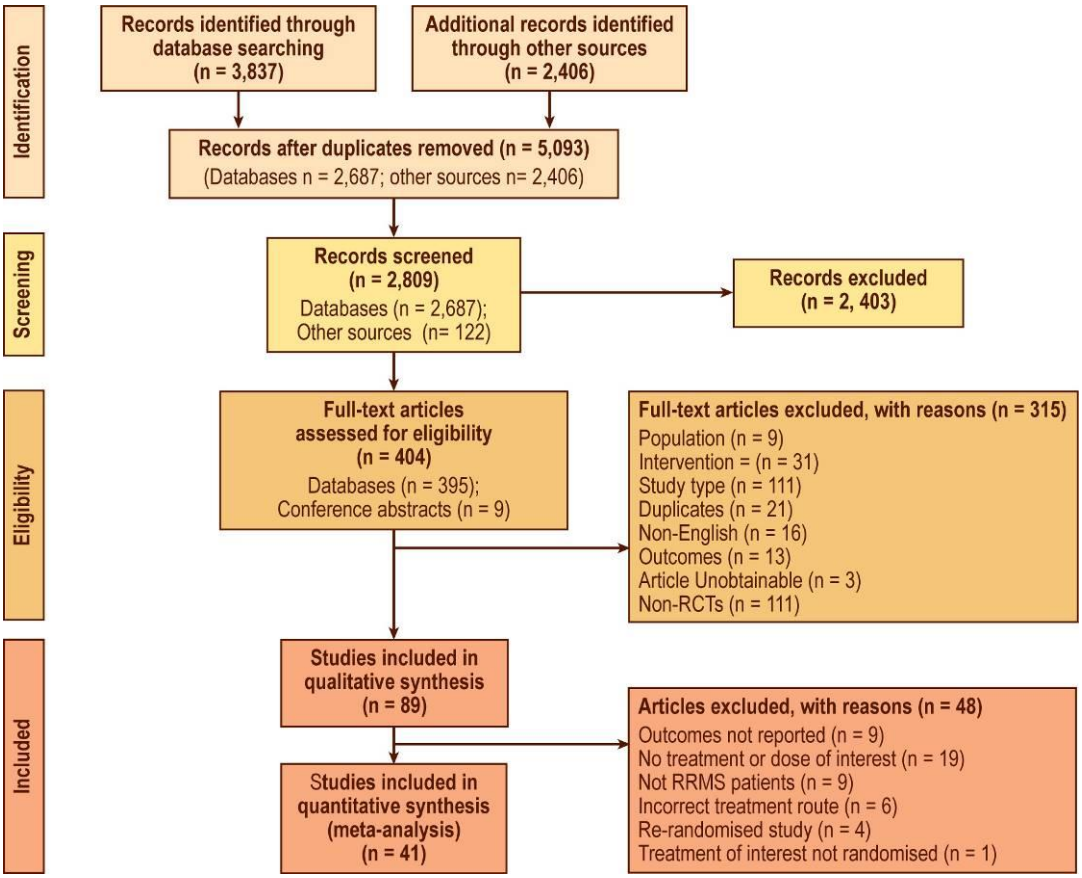
The database searches using the predefined search strategy yielded a total of 3,837 titles (PubMed = 1,151; Cochrane = 484; EMBASE = 2,202), of which 1,151 records were duplicates and therefore were excluded.

Hence, 2,686 titles or abstracts were eligible for further screening and were imported into the reference management software. In addition, 1 study was identified by hand searching the bibliographic references of systematic reviews and meta-analyses. Therefore, a total of 2,687 titles were eligible for Level 1 screening.

Studies identified through the electronic searches were screened by two researchers in duplicate and in parallel; differences were resolved by consensus. A total of 404 titles or abstracts were identified for Level 2 screening, inclusive of conference abstracts. A total of 89 articles were included in the qualitative synthesis. Of these, 41 unique records were deemed relevant for inclusion in the quantitative synthesis (meta-analysis), which related to 19 unique trials. Once cladribine was removed from the scope, 37 records were deemed relevant, which were associated with 18 unique trials. **Error! Reference source not found.** provides details these 37 records.

Reasons for exclusion are presented in Figure 1.

Figure 1 Study identification, inclusion and exclusion: primary systematic review*



RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis.

* Please note that of the 315 articles excluded at the level 2 screening, 111 were excluded based on "study type", which included reviews, commentaries, diagnostics studies, genetics studies, etc; another 111 were excluded based on the study being a non-RCT, which included 90 prospective observational studies, 11 open-label follow-up studies and 10 clinical trials that were not randomised.

5.2.3 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.

Complete list of relevant RCTs

5.2.4 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. A suggested format is presented below.

Table 7 presents all the completed RCTs with fingolimod, and Table 8 presents an extension study of an RCT investigating fingolimod.

Table 7 RCTs investigating fingolimod

Trial number (acronym)	Intervention (dosage)	Comparator (dosage)	Population	Primary study reference
FTY720 D2201 Core study	Oral 1.25 and 5.0 mg of fingolimod capsules once daily for 6 months	Matching placebo once daily for 6 months	Patients with a diagnosis of relapsing MS (RRMS and SPMS) aged 18-60 years; EDSS score from 0-6; two or more documented relapses during the previous 2 years, or one or more documented relapses in the year prior to enrolment; and no evidence of relapse for at least 30 days before screening	Kappos et al., 2006
Study D2302 (TRANSFORMS)	Oral 1.25 and 0.5 mg of fingolimod capsules once daily for 12 months	30 µg interferon-beta-1a given intramuscularly weekly	Patients with a diagnosis of RRMS aged 18-55 years; EDSS score from 0-5.5; two or more documented relapses during the previous 2 years, or one or more documented relapses in the year prior to enrolment	Cohen et al., 2010a
Study D2301 (FREEDOMS)	Oral 1.25 and 0.5 mg of fingolimod capsules once daily for 24 months	Matching placebo once daily for 24 months	Patients with a diagnosis of RRMS aged 18-55 years; EDSS score from 0-5.5; two or more documented relapses during the previous 2 years, or one or more documented relapses in the year prior to enrolment	Kappos et al., 2010

EDSS, Expanded Disability Status Scale; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Table 8 Extension studies of RCTs investigating fingolimod

Trial number (acronym)	Intervention and comparator (dosage)	Population	Primary study reference
FTY720 D2201 Extension study (2-year results)	Some of the patients in the placebo group were re-randomised to oral 1.25-mg fingolimod capsules once daily from month 7-24. The remaining patients in the placebo group were re-randomised to oral 5.0-mg fingolimod capsules once daily from month 7-24. The original group on oral 1.25-mg fingolimod capsules continued the treatment once daily from month 7-24. The original group on oral 5.0-mg fingolimod capsules continued the treatment once daily from month 7-24. During the study visits between months 15 and 24, all patients receiving 5.0-mg fingolimod capsules once daily were switched to 1.25 mg	Patients with a diagnosis of relapsing MS (RRMS and SPMS) aged 18-60 years; EDSS score ranging 0-6; with two or more documented relapses during the previous 2 years or one or more documented relapses in the year prior to enrolment; and with no evidence of relapse for at least 30 days before screening	O'Connor et al., 2009a (2-year data)
FTY720 D2201 Extension study (3-year results)	Extension of study FTY720 D2201 At month 24, all patients continued treatment with fingolimod 1.25 mg	Patients completing month 24 of FTY720 D2201	Comi et al., 2010 (3-year data)

EDSS, Expanded Disability Status Scale; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

5.2.5 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.

One RCT, Study D2302 (TRANSFORMS), compared fingolimod with the relevant active comparator interferon-beta-1a. Study D2301 (FREEDOMS) compared fingolimod with placebo, and this study supports analyses of fingolimod compared with the comparator best supportive care (BSC).

Both studies have been used in the submission as part of a mixed-treatment comparison to synthesise outcome data for fingolimod, active comparators, and BSC.

5.2.6 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.

Study D2201 compared fingolimod 1.25 mg and fingolimod 5.0 mg with placebo. This core study and the manuscripts reporting 2-year and 3-year data from the extension study do not include fingolimod 0.5 mg, which is the recommended and licensed dose intended for clinical practice, As such, these efficacy data are not considered relevant for this submission and will not be presented here.

List of relevant non-RCTs

5.2.7 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 5.8 and key details should be presented in a table; the following is a suggested format.

No relevant non-RCTs were identified for fingolimod.

Novartis undertook a burden-of-Illness study to establish treatment experience, costs, and health outcomes. This study was conducted in several countries during 2010; 189 people from the UK with MS took part in the study. The UK-specific results will be published in 2011. Some of the data points from the study have been used in the health economics model; this is indicated in the appropriate sections. The reason for including this data in the submission is that it is from a UK RRMS population and updates previous UK burden-of-illness studies that have been identified in the literature review.

5.3 Summary of methodology of relevant RCTs

5.3.1 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 Consolidated Standards of Reporting Trials (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**.

See Section 5.3.2.

Methods

5.3.2 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. The following tables provide a suggested format for when there is more than one RCT.

Table 9 presents the design of Study D2302 (TRANSFORMS). Table 10 presents the design of Study D2301 (FREEDOMS). The design of Study D2201 is presented in **Error! Reference source not found.** in Section **Error! Reference source not found.**. The design of the studies of the comparator

interventions for inclusion in the meta-analysis is presented in **Error! Reference source not found.** in Section **Error! Reference source not found.**.

Table 9 Summary of design of the Study D2302 (the TRANSFORMS study)

Trial number (acronym)	**Study D2302 (TRANSFORMS)**
Location	• 172 centres in 18 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Egypt, France, Germany, Greece, Hungary, Italy, Republic of Korea, Portugal, Spain, Switzerland, UK, US)
Design	• Phase III, international, multicentre, randomised, double-blind, double-dummy, parallel-group study
Duration of study	• 12 months
Method of randomisation	• Subjects were randomised (1:1:1) in a double-blinded fashion to receive oral fingolimod 0.5 mg/day, oral fingolimod 1.25 mg/day, or intramuscular interferon-beta-1a 30 µg once weekly • Randomisation was performed centrally in blocks of 6 within each site, and stratified according to site
Method of blinding (care provider, patient and outcome assessor)	• Study group assignments were performed with the use of an interactive voice-response system • During the trial, patients, study personnel, MRI evaluators, steering-committee members, and the study statistician were unaware of study-group assignments and leukocyte counts • Capsules, syringes, and packaging materials for the two treatments were indistinguishable • Patients were instructed to cover injection sites at visits and not to discuss adverse events with clinical evaluators • An independent physician monitored patients after the first dose of the oral study drug was administered and was instructed not to discuss heart-rate changes with patients or study personnel
Intervention(s) (n =) and comparator(s) (n =)	• Oral fingolimod 0.5 mg (n = 431) • Oral fingolimod 1.25 mg (n = 426) • Interferon-beta-1a 30 µg/week (n = 435)

Trial number (acronym)	Study D2302 (TRANSFORMS)
Primary outcomes (including scoring methods and timings of assessments)	• Annualised relapse rate (the number of confirmed relapses during a 12-month period) • Relapse was defined as new, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and that were accompanied by an increase of at least half a point on the EDSS or an increase of at least 1 point in two functional-systems scores or of at least 2 points in one functional-system score (excluding changes in bowel or bladder function and cognition)
Secondary outcomes (including scoring methods and timings of assessments)	• The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months • Time to confirmed disability progression. Progression of disability was defined as a 1-point increase in the EDSS score (or a half-point increase for patients with a baseline score ≥ 5.5) that was confirmed 3 months later in the absence of relapse. EDSS scores were determined every 3 months by a specially trained and certified examining neurologist
Duration of follow-up	• Patients were followed up for 12 months

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; UK, United Kingdom; US, United States.

Source: Cohen et al., 2010a.

Table 10 Summary of design of the Study D2301 (the FREEDOMS study)

Trial number (acronym)	Study D2301 (FREEDOMS)
Location	• 138 centres in 22 countries (Australia, Belgium, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, the Netherlands, Poland, Romania, Russia, Slovakia, South Africa, Sweden, Switzerland, Turkey, UK)
Design	• Phase III, international, multicentre, randomised, double-blind, placebo-controlled study
Duration of study	• 24 months
Method of randomisation	• Subjects were randomised (1:1:1) in a double-blinded fashion to receive oral fingolimod 0.5 mg, oral fingolimod 1.25 mg, or matching placebo once daily • Randomisation was performed centrally with the use of a validated system and stratified according to site, with a block size of 6 within each site
Method of blinding (care provider,	• The study medication was package-blinded for the entire double-blind treatment phase. The active study medication and its corresponding placebo were identical in appearance.

Trial number (acronym)	Study D2301 (FREEDOMS)
patient and outcome assessor)	Patients, investigator, site personnel, independent evaluating physician, first-dose administrator, and the sponsor. All Novartis personnel involved in Study D2301 (FREEDOMS), with the exception of Novartis Drug Supply Management, the Novartis independent statistician, and the independent programmer for DSMB, were blinded • An independent, specially trained, and certified examining neurologist determined all EDSS scores • Another independent physician monitored patients for 6 or more hours after administration of the first dose of the study drug • MRI scans were analysed at a central MRI evaluation centre by radiologists who were unaware of the study-group assignments, and an independent data and safety monitoring board evaluated the safety and overall benefit-risk profiles
Intervention(s) (n =) and comparator(s) (n =)	• Oral fingolimod 0.5 mg (n = 425) • Oral fingolimod 1.25 mg (n = 429) • Placebo (n = 418)
Primary outcomes (including scoring methods and timings of assessments)	• Annualised relapse rate (the number of confirmed relapses per year) • Relapses were verified by the examining neurologist within 7 days after the onset of symptoms • To constitute a confirmed relapse, the symptoms must have been accompanied by an increase of at least half a point in the EDSS score, of 1 point in each of two EDSS functional-system scores, or of 2 points in one EDSS functional-system score (excluding scores for the bowel-bladder or cerebral functional systems)
Secondary outcomes (including scoring methods and timings of assessments)	• Time to confirmed disability progression, defined as an increase of 1 point in the EDSS score (or a half-point if the baseline EDSS score = 5.5) confirmed after 3 months, with an absence of relapse at the time of assessment, and with all EDSS scores measured during that time meeting the criteria for disability progression. EDSS scores were determined every 3 months by a specially trained and certified examining neurologist • Time to a first relapse • Time to disability progression (confirmed after 6 months) • Changes in the EDSS score between baseline and 24 months • Changes in the MSFC z score between baseline and 24 months; MSFC z scores were determined every 6 months • Number of gadolinium-enhancing lesions • Proportion of patients free from gadolinium- enhancing lesions • Number of new or enlarged lesions on T2-weighted MRI scans • Proportion of patients free from new or enlarged lesions on T2-

Trial number (acronym)	Study D2301 (FREEDOMS)
	weighted scans • Volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans • Change in brain volume between baseline and 24 months • Safety and tolerability measures

Trial number (acronym)	Study D2301 (FREEDOMS)
Duration of follow-up	• Patients were followed up for 24 months

DSMB, Data and Safety Monitoring Board; EDSS, Expanded Disability Status Scale; MSFC z, Multiple Sclerosis Functional Composite (a quantitative measure of impairment in ambulation, upper-extremity function, and cognitive function, expressed as z scores, with higher scores indicating improvement); MRI, magnetic resonance imaging; MS, multiple sclerosis; RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SIENA, Structural Image Evaluation Using Normalisation of Atrophy; UK, United Kingdom.

Source: Kappos et al., 2010.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table 11 presents the inclusion and exclusion criteria for Study D2302 (TRANSFORMS). Table 12 presents the inclusion and exclusion criteria for Study D2301 (FREEDOMS). The inclusion and exclusion criteria for Study D2201 are presented in **Error! Reference source not found.** in Section **Error! Reference source not found.**.

Table 11 Eligibility criteria in Study D2302 (the TRANSFORMS study)

Trial number (acronym)	Inclusion criteria	Exclusion criteria
Study D2302 (TRANSFORMS)	• Aged 18-55 years • Received a diagnosis of MS that met the revised McDonald criteria* • Disease with a relapsing-remitting course • Had ≥ 1 documented relapse during the previous year or ≥ 2 documented relapses during the previous 2 years preceding enrolment in the study† • EDSS score of 0-5.5	• Documented relapse or corticosteroid treatment within 30 days before randomisation • Active infection, macular oedema, immunosuppression (either drug or disease induced), and clinically significant co-existing systemic disease (Note that previous recent therapy with either any type of interferon-beta or glatiramer acetate was not a criterion for exclusion)

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; RCT, randomised controlled trial.

* Refer to Polman et al., 2005, for full details of revised McDonald criteria.

† The relapse was recorded in a documented dialogue with the patient's primary treating physician.

Source: Cohen et al., 2010a.

Table 12 Eligibility criteria in Study D2301 (FREEDOMS)

Trial number (acronym)	Inclusion criteria	Exclusion criteria
Study D2301 (FREEDOMS)	• Aged 18-55 years • Received a diagnosis of MS that met the revised McDonald criteria* • Disease with a relapsing-remitting course • Had ≥ 1 documented relapse during the previous year or ≥ 2 documented relapses during the previous 2 years preceding enrolment in the study† • EDSS score of 0-5.5	• Documented relapse or corticosteroid treatment within the 30 days before randomisation • Active infection, macular oedema, diabetes mellitus, immunosuppression (either drug or disease induced), or clinically significant systemic disease • Patients stopped therapy with interferon-beta or glatiramer acetate for ≥ 3 months before randomisation

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; RCT, randomised controlled trial.

* Refer to Polman et al., 2005, for full details of revised McDonald criteria.

† The relapse was recorded in a documented dialogue with the patient's primary treating physician.

Source: Kappos et al., 2010.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 13 presents the baseline characteristics of patients in Study D2302 (TRANSFORMS), and Table 14 presents the baseline characteristics of patients in Study D2301 (FREEDOMS).

Table 13 Baseline characteristics for patients randomised in Study D2302 (the TRANSFORMS study)

Baseline characteristic	Fingolimod 0.5 mg (n = 431)	Fingolimod 1.25 mg (n = 426)	Interferon-beta-1a (n = 435)
Age, years			
Mean (SD)	35.8 (8.4)	36.7 (8.8)	36.0 (8.3)
Median (range)	36 (18-54)	37 (18-55)	36 (18-55)

Baseline characteristic	**Fingolimod 0.5 mg (n = 431)**	**Fingolimod 1.25 mg (n = 426)**	**Interferon-beta-1a (n = 435)**
Female, n (%)	293 (68.8)	282 (65.4)	295 (67.8)
White race, n (%)	404 (94.8)	404 (93.7)	408 (93.8)
Clinical characteristics			
Interval from onset of symptoms to randomisation (years)			
Mean (SD)	7.3 (6.0)	7.5 (6.2)	7.4 (6.3)
Median (range)	6 (0-33)	6 (0-34)	6 (0-40)
Relapses in previous year			
Mean (SD)	1.5 (0.9)	1.5 (1.2)	1.5 (0.8)
Median (range)	1 (0-7)	1 (0-20)	1 (0-6)
Relapses in previous 2 years			
Mean (SD)	2.2 (1.2)	2.3 (2.2)	2.3 (1.2)
Median (range)	2 (1-8)	2 (1-40)	2 (1-12)
EDSS score			
Mean (SD)	2.21 (1.31)	2.24 (1.33)	2.19 (1.26)
Median (range)	2.0 (0-5.5)	2.0 (0-5.5)	2.0 (0-5.5)
Treatment history			
Any therapy, n (%)	249 (58.5)	238 (55.2)	245 (56.3)
Any interferon-beta	209 (49.1)	219 (50.8)	207 (47.6)
Glatiramer acetate	67 (15.7)	57 (13.2)	67 (15.4)
Natalizumab	3 (0.7)	4 (0.9)	1 (0.2)
MRI findings			
Patients with no gadolinium-enhancing lesions on T_1-weighted images, number/total (%)	270/412 (65.5)	288/427 (67.4)	268/425 (63.1)
Number of gadolinium-enhancing lesions on T_1-weighted images			
Mean (SD)	1.49 (4.77)	0.98 (2.81)	1.06 (2.80)
Median (range)	0 (0-66)	0 (0-29)	0 (0-36)
Volume of lesions on T_2-weighted images, mm^3			
Mean (SD)	5085 (5962)	5170 (6642)	4924 (5711)

Baseline characteristic	Fingolimod 0.5 mg (n = 431)	Fingolimod 1.25 mg (n = 426)	Interferon-beta-1a (n = 435)
Median (range)	3096 (0-38,870)	2382 (0-46,280)	2901 (0-38,712)
Normalised brain volume, cm^3			
Mean (SD)	1526.2 (76.4)	1524.1 (83.9)	1526.7 (77.9)
Median (range)	1528 (1300-1794)	1526 (1185-1862)	1533 (1231-1762)

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; N/A, not available; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Table 14 Baseline characteristics for patients randomised in Study D2301 (the FREEDOMS study)*

Baseline characteristic†	Fingolimod 1.25 mg (n = 429)	Fingolimod 0.5 mg (n = 425)	Placebo (n = 418)
Age, years			
Mean (SD)	37.4 (8.9)	36.6 (8.8)	37.2 (8.6)
Median (range)	38.0 (17-55)	36.0 (18-55)	37.0 (18-55)
Female, n (%)	295 (68.8)	296 (69.6)	298 (71.3)
Disease and treatment history			
Time from first MS symptom to randomisation, years			
Mean (SD)	8.4 (6.9)	8.0 (6.6)	8.1 (6.4)
Median (range)	6.9 (0-37)	6.6 (0-35)	7.0 (0-32)
Number of relapses within previous year			
Mean (SD)	1.5 (0.8)	1.5 (0.8)	1.4 (0.7)
Median (range)	1.0 (0-6)	1.0 (0-5)	1.0 (0-6)
Number of relapses within previous 2 years			
Mean (SD)	2.1 (1.3)	2.1 (1.1)	2.2 (1.2)
Median (range)	2.0 (1-10)	2.0 (1-11)	2.0 (1-10)
EDSS score‡			
Mean	2.4 (1.4)	2.3 (1.3)	2.5 (1.3)
Median (range)	2.0 (0-5.5)	2.0 (0-5.5)	2.0 (0-5.5)
No history of disease-modifying treatment, n (%)	259 (60.4)	244 (57.4)	249 (59.6)
Features on MRI§			
Absence of gadolinium-enhancing lesions, n (%)	257 (60.6)	263 (62.0)	262 (63.0)

Baseline characteristic†	Fingolimod 1.25 mg (n = 429)	Fingolimod 0.5 mg (n = 425)	Placebo (n = 418)
Number of gadolinium-enhancing lesions on T_1-weighted images			
Mean (SD)	1.8 (4.7)	1.6 (5.6)	1.3 (2.9)
Median (range)	0 (0-50)	0 (0-84)	0 (0-26)
Volume of lesions on T_2-weighted images (mm^3)			
Mean (SD)	6829 (8491)	6128 (7623)	6162 (7085)
Median (range)	3557 (0-47,734)	3303 (0-47,148)	3416 (0-37,148)
Volume of hypo-intense lesions on T_1-weighted images (mm^3)			
Mean (SD)	2114 (3220)	1898 (2854)	1962 (3131)
Median (range)	860 (0-25,886)	814 (0-22,378)	811 (0-20,956)
Normalised brain volume (mL)			
Mean (SD)	1511 (86)	1521 (83)	1512 (85)
Median (range)	1515 (1217-1764)	1529 (1144-1734)	1515 (1230-1723)

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; N/A, not available; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

* Means and medians were calculated on the basis of all images, not just those showing lesions.

† There were no significant between-group differences at baseline for any characteristic.

‡ The EDSS ranges from 0 to 10, with higher scores indicating greater disability.

§ MRI data were available for 424 patients in each of the fingolimod groups and for 416 patients in the placebo group.

We also have baseline demographics data for the patient subpopulations of interest in the label indication. For patients who received prior treatment with any disease-modifying therapy in the year before the study and who had at least one relapse in the previous year while on therapy and either at least one gadolinium-enhancing lesion or a T2 lesion volume of at least 500 mm^2, Table 15 presents the baseline characteristics of patients in Study D2302 (TRANSFORMS) and

Table 16 presents the baseline characteristics of patients in Study D2301 (FREEDOMS). For non-responder patients who received prior treatment with any disease-modifying therapy in the year before the study and who had an

unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year,

Table 17 presents the baseline characteristics of patients in Study D2302 (TRANSFORMS) and

Table 18 presents the baseline characteristics of patients in Study D2301 (FREEDOMS).

Table 15 Baseline characteristics for patients receiving any prior DMT in the year before the study, with ≥ 1 relapse while on therapy and either ≥ 1 gadolinium-enhancing lesion or a T2 lesion volume of ≥ 500 mm^2, randomised in Study D2302 (the TRANSFORMS study)

Baseline characteristic	**Fingolimod 0.5 mg (n = 189)**	**Fingolimod 1.25 mg (n = 182)**	**Interferon-beta-1a (n = 191)**
Age, years			
Mean (SD)	37.09 (8.81)	36.28 (8.38)	37.06 (8.38)
Median (range)	37.0 (19-55)	37.5 (19-54)	37.0 (18-55)
Female, n (%)	134 (70.9%)	134 (73.6%)	129 (67.5%)
Clinical characteristics			
Time since onset of symptoms (years)			
Mean (SD)	6.44 (4.69)	5.80 (4.59)	6.78 (5.98)
Median (range)	5.4 (0-21)	4.6 (0-25)	5.6 (0-40)
Relapses in previous year before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Relapses in previous 2 years before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
EDSS score			
Mean (SD)	2.53 (1.36)	2.38 (1.36)	2.43 (1.22)
Median (range)	2.5 (0.0-5.5)	2.0 (0.0-5.5)	2.5 (0.0-5.5)
EDSS score, n (%)			
0.0	[redacted]	[redacted]	[redacted]
1.0	[redacted]	[redacted]	[redacted]
1.5	[redacted]	[redacted]	[redacted]
2.0	[redacted]	[redacted]	[redacted]

Baseline characteristic	Fingolimod 0.5 mg (n = 189)	Fingolimod 1.25 mg (n = 182)	Interferon-beta-1a (n = 191)
2.5	[redacted]	[redacted]	[redacted]
3.0	[redacted]	[redacted]	[redacted]
3.5	[redacted]	[redacted]	[redacted]
4.0	[redacted]	[redacted]	[redacted]
4.5	[redacted]	[redacted]	[redacted]
5.0	[redacted]	[redacted]	[redacted]
5.5	[redacted]	[redacted]	[redacted]
MRI findings			
Patients with no gadolinium-enhancing lesions on T_1-weighted images, n (%)	[redacted]	[redacted]	[redacted]
Number of gadolinium-enhancing lesions on T_1-weighted images			
Mean (SD)	1.01 (2.71)	1.28 (3.63)	1.04 (2.37)
Median (range)	0.0 (0-29)	0.0 (0-27)	0.0 (0-17)
Volume of lesions on T_2-weighted images, mm^3			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; N/A, not available; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Table 16 Baseline characteristics for patients receiving any prior DMT in the year before the study, with ≥ 1 relapse while on therapy and either ≥ 1 gadolinium-enhancing lesion or a T2 lesion volume of ≥ 500 mm^2, randomised in Study D2301 (the FREEDOMS study)*

Baseline characteristic	Fingolimod 0.5 mg (n = 88)	Fingolimod 1.25 mg (n = 79)	Placebo (n = 88)
Age, years			
Mean (SD)	37.83 (9.13)	37.23 (8.82)	37.31 (8.93)
Median (range)	37.0 (19-55)	38.0 (19-55)	39.0 (19-54)
Female, n (%)	62 (70.5%)	54 (68.4%)	58 (65.9%)
Clinical characteristics			
Time since onset of symptoms (years)			
Mean (SD)	6.11 (4.88)	8.11 (5.98)	5.96 (4.83)

Baseline characteristic	**Fingolimod 0.5 mg (n = 88)**	**Fingolimod 1.25 mg (n = 79)**	**Placebo (n = 88)**
Median (range)	4.6 (0-24)	7.0 (0-28)	4.7 (1-24)
Relapses in previous year before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Relapses in previous 2 years before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
EDSS score			
Mean (SD)	2.49 (1.24)	2.84 (1.31)	2.91 (1.51)
Median (range)	2.5 (0.0 -5.5)	3.0 (0.0-5.5)	3.0 (0.0-5.5)
EDSS score, n (%)			
0.0	[redacted]	[redacted]	[redacted]
1.0	[redacted]	[redacted]	[redacted]
1.5	[redacted]	[redacted]	[redacted]
2.0	[redacted]	[redacted]	[redacted]
2.5	[redacted]	[redacted]	[redacted]
3.0	[redacted]	[redacted]	[redacted]
3.5	[redacted]	[redacted]	[redacted]
4.0	[redacted]	[redacted]	[redacted]
4.5	[redacted]	[redacted]	[redacted]
5.0	[redacted]	[redacted]	[redacted]
5.5	[redacted]	[redacted]	[redacted]
MRI findings			
Patients with no gadolinium-enhancing lesions on T1-weighted images, n (%)	[redacted]	[redacted]	[redacted]
Number of gadolinium-enhancing lesions on T1-weighted images			
Mean (SD)	2.75 (9.88)	1.76 (4.28)	1.85 (4.24)
Median (range)	0.0 (0-84)	0.0 (0-26)	0.0 (0-25)
Volume of lesions on T2-weighted images, mm3			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; N/A, not available; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Table 17 Baseline characteristics for non-responder patients receiving any prior DMT in the year before the study, with an unchanged or increased relapse rate or ongoing severe relapses, as compared with the previous year, as randomised in Study D2302 (the TRANSFORMS study)

Baseline characteristic	**Fingolimod 0.5 mg (n = 191)**	**Fingolimod 1.25 mg (n = 189)**	**Interferon-beta-1a (n = 183)**
Age, years			
Mean (SD)	37.21 (8.66)	36.27 (8.47)	37.11 (8.44)
Median (range)	38.0 (19-55)	37.0 (19-54)	37.0 (18-55)
Female, n (%)	137 (71.7%)	135 (71.4%)	127 (69.4%)
Clinical characteristics			
Time since onset of symptoms (years)			
Mean (SD)	6.10 (4.64)	5.63 (4.55)	6.81 (6.10)
Median (range)	5.0 (0-21)	4.4 (0-25)	5.6 (0-40)
Relapses in previous year before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Relapses in previous 2 years before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
EDSS score			
Mean (SD)	2.50 (1.34)	2.34 (1.37)	2.45 (1.23)
Median (range)	2.0 (0.0-5.5)	2.0 (0.0-5.5)	2.5 (0.0-5.5)
EDSS score, n (%)			
0.0	[redacted]	[redacted]	[redacted]
1.0	[redacted]	[redacted]	[redacted]
1.5	[redacted]	[redacted]	[redacted]
2.0	[redacted]	[redacted]	[redacted]
2.5	[redacted]	[redacted]	[redacted]
3.0	[redacted]	[redacted]	[redacted]
3.5	[redacted]	[redacted]	[redacted]
4.0	[redacted]	[redacted]	[redacted]
4.5	[redacted]	[redacted]	[redacted]
5.0	[redacted]	[redacted]	[redacted]
5.5	[redacted]	[redacted]	[redacted]

Baseline characteristic	Fingolimod 0.5 mg (n = 191)	Fingolimod 1.25 mg (n = 189)	Interferon-beta-1a (n = 183)
MRI findings			
Patients with no gadolinium-enhancing lesions on T_1-weighted images, n (%)	[redacted]	[redacted]	[redacted]
Number of gadolinium-enhancing lesions on T_1-weighted images			
Mean (SD)	0.94 (2.69)	1.02 (3.00)	1.06 (2.42)
Median (range)	0.0 (0-29)	0.0 (0-25)	0.0 (0-17)
Volume of lesions on T_2-weighted images, mm^3			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; N/A, not available; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Table 18 Baseline characteristics for non-responder patients receiving any prior DMT in the year before the study, with an unchanged or increased relapse rate or ongoing severe relapses, as compared with the previous year, as randomised in Study D2301 (the FREEDOMS study)*

Baseline characteristic	Fingolimod 0.5 mg (n = 90)	Fingolimod 1.25 mg (n = 81)	Placebo (n = 79)
Age, years			
Mean (SD)	38.13 (9.28)	37.06 (8.71)	37.68 (8.49)
Median (range)	38.0 (19-55)	38.0 (19-55)	39.0 (19-54)
Female, n (%)	65 (72.2%)	56 (69.1%)	51 (64.6%)
Clinical characteristics			
Time since onset of symptoms (years)			
Mean (SD)	6.27 (5.44)	7.27 (5.49)	5.63 (5.07)
Median (range)	4.6 (0-30)	6.2 (0-22)	3.5 (1-24)
Relapses in previous year before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Baseline characteristic	Fingolimod 0.5 mg (n = 90)	Fingolimod 1.25 mg (n = 81)	Placebo (n = 79)
Relapses in previous 2 years before baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
EDSS score			
Mean (SD)	2.47 (1.21)	2.77 (1.37)	2.97 (1.53)
Median (range)	2.5 (0.0-5.5)	3.0 (0.0-5.5)	3.0 (0.0-5.5)
EDSS score, n (%)			
0.0	[redacted]	[redacted]	[redacted]
1.0	[redacted]	[redacted]	[redacted]
1.5	[redacted]	[redacted]	[redacted]
2.0	[redacted]	[redacted]	[redacted]
2.5	[redacted]	[redacted]	[redacted]
3.0	[redacted]	[redacted]	[redacted]
3.5	[redacted]	[redacted]	[redacted]
4.0	[redacted]	[redacted]	[redacted]
4.5	[redacted]	[redacted]	[redacted]
5.0	[redacted]	[redacted]	[redacted]
5.5	[redacted]	[redacted]	[redacted]
MRI findings			
Patients with no gadolinium-enhancing lesions on T1-weighted images, n (%)	[redacted]	[redacted]	[redacted]
Number of gadolinium-enhancing lesions on T1-weighted images			
Mean (SD)	2.62 (9.79)	1.77 (4.31)	1.76 (4.42)
Median (range)	0.0 (0-84)	0.0 (0-26)	0.0 (0-25)
Volume of lesions on T2-weighted images, mm3			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; N/A, not available; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.

Outcomes

5.3.5 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 following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table 19 presents the outcomes and assessments for Study D2302 (TRANSFORMS), and Table 20 presents the outcomes and assessments for Study D2301 (FREEDOMS).

Table 19 Primary and secondary outcomes of Study D2302 (the TRANSFORMS study)

Trial number (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/ validity/ current use in clinical practice
Study D2302 (TRANSFORMS)	Annualised relapse rate, defined as the number of confirmed relapses during a 12-month period	Annualised relapse rate is recognised and used in clinical practice. Relapses were rigorously evaluated by independent evaluating physicians on the basis of changes in functional systems and EDSS scores, to verify that the relapses conformed to the definition of a "confirmed relapse" within 7 days after the onset of symptoms To constitute a confirmed relapse, the symptoms must have been accompanied by an increase of at least a half of a point in the EDSS score or by 2 points in one EDSS functional-system score (excluding scores for the bowel-bladder or cerebral functional systems)*	• Number of new or enlarged hyperintense lesions on T_2-weighted MRI scans at 12 months • Time to confirmed disability progression, defined as a 1-point increase in EDSS score (0.5-point increase for baseline EDSS score, ≥ 5.5), confirmed 3 months later in the absence of relapse • Time to first relapse • Proportion of participants with confirmed disability progression • Changes in the EDSS score and MSFC z score between baseline and 12 months • Proportion of participants free from new or enlarged T_2 or gadolinium-enhancing T_1 lesions • Number and volume of gadolinium-enhancing T_1 lesions	These endpoints are used within UK clinical practice

EDSS, Expanded Disability Status Scale; FS, functional system; MRI, magnetic resonance imaging; MSFC z, Multiple Sclerosis Functional Composite (a quantitative measure of impairment in ambulation, upper-extremity function, and cognitive function, expressed as z scores, with higher scores indicating improvement); N/A, not applicable; RCT, randomised controlled trial; UK, United Kingdom.

[*] Mild relapse = EDSS increase of 0.5- or 1-point FS change in one to three systems; moderate relapse = EDSS increase of 1 or 2 points or 2-point FS change in one or two systems or 1-point change in four or more systems; severe relapse = exceeding EDSS increase of 1 or 2 points or exceeding 2-point FS change in one or two systems or exceeding 1-point change in four or more systems.

Table 20 Primary and secondary outcomes of Study D2301 (the FREEDOMS study)

Trial number (acronym)	**Primary outcome(s) and measures**	**Reliability/validity/ current use in clinical practice**	**Secondary outcome(s) and measures**	**Reliability/ validity/ current use in clinical practice**
Study D2301 (FREEDOMS)	Annualised relapse rate, defined as the number of confirmed relapses per year	Relapses were rigorously evaluated by independent evaluating physicians on the basis of changes in functional systems and EDSS scores, to verify that the relapses conformed to the definition of a "confirmed relapse" within 7 days after the onset of symptoms To constitute a confirmed relapse, the symptoms must have been accompanied by an increase of at least a half of a point in the EDSS score or of 2 points in 1 EDSS functional-system score (excluding scores for the bowel-bladder or cerebral functional systems)[*]	• Time to confirmed disability progression, defined as an increase of 1 point in the EDSS score (or a half of a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression • Time to first relapse • Time to disability progression (confirmed after 6 months) • Changes in the EDSS score and MSFC z score between baseline and 24 months • Number of gadolinium-enhancing lesions • Proportion of patients free from gadolinium-enhancing lesions	These endpoints are used within UK clinical practice

Trial number (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/ validity/ current use in clinical practice
			• Number of new or enlarged lesions on T_2-weighted MRI scans • Proportion of patients free from new or enlarged lesions on T_2-weighted scans • Volumes of hyperintense lesions on T_2-weighted scans and hypo-intense lesions on T_1-weighted scans • Change in brain volume between baseline and 24 months • Safety and tolerability measures	

EDSS, Expanded Disability Status Scale; FS, functional system; MRI, magnetic resonance imaging; MSFC z, Multiple Sclerosis Functional Composite (a quantitative measure of impairment in ambulation, upper-extremity function, and cognitive function, expressed as z scores, with higher scores indicating improvement); N/A, not applicable; UK, United Kingdom.

* Mild relapse = EDSS increase of 0.5- or 1-point FS change in one to three systems; moderate relapse = EDSS increase of 1 or 2 points or 2-point FS change in one or two systems or 1-point change in four or more systems; severe relapse = exceeding EDSS increase of 1 or 2 points or exceeding 2-point FS change in one or two systems or exceeding 1-point change in four or more systems. These definitions of relapse severity were approved by the scientific steering committee and ethics and data safety monitoring committees, which would have included members engaged in clinical practice and thus would have validated the definitions' clinical validity.

Statistical analysis and definition of study groups

5.3.6 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). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 21 presents information on the statistical analyses conducted in Study D2302 (TRANSFORMS). Table 22 presents information on the statistical analyses conducted in Study D2301 (FREEDOMS).

Table 21 Summary of statistical analyses in Study D2302 (the TRANSFORMS study)

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study D2302 (TRANSFORMS)	The study was designed to test the null hypothesis that there would be no significant differences in the annualised relapse rate between either of the fingolimod groups and the interferon group with the use of a negative binomial regression model with adjustment for study group, country, number of relapses in the previous 2 years, and baseline EDSS score	• The modified intention-to-treat cohort, which consisted of all patients who underwent randomisation and received at least one dose of study drug, was the primary focus for efficacy and safety analyses • To control for type I errors, multiplicity adjustment was applied to testing for comparisons between fingolimod and interferon-beta-1a in a hierarchical order, according to the dose of fingolimod, for the study endpoints. Each test was performed at a significance level of 0.05. However, the lower-rank testing was performed only when every higher-rank test indicated statistical significance	Using the Wilcoxon-Mann-Whitney rank-sum test, it was estimated that an enrolment of 425 patients per study group would be needed to provide a power of 90% at a two-sided significance level of 0.05	All participants were encouraged to continue in the study for follow-up assessments after discontinuation of study drug; and all data available for these participants, including data acquired after study drug discontinuation, were included in the analyses, i.e., relapses reported after study drug discontinuation were included For participants who withdrew from the study prior to month 12, the number of relapses up to the time of discontinuation was used in the negative binomial regression model, and no imputation was applied for the time from study discontinuation to month 12

EDSS, Expanded Disability Status Scale; N/A, not applicable; RCT, randomised controlled trial.

Table 22 Summary of statistical analyses in Study D2301 (the FREEDOMS study)

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study D2301 (FREEDOMS)	The study tested 2 null hypotheses: that there were no differences in the annualised relapse rate between the group receiving fingolimod at a dose of 1.25 mg and the group receiving placebo or between the group receiving fingolimod at a dose of 0.5 mg and the group receiving placebo	Both the intention-to-treat population and the safety population included all patients who had undergone randomisation The aggregate annualised relapse rate was estimated by means of a negative binomial regression model with adjustment for study group, country, number of relapses within 2 years before baseline, and EDSS score at baseline The time to relapse or progression was estimated with the use of the Kaplan-Meier method Times to disability progression (confirmed after 3 or 6 months) were compared in the main analysis by means of the log-rank test and in the supportive analysis by means of a Cox proportional-hazards model, with adjustment for study group, country, baseline EDSS score, and age	The authors calculated that a sample of 1,250 patients would provide 95% statistical power to detect a relative reduction of 40% or more in the annualised relapse rate with fingolimod, as compared with placebo, after 24 months With this sample size, using a log-rank test and a 2-sided α level of 0.05 (assuming a study-discontinuation rate of 25%), the study would have a statistical power of more than 90% to detect an absolute difference between the 2 groups of 12% in the proportion of patients with disability progression (confirmed after 3 months) at month 24, which was expected to be approximately 30% in the placebo group	All participants were encouraged to continue in the study for follow-up assessments after discontinuation of study drug; and all data available for these participants, including data acquired after study drug discontinuation, were included in the analyses, i.e., relapses reported after study drug discontinuation were included For participants who withdrew from the study prior to month 24, the number of relapses up to the time of discontinuation was used in the negative binomial regression model, and no imputation was applied for the time from study discontinuation to month 12

EDSS, Expanded Disability Status Scale.

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

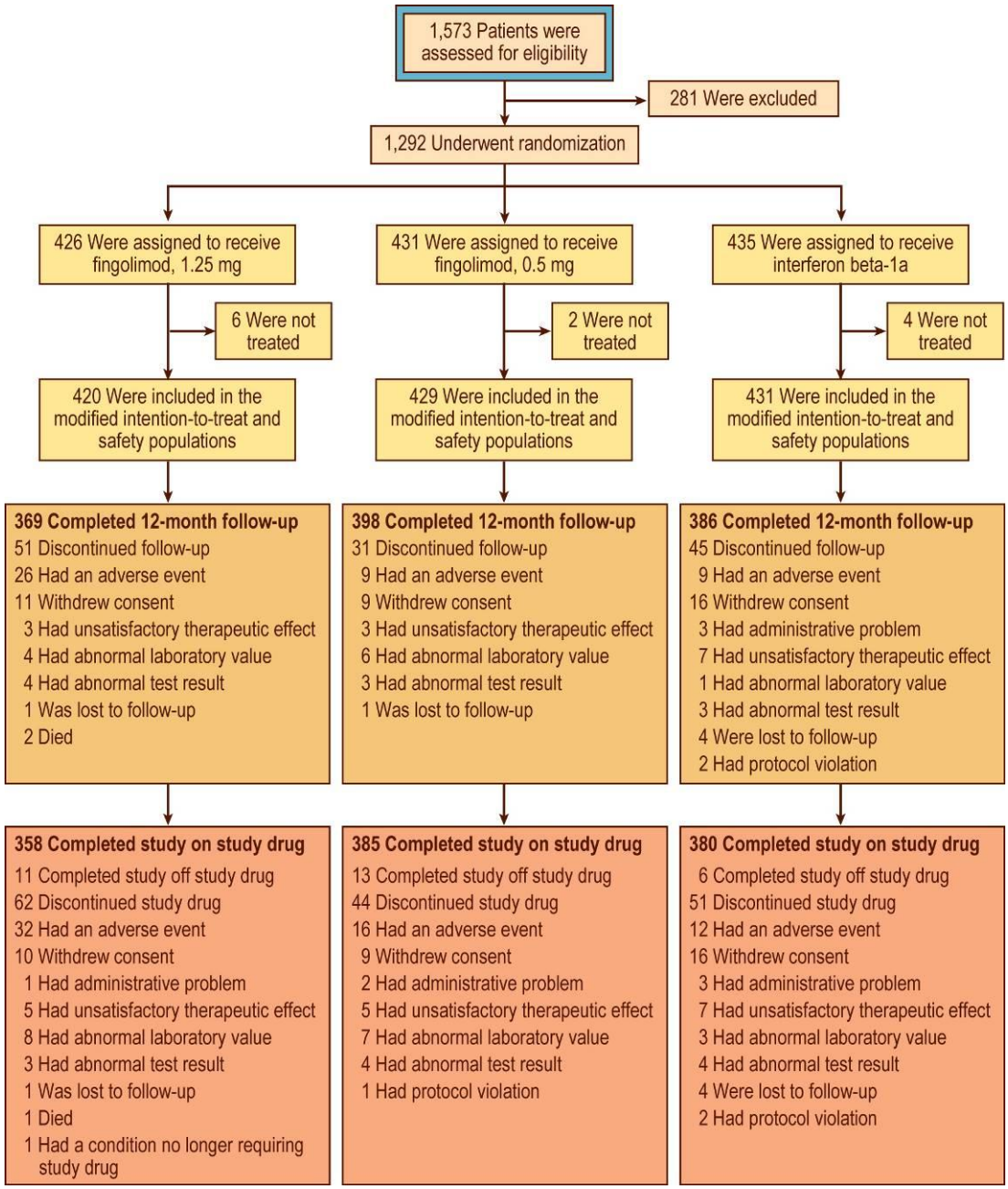
The proposed licensed population for fingolimod in the UK is a restricted population of the entire trial populations of Study D2302 (TRANSFORMS) and D2301 (FREEDOMS). Specific clinical data for the entire restricted population, for patients with high disease activity despite treatment with a beta-interferon, and for patients with RES relapsing remitting MS are not available. However, data for components of the restricted populations are discussed in Section 5.5.

Participant flow

5.3.8 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.

Figure 2 and Figure 3 present CONSORT flow charts that provide details of the numbers of patients who were eligible to enter Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS), respectively, who underwent randomisation, and who were allocated to each treatment.

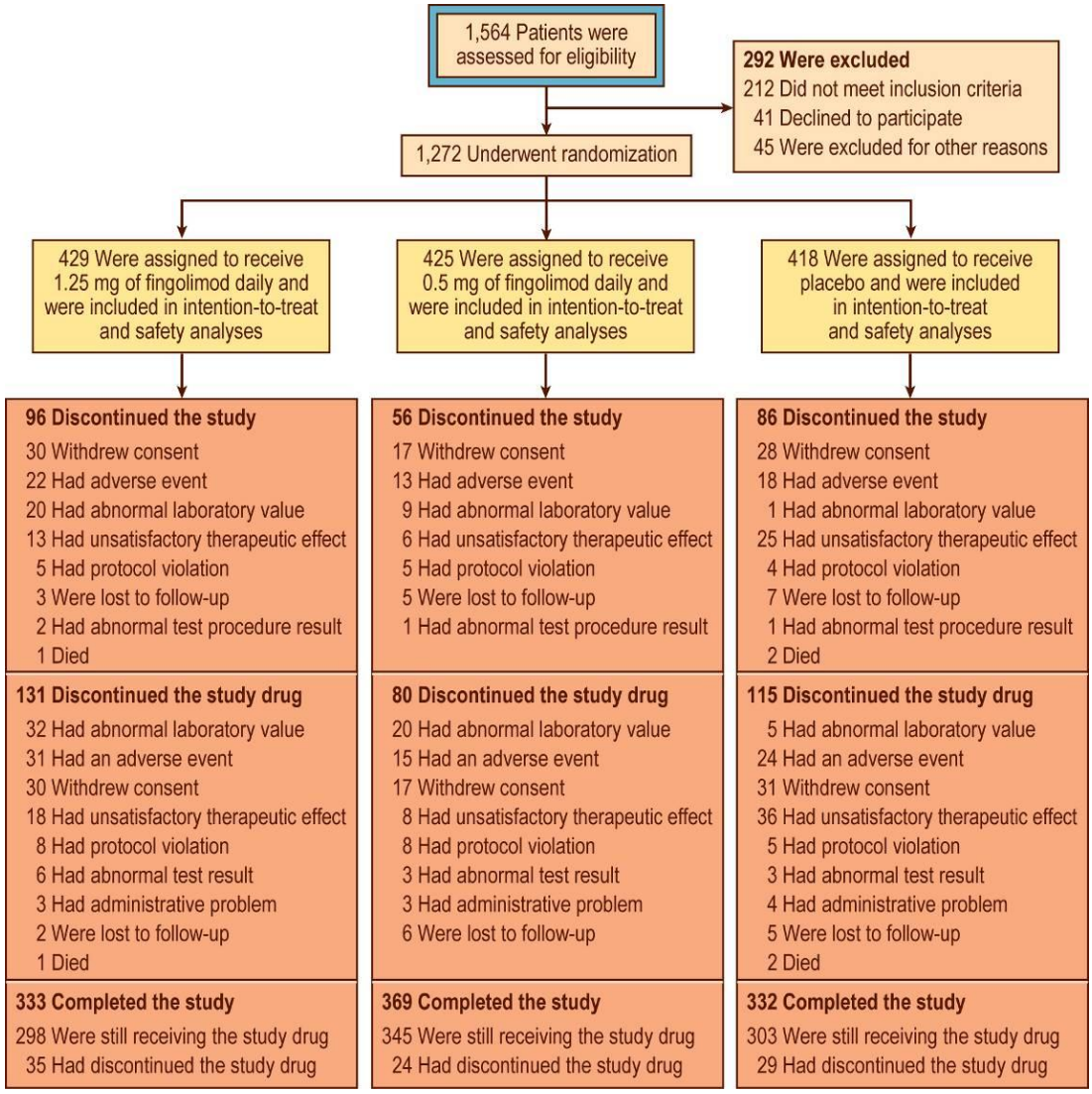
Figure 2 CONSORT flow chart for Study D2302 (the TRANSFORMS study)



CONSORT, Consolidated Standards of Reporting Trials.

Source: Cohen et al., 2010a.

Figure 3 CONSORT flow chart for Study D2301 (the FREEDOMS study)



CONSORT, Consolidated Standards of Reporting Trials.
Source: Kappos et al., 2010.

5.4 Critical appraisal of relevant RCTs

5.4.1 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. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See Section **Error! Reference source not found.**, Appendix 3, for a suggested format.

Please see Section **Error! Reference source not found.**.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 23 presents the overall quality assessment for Study D2302 (TRANSFORMS), Study D2301 (FREEDOMS), and Study D2201. Table 24 presents further detail of the quality assessment for Study D2302 (TRANSFORMS). Table 25 presents further details on the quality assessment for Study D2301 (FREEDOMS). Further details on the quality assessment for

Study D2201 are presented in **Error! Reference source not found.** in Section **Error! Reference source not found.**.

Table 23 Quality-assessment results for RCTs

Trial number (acronym)	Study D2302 (TRANSFORMS)	Study D2301 (FREEDOMS)	FTY720 D2201
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	Yes	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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	Yes

RCT, randomised controlled trial.

Source: adapted from Centre for Reviews and Dissemination, 2008.

Table 24 Quality-assessment results for Study D2302 (the TRANSFORMS study)

Study ID: TRANSFORMS		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**

Study ID: TRANSFORMS		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation was performed centrally in blocks of 6 within each site and stratified according to site	Yes
Was the concealment of treatment allocation adequate?	The treatment allocation was by interactive voice response system	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics (age, sex, course of disease, number of relapse in previous year, EDSS scores, and treatment history) were similar	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and site personnel (care providers and outcome assessors) were blinded	Yes
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Percentage of patients who discontinued follow-up in fingolimod 0.5-mg group was 7.2% compared with 1.25 mg fingolimod (12%) and interferon (10%)*	Yes
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?	All patients who underwent randomisation and who received at least 1 dose of the study drug were included in the efficacy and safety analysis	Yes

EDSS, Expanded Disability Status Scale; ID, identification; N/A, not applicable.

* These are the numbers of patients discontinuing the study. The manuscript by Cohen and colleagues (2010a) also presents the number of patients discontinuing study drug, as follows: fingolimod 0.5 mg: 10.3%; fingolimod 1.25 mg: 14.8%; interferon-beta-1a: 11.8%.

Table 25 Quality-assessment results for Study D2301 (the FREEDOMS study)

Study ID: FREEDOMS		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation was performed centrally using a validated system and stratified according to site with a block size of 6 within each site	Yes
Was the concealment of treatment allocation adequate?	The treatment allocation was centralised	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics (age, sex, course of disease, number of relapse in previous year, EDSS scores, and treatment history) were similar	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators, and site personnel (care providers and outcome assessors) were blinded	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The percentage of patients who discontinued treatment in the fingolimod 1.25-mg group was 22% compared with 0.5 mg fingolimod (13%) and placebo (20%)* The most frequent reasons for discontinuation (> 5% of patients) in the 2 fingolimod groups were abnormal laboratory values, AEs, and withdrawal of consent; in the placebo group, the most frequent reasons were unsatisfactory therapeutic effect, AEs, and withdrawal of consent No adjustment has been made; the power calculation assumed a discontinuation rate of 25%	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No

Study ID: FREEDOMS		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All patients who underwent randomisation were included in the efficacy and safety analyses	Yes

AE, adverse event; EDSS, Expanded Disability Status Scale; ID, identification; N/A, not applicable.

* These are the numbers of patients discontinuing the study. The manuscript by Kappos and colleagues (2010) also presents the number of patients discontinuing study drug, as follows: fingolimod 0.5 mg: 18.8%; fingolimod 1.25 mg: 30.5%; placebo: 27.5%.

5.5 Results of the relevant RCTs

5.5.1 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. **If there is more than one RCT, tabulate the responses.**

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

5.5.3 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 is 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 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.

Efficacy results from Study D2302 (the TRANSFORMS study)

The efficacy results for the relapse, magnetic resonance imaging (MRI), and disability study endpoints are presented below. Please note the proposed licensed population for fingolimod in the UK is a restricted population of the entire trial populations of Study D2302 (TRANSFORMS) population. This means part of the trial population will be outside the potential UK licence. Specific clinical data comprising only the licensed population are not available. However, data for components of the licensed population is presented below alongside the data for the intention-to-treat (ITT) population. Other subgroups of the TRANSFORMS data were also discussed by the EMEA and details of these will be in the EPAR.

Relapse

Table 26 presents the clinical and MRI results at 12 months. There was a significantly greater reduction in the annualised relapse rates in both

fingolimod groups than in the interferon group. There were fewer patients with severe relapse in the fingolimod groups after 12 months (fingolimod 0.5 mg, 10/89 [11%]; fingolimod 1.25 mg, 17/105 [16%]; interferon-beta-1a, 30/179 [17%]). In addition, fewer patients in the fingolimod groups required relapse-related steroid treatment (fingolimod 0.5 mg, 95 [73%]; fingolimod 1.25 mg, 107 [79%]; interferon-beta-1a, 213 [81%]) or hospitalisation (fingolimod 0.5 mg, 11 [12%]; fingolimod 1.25 mg, 18 [17%]; interferon-beta-1a, 36 [20%]) after 24 months.

Additional relapse-related measures that significantly favoured fingolimod included the proportion of patients who were relapse free, the proportion of patients with multiple relapses, and the time to first relapse (Figure 4). There was no significant difference between patients who had previously received disease treatment and those who had not. In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with fingolimod 0.5 mg resulted in a significantly lower ARR compared with interferon-beta-1a (ARR ratio of 0.50; $P < 0.001$; Table 26). Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower ARR compared with interferon-beta-1a (ARR ratio of 0.48; $P < 0.001$; Table 26).

Table 26 Clinical and MRI results at 12 months for Study D2302 (the TRANSFORMS study)*

Endpoint	Fingolimod 1.25 mg (n = 420)	Fingolimod 0.5 mg (n = 429)	Interferon-beta-1a (n = 431)	*P* values	
				Fingolimod 1.25 mg vs. Interferon-beta-1a	Fingolimod 0.5 mg vs. Interferon-beta-1a
Annualised relapse rate (primary endpoint), number (95% CI)	0.20 (0.16-0.26)	0.16 (0.12-0.21)	0.33 (0.26-0.42)	< 0.001	< 0.001
Annualised relapse rate for patients who had no previous disease-modifying therapy, number (95% CI)†	0.17 (0.11-0.25)	0.15 (0.10-0.23)	0.31 (0.22-0.41)		
Annualised relapse rate for patients who had previous disease-modifying therapy, number (95% CI)	0.33 (0.26-0.42)	0.26 (0.19-0.34)	0.53 (0.43-0.65)		
Annualised relapse rate for patients who received DMT in the previous year, with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	0.351	0.252	0.506	N/A	< 0.001
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	0.329	0.250	0.523	N/A	< 0.001
Ratio (95% CI) of annualised relapse rate for fingolimod 0.5 mg vs. interferon-beta-1a in patients who received DMT in the previous year with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	N/A	0.50 (0.33-0.74)	N/A	N/A	< 0.001

Endpoint	Fingolimod 1.25 mg (n = 420)	Fingolimod 0.5 mg (n = 429)	Interferon-beta-1a (n = 431)	*P* values	
				Fingolimod 1.25 mg vs. Interferon-beta-1a	Fingolimod 0.5 mg vs. Interferon-beta-1a
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	N/A	0.48 (0.32-0.71)	N/A	N/A	< 0.001
Patients with no confirmed relapse, % (95% CI)[‡]	79.8 (75.9-83.7)	82.6 (79.0-86.3)	69.3 (64.8-73.8)	< 0.001	< 0.001
Patients with confirmed relapse, number (%)					
0 relapse	338 (80.5)	354 (82.5)	302 (70.1)	< 0.001	< 0.001
1 relapse	61 (14.5)	63 (14.7)	90 (20.9)		
2 relapses	19 (4.5)	11 (2.6)	30 (7.0)		
≥ 3 relapses	2 (0.5)	1 (0.2)	9 (2.1)		
Total number of relapses, n (% of these that are severe)	105 (16.2)	89 (11.2)	179 (16.8)		
Number of relapses in patients who received DMT in the previous year with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	64	48	89		
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	58	47	96		

Endpoint	Fingolimod 1.25 mg (n = 420)	Fingolimod 0.5 mg (n = 429)	Interferon-beta-1a (n = 431)	*P* values	
				Fingolimod 1.25 mg vs. Interferon-beta-1a	Fingolimod 0.5 mg vs. Interferon-beta-1a
MRI outcome[§]					
New or enlarged lesions on T_2-weighted images, number					
Mean (SD)	1.5 (2.7)	1.7 (3.9)	2.6 (5.8)	< 0.001	0.004
Median (range)	1 (0-26)	0 (0-38)	1 (0-63)		
Gadolinium-enhancing lesions on T_1-weighted images, number					
Mean (SD)	0.14 (0.58)	0.23 (0.97)	0.51 (1.86)	< 0.001	< 0.001
Median (range)	0 (0-6)	0 (0-11)	0 (0-24)		
Patients with no new or enlarged lesions on T_2-weighted images, number/total number (%)	168/350 (48.0)	204/372 (54.8)	165/361 (45.7)	0.37	0.01
Patients with no gadolinium-enhancing lesions on T_1-weighted images, number/total number (%)	321/352 (91.2)	337/374 (90.1)	286/354 (80.8)	< 0.001	< 0.001
Volume of gadolinium-enhancing lesions on T_1-weighted images, mm^3					
Mean (SD)	19.54 (109.10)	22.61 (111.59)	50.68 (198.16)	< 0.001	< 0.001
Median (range)	0 (0-1442)	0 (0-1359)	0 (0-2238)		
Change from baseline in volume of hyperintense lesions on T_2-weighted images, %					
Mean (SD)	6.7 (31.0)	9.9 (37.3)	10.4 (42.8)	0.48	0.63
Median (range)	2.9 (–76.1 to	6.2 (–100.0 to	3.0 (–60.7 to		

Endpoint	Fingolimod 1.25 mg (n = 420)	Fingolimod 0.5 mg (n = 429)	Interferon-beta-1a (n = 431)	*P* values	
				Fingolimod 1.25 mg vs. Interferon-beta-1a	Fingolimod 0.5 mg vs. Interferon-beta-1a
	247.1)	318.2)	494.1)		
Change from baseline in volume of hypointense lesions on T_1-weighted images, %					
Mean (SD)	34.7 (122.3)	24.1 (127.3)	15.0 (70.3)	0.09	0.17
Median (range)	4.4 (–100.0 to 1291.8)	3.2 (–100.0 to 2061.1)	1.2 (–100.0 to 636.4)		
Change from baseline in brain volume, %					
Mean (SD)	–0.30 (0.65)	–0.31 (0.65)	–0.45 (0.73)	< 0.001	< 0.001
Median (range)	–0.20 (–2.90 to 2.20)	–0.20 (–3.70 to 2.00)	–0.40 (–3.40 to 2.60)		
Disability					
Patients with no confirmed disability progression, % (95% CI)[‡,¶]	93.3 (90.9-95.8)	94.1 (91.8-96.3)	92.1 (89.4-94.7)	0.5	0.25
Hazard ratio (95% CI) for disability progression for fingolimod 0.5 mg vs. interferon-beta-1a in patients who received DMT in the previous year with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Endpoint	Fingolimod 1.25 mg (n = 420)	Fingolimod 0.5 mg (n = 429)	Interferon-beta-1a (n = 431)	*P* values	
				Fingolimod 1.25 mg vs. Interferon-beta-1a	Fingolimod 0.5 mg vs. Interferon-beta-1a
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in EDSS score‖					
Mean (SD)	–0.11(0.90)	–0.08 (0.79)	0.01 (0.78)	0.02	0.06
Median (range)	0 (–3.0 to 5.0)	0 (–3.0 to 2.5)	0 (–2.0 to 3.0)		
Change from baseline in MSFC z score**					
Mean (SD)	0.08 (0.46)	0.04 (0.42)	–0.03 (0.48)	< 0.001	0.02
Median (range)	0.06 (–1.90 to 3.60)	0.20 (–2.10 to 4.70)	–0.01 (–5.30 to 1.70)		

CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MSFC z, Multiple Sclerosis Functional Composite (expressed as z scores); N/A, not applicable; SD, standard deviation.

* Data are for the modified intention-to-treat population, which consisted of all patients who underwent randomisation and received at least one dose of a study drug.

† Among patients receiving fingolimod, *P* values for the interaction between therapy during the study period and before baseline, as compared with the interferon group, were 0.49 for the 1.25-mg group and 0.81 for the 0.5-mg group.

‡ Values are Kaplan–Meier estimates from the analysis of time to first relapse.

§ All MRI outcomes were based on all images that could be evaluated.

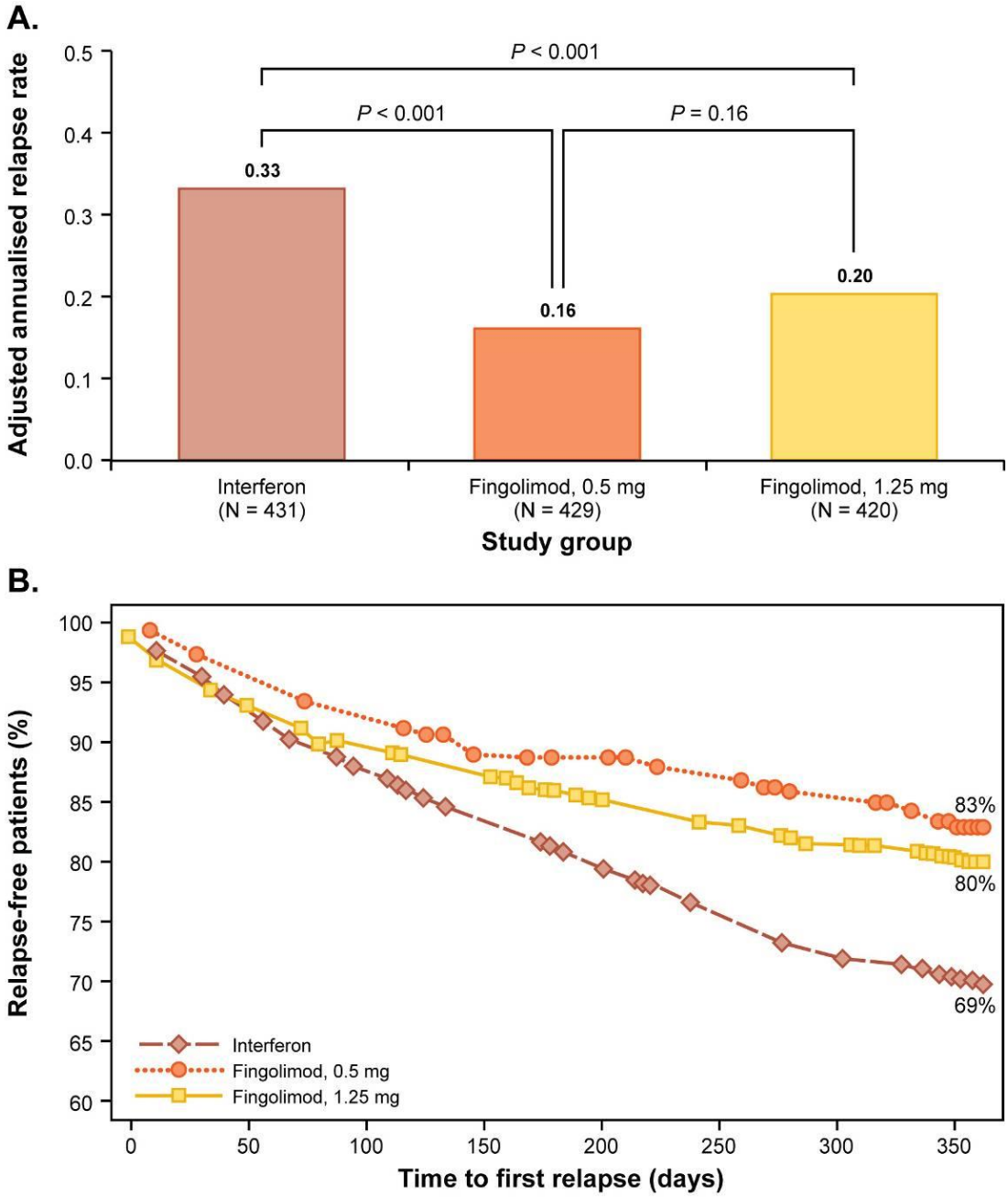
¶ Confirmed disability progression was defined as an increase of 1 point from baseline in the EDSS score if baseline EDSS was between 0 and 5.0 (or an increase of 0.5 points if the baseline EDSS score was 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.

‖ Scores on the EDSS range from 0 to 10, with higher scores indicating a greater degree of disability.

** Scores on the Multiple Sclerosis Functional Composite (MSFC) are expressed as z scores, with higher scores indicating improvement in disability.

Source: Cohen et al., 2010a.

Figure 4 Annualised relapse rate at 12 months and the time to the first relapse for Study D2302 (the TRANSFORMS study)



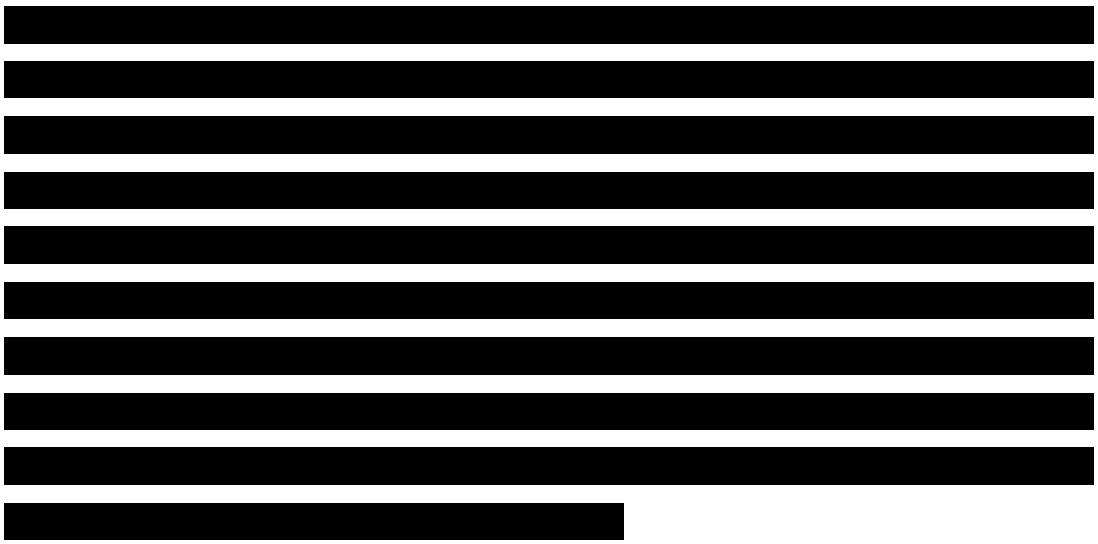
Source: Cohen et al., 2010a.

A: Annualised rate of relapse from baseline to 12 months, with adjustment for study group, country, number of relapses in the previous 2 years and baseline disability score.

B: Kaplan-Meier estimates of the time to the first relapse, indicating the proportion of relapse-free patients ($P < 0.001$ for both comparisons with interferon).

MRI outcomes

The two fingolimod groups had significantly fewer new or enlarged hyperintense lesions on T_2-weighted images and fewer gadolinium-enhanced lesions on T_1-weighted images at 12 months than the interferon group (Table 26). In addition, the mean percentage reduction in brain volume from baseline to 12 months was significantly lower in the two fingolimod groups than in the interferon group. Change from baseline in volume of hyperintense and hypointense lesions on T_2- and T_1-weighted images, respectively, at 12 months did not differ significantly among the study groups.



Disability

Confirmed disability progression was infrequent in all of the study groups. There were no significant differences in the time to progression of disability or in the proportion of patients with confirmed progression between the study groups. There was improvement in terms of change in the EDSS and the Multiple Sclerosis Functional Composite (MSFC z) scores for the fingolimod groups compared with the interferon-beta-1a group (Table 26). In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with fingolimod 0.5 mg resulted in a lower rate of disability progression compared with interferon-beta-1a

[redacted] 26[redacted]. Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and who had either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower rate of disability progression compared with interferon-beta-1a [redacted] 26[redacted].

Patient-reported outcomes

Patient health-related quality of life (HRQL) has been shown to deteriorate significantly with MS progression (Nortvedt et al., 2000), and HRQL assessment was incorporated in Study D2302 (TRANSFORMS).

[redacted]

The Patient-Reported Indices for Multiple Sclerosis – Activities (PRIMUS-Activities) scale was used in Study D2302 (TRANSFORMS) to detect changes in the daily functioning (Cohen et al., 2010b). Patients treated with fingolimod experienced significantly less deterioration in their ability to perform daily activities compared with patients treated with interferon-beta-1a at month 12 (PRIMUS-Activities score change from baseline, mean ± standard deviation: fingolimod 0.5 mg, 0.08 ± 4.47 ($P < 0.05$); fingolimod 1.25 mg, 0.12 ± 4.54 ($P < 0.05$); interferon-beta-1a, 0.43 ± 4.71).

The patient-reported impact of fatigue was assessed in Study D2302 (TRANSFORMS) using the Unidimensional Fatigue Impact Scale (UFIS). There was a statistically significant improvement in UFIS score at month 6 for the fingolimod 0.5-mg group compared with the interferon-beta-1a group (Table 27).The mean change from baseline in UFIS scores at month 12

numerically favoured both fingolimod groups compared with the interferon-beta-1a group, although this was not statistically significant (Table 27).

Table 27 Unidimensional Fatigue Impact Scale scores from baseline in Study D2302 (the TRANSFORMS study)

Study, n		Comparator	Fingolimod	
		Interferon-beta-1a	0.5 mg	1.25 mg
UFIS score change from baseline*				
Month 6	845	0.84 ± 9.47	–1.00 ± 9.05; P < 0.05	0.21 ± 8.93
Month 12	807	1.10 ± 10.35	–0.39 ± 10.45	0.06 ± 9.90

SD, standard deviation; UFIS, Unidimensional Fatigue Impact Scale.

* A positive score change indicates increasing fatigue; a negative score change indicates lessening fatigue. All data are presented as mean ± SD. *P* values for fingolimod versus interferon-beta-1a were calculated using Wilcoxon rank-sum test of median values.

Efficacy results from Study D2301 (the FREEDOMS study)

The efficacy results for the relapse, disability, and MRI study endpoints are presented in Table 28. Please note the proposed licensed population for fingolimod in the UK is a restricted population of the entire trial populations of Study D2301 (FREEDOMS) population. This means part of the trial population will be outside the potential UK licence. Specific clinical data comprising only the licensed population are not available. However, data for components of the restricted populations are presented below alongside the data for the ITT population. Other subgroups of the FREEDOMS data were also discussed by the EMEA and details of these will be in the EPAR.

Relapse

The aggregate ARR was lower with fingolimod 0.5 mg (0.18) and fingolimod 1.25 mg (0.16) than with placebo (0.40) (see Table 28), with relative reductions in the annualised relapse rate of 54% and 60%, respectively. Both doses of fingolimod reduced the annualised relapse rate in patients who had not previously received DMTs as well as in patients who had been treated previously, when compared with placebo ($P < 0.01$ for all comparisons). There were fewer patients in the fingolimod groups with severe relapse compared with the placebo group after 24 months (fingolimod 0.5 mg, 10/172 [6%]; fingolimod 1.25 mg, 19/148 [13%]; placebo, 35/359 [10%]).

In addition, the time to a first relapse was longer (Figure 5A), the risk of relapse was reduced, and proportionally more patients remained free of relapse during the 24-month period (Figure 5A) for patients in the fingolimod groups compared with patients in the placebo group.

In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with fingolimod 0.5 mg resulted in a significantly lower ARR compared with placebo (ARR ratio of 0.38; $P < 0.001$; Table 28). Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower ARR compared with placebo (ARR ratio of 0.52; $P = 0.005$; Table 28).

Table 28 Clinical and MRI endpoints, according to study group, for Study D2301 (the FREEDOMS study)*

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
Primary endpoint					
Annualised relapse rate over 24 months (95% CI)[†,‡]	0.16 (0.13-0.19)	0.18 (0.15-0.22)	0.40 (0.34-0.47)	< 0.001	< 0.001
Rate for patients who had no previous disease-modifying therapy (95% CI)		0.17 (0.13, 0.21)	0.46 (0.38, 0.54)		< 0.001
Rate for patients who had previous disease-modifying therapy (95% CI)		0.28 (0.22, 0.36)	0.53 (0.43, 0.65)		< 0.001
Rate for patients who received DMT in the previous year and who had unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	0.244	0.214	0.542	N/A	<0.001
Rate for patients who received DMT in the previous year and who had ≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	0.263	0.263	0.490	N/A	0.005
Relapse-related secondary endpoints					
Absence of relapse during the 24-month period[§]					
Percentage (SE); (95% CI)[¶]	74.7 (2.2); (70.4-78.9)	70.4 (2.3); (66.0-74.8)	45.6 (2.5); (40.7-50.6)	< 0.001	< 0.001

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
Hazard ratio for fingolimod vs. placebo (95% CI)‖	0.38 (0.30-0.48)	0.48 (0.39-0.61)		< 0.001	< 0.001
Ratio (95% CI) of annualised relapse rate for fingolimod 0.5 mg vs. placebo for patients who received DMT in the previous year with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	N/A	0.38 (0.24-0.62)	N/A	N/A	<0.001
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	N/A	0.52 (0.33-0.82)	N/A	N/A	0.005
Total number of relapses, n (% of these that are severe)	148 (12.8)	172 (5.8)	359 (9.7)		
Number of relapses in patients in patients who received DMT in the previous year with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	37	36	74		
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	39	43	77		

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
Disability-related secondary endpoints					
Key secondary endpoint: absence of disability progression, confirmed after 3 months, during the 24-month period[§]					
Percentage (SE); (95% CI)[¶]	83.4 (1.9); (79.7-87.1)	82.3 (1.9); (78.6-86.1)	75.9 (2.2); (71.7-80.2)	0.01	0.03
Hazard ratio for fingolimod vs. placebo (95% CI)**	0.68 (0.50-0.93)	0.70 (0.52-0.96)		0.02	0.02
Absence of disability progression, confirmed after 3 months, during the 24-month period, in patients who had no previous disease-modifying therapy					
Proportion of patients free from disability (95% CI)[¶]	N/A	84.0 (79.3, 88.6)	75.7 (70.2, 81.2)	N/A	0.029
Hazard ratio for fingolimod vs. placebo (95% CI)**	N/A	0.63 (0.41, 0.95)			
Absence of disability progression, confirmed after 3 months, during the 24-month period, in patients who had previous disease-modifying therapy					
Proportion of patients free from disability (95% CI)[¶]	N/A	80.1 (74.1, 86.1)	76.3 (69.6, 83.0)	N/A	0.148
Hazard ratio for fingolimod vs. placebo (95% CI)**	N/A	0.70 (0.43, 1.14)			

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
Absence of disability progression, confirmed after 6 months, during the 24-month period[§,††]					
Percentage (SE); (95% CI)[¶]	88.5 (1.6); (85.3-91.6)	87.5 (1.6); (84.3-90.7)	81.0 (2.0); (77.1-84.9)	0.004	0.01
Hazard ratio for fingolimod vs. placebo (95% CI)**	0.60 (0.41-0.86)	0.63 (0.44-0.90)		0.006	0.01
Hazard ratio (95% CI) for disability progression for fingolimod 0.5 mg vs. placebo for patients who received DMT in the previous year with					
Unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1 relapse in previous year and either ≥ 1 gadolinium-enhancing lesions or T2 volume > 0.5 mL at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EDSS score at 24 months					
Mean (SD)[‡‡]	–0.03 (0.88)	0.00 (0.88)	0.13 (0.94)	0.002	0.002
Median (range)	0.0 (–3.0 to 4.0)	0.0 (–3.0 to 3.5)	0.0 (–3.0 to 3.5)		

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
MSFC z score at 24 months					
Mean (SD)[‡‡]	0.01 (0.40)	0.03 (0.39)	–0.06 (0.57)	0.02	0.01
Median (range)	0.05 (–2.4 to 1.3)	0.07 (–2.1 to 1.2)	–0.01 (–3.8 to 5.5)		
MRI-related secondary endpoints[§§]					
Measures of inflammatory activity or scar formation					
Number of gadolinium-enhancing lesions at 24 months[¶¶]					
Number of patients with data	343	369	332		
Mean (SD)[‖‖]	0.2 (1.1)	0.2 (0.8)	1.1 (2.4)	< 0.001	< 0.001
Median (range)	0.0 (0-11)	0.0 (0-8)	0.0 (0-21)		
Absence of gadolinium-enhancing lesions at 24 months, number/total number (%)[¶¶,***]	308/343 (89.8)	331/369 (89.7)	216/332 (65.1)	< 0.001	< 0.001
Number of new or enlarged lesions on T_2-weighted images, baseline to 24 months[†††]					
Number of patients with data	337	370	339		
Mean (SD)[‡‡‡]	2.5 ± 5.5	2.5 ± 7.2	9.8±13.2	< 0.001	< 0.001
Median (range)	0.0 (0-41)	0.0 (0-107)	5.0 (0-99)		

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
Absence of new or enlarged T_2-weighted lesions at 24 months, number/total number (%)[†††,§§§]	175/337 (51.9)	187/370 (50.5)	72/339 (21.2)	< 0.001	< 0.001
Change in lesion volume on T_2-weighted images, baseline to 24 months (%)					
Number of patients with data	343	368	339		
Mean (SD)[¶¶¶]	1.6 (30.7)	10.6 (103.5)	33.8 (106.9)	< 0.001	< 0.001
Median (range)	–3.10 (–68.2 to 221.5)	–1.69 (–100.0 to 1828.5)	8.61 (–84.5 to 1378.7)		
Measures of tissue damage or loss					
Change in volume of hypo-intense lesions on T_1-weighted images, baseline to 24 months (%)					
Number of patients with data	317	346	305		
Mean (SD)[¶¶¶]	12.2 (85.5)	8.8 (76.3)	50.7 (388.3)	0.02	0.01
Median (range)	–0.20 (–100.0 to 888.4)	0.00 (–100.0 to 1037.1)	1.59 (–100.0 to 5285.3)		
Change in brain volume, baseline to 6 months (%)					
Number of patients with data	384	395	383		
Mean (SD)[‖‖‖]	–0.21 (0.86)	–0.22 (0.81)	–0.34 (0.73)	0.003	0.006
Median (range)	–0.12 (–4.71 to 3.37)	–0.14 (–5.62 to 2.25)	–0.29 (–4.02 to 2.57)		

Endpoint	Fingolimod		Placebo (n = 418)	*P* value	
	1.25 mg (n = 429)	0.5 mg (n = 425)		Fingolimod 1.25 mg vs. placebo	Fingolimod 0.5 mg vs. placebo
Change in brain volume, baseline to 12 months (%)					
Number of patients with data	371	383	358		
Mean (SD)‖¶‖	–0.44 (1.08)	–0.50 (1.05)	–0.65 (1.05)	0.001	0.03
Median (range)	–0.30 (–4.91 to 4.34)	–0.38 (–8.11 to 2.40)	–0.56 (–3.89 to 2.78)		
Change in brain volume, 12-24 months (%)					
Number of patients with data	327	356	329		
Mean (SD)‖¶‖	–0.42 (0.83)	–0.37 (0.81)	–0.67(1.07)	0.002	< 0.001
Median (range)	–0.38 (–5.40 to 2.24)	–0.34 (–6.24 to 1.90)	–0.57 (–5.60 to 2.43)		
Change in brain volume, baseline to 24 months (%)					
Number of patients with data	334	357	331		
Mean (SD)‖¶‖	–0.89 (1.39)	–0.84 (1.31)	–1.31 (1.50)	< 0.001	< 0.001
Median (range)	–0.70 (–6.33 to 3.04)	–0.67 (–13.50 to 2.16)	–0.98 (–7.58 to 2.38)		

CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; ITT, intent-to-treat; MRI, magnetic resonance imaging; MSFC z, Multiple Sclerosis Functional Composite (expressed as z scores); N/A, not applicable; SD, standard deviation; SE, standard error.

* All *P* values are two-sided.

† Data used in analyses were confirmed cases of relapse.

‡ *P* values were calculated with the use of a negative-binomial regression model with adjustment for study group, country, number of relapses within 2 years before the baseline value was measured, and the EDSS score (which ranges from 0 to 10, with higher scores indicating greater disability) at baseline. For the prior treatment/no prior treatment subgroups, the negative-binomial regression model was adjusted for treatment, corresponding baseline subgroup parameter, and treatment by subgroup interaction in the ITT population. The study was not powered for subgroup analyses and was not adjusted for multiple comparisons.

§ Data regarding absence of relapse and absence of confirmed disability progression during the 24-month period are based on Kaplan-Meier estimates.

¶ *P* values were calculated with the use of a log-rank test including data from baseline through 24 months.

‖ *P* values were calculated with the use of the Cox proportional-hazards model with adjustment for study group, country, number of relapses within 2 years before the baseline value was measured, and the EDSS score at baseline. For the no prior treatment/prior treatment subgroups, *P* values were calculated using the Cox proportional hazards model, adjusted for study group, country, EDSS score at baseline, and age.

** *P* values were calculated with the use of the Cox proportional-hazards model with adjustment for study group, country, the EDSS score at baseline, and age.

†† Confirmed disability progression was defined as an increase of 1 point from baseline in the EDSS score if baseline EDSS was between 0 and 5.0 (or an increase of 0.5 points if the baseline EDSS score was 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.

‡‡ *P* values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, baseline value of the given endpoint, and age.

§§ The MRI-related secondary endpoints presented here are descriptive measures of inflammatory activity or scar formation and measures of tissue damage or loss rather than outputs of the analysis models.

¶¶ Any data regarding gadolinium-enhancing lesions obtained within 30 days after corticosteroid treatment for a relapse of multiple sclerosis were excluded from the analysis.

‖‖ *P* values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, and number of lesions at baseline.

*** *P* values were calculated with the use of a logistic-regression model with adjustment for study group, country, and number of lesions at baseline.

††† For each patient, the number of new or enlarged T_2 hyperintense lesions was counted from baseline through 24 months by summing the count for the first 12 months and the count for the second 12 months.

‡‡‡ *P* values were calculated with the use of a negative-binomial regression model with adjustment for study group and country.

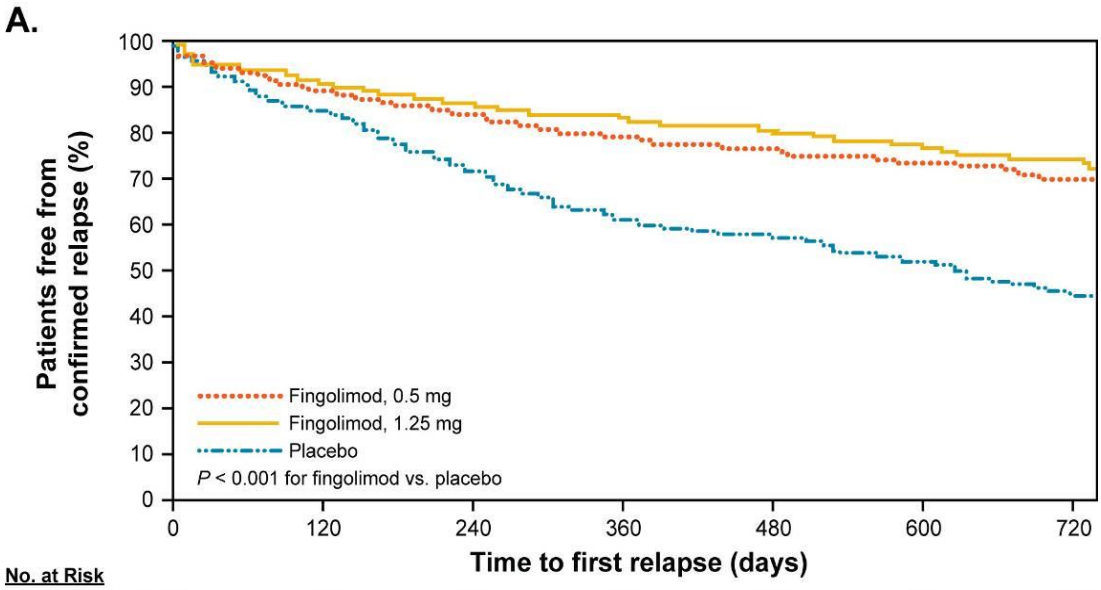
§§§ *P* values were calculated with the use of a logistic-regression model with adjustment for study group and country.

¶¶¶ *P* values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, and lesion volume at baseline.

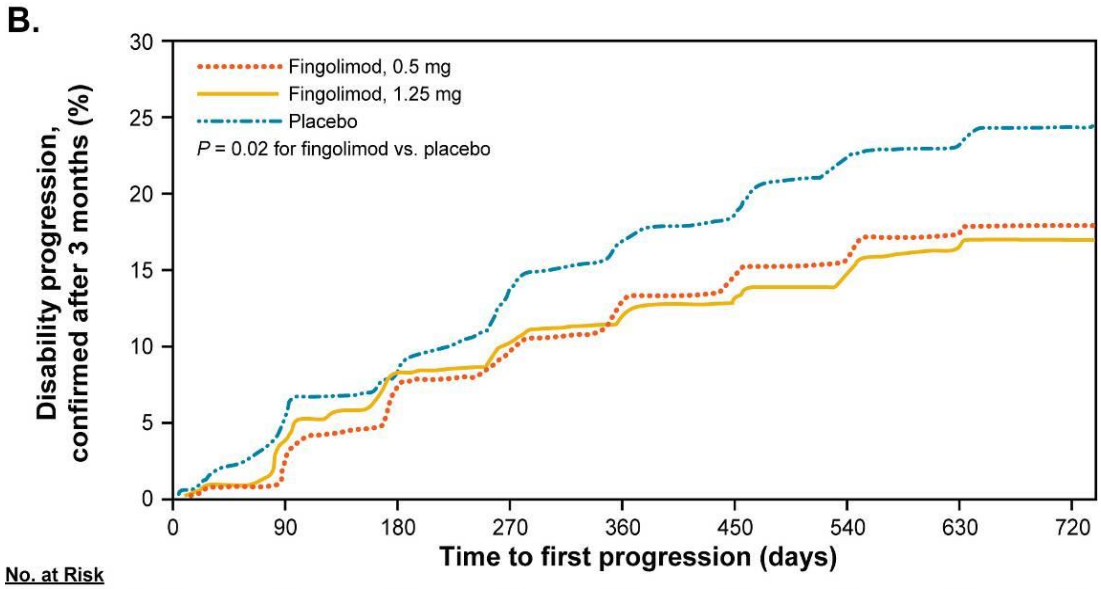
‖‖‖ *P* values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, and normalised brain volume at baseline.

Sources: Kappos et al., 2010; von Rosenstiel et al., 2010 (in press); Novartis data on file, 2009.

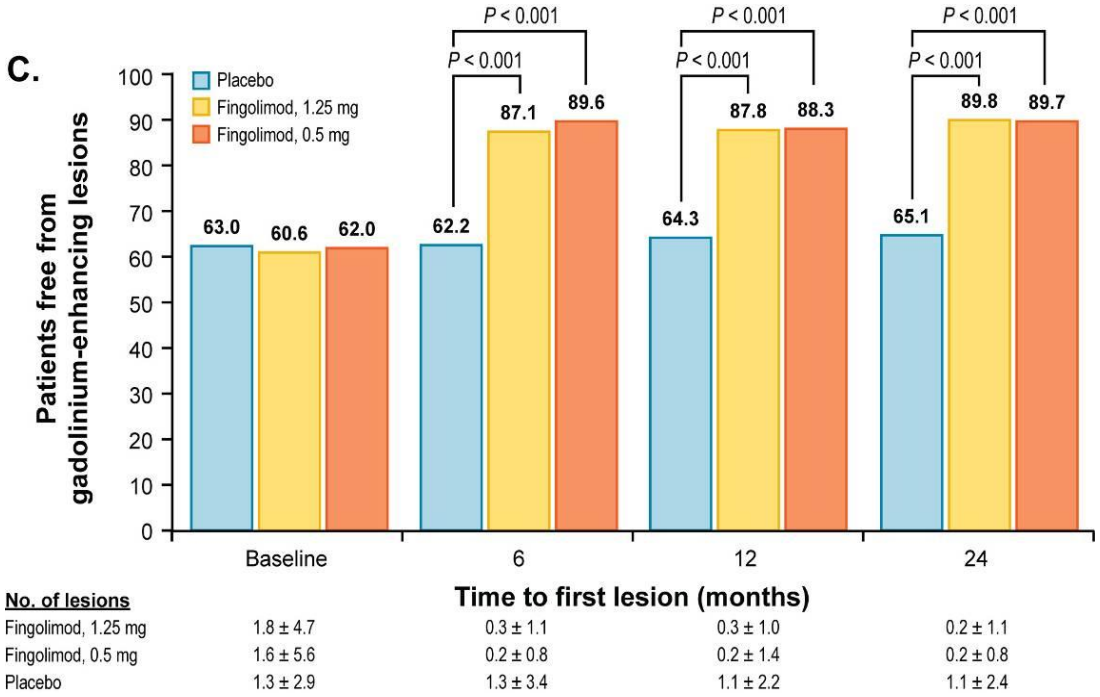
Figure 5 Study endpoints for Study D2301 (the FREEDOMS study)[*,†]



No. at Risk							
Fingolimod, 1.25 mg	429	383	356	333	313	299	239
Fingolimod, 0.5 mg	425	374	349	324	309	295	219
Placebo	418	346	293	242	223	198	145



No. at Risk									
Fingolimod, 1.25 mg	429	401	373	356	344	332	322	305	165
Fingolimod, 0.5 mg	425	416	388	370	354	340	332	321	152
Placebo	418	391	371	341	320	308	290	279	143



EDSS, Expanded Disability Status Scale; SD, standard deviation.

* A: Kaplan-Meier estimates for the time to a first relapse. B: Kaplan-Meier estimates for the time to disability progression, confirmed after 3 months, as measured by the EDSS. C: Proportions of patients free from gadolinium-enhancing lesions and the mean (± SD) number of gadolinium-enhancing lesions at baseline and at 6, 12 and 24 months.

† Data on gadolinium-enhancing lesions were available for 416 patients assigned to receive placebo, 424 assigned to receive fingolimod 1.25 mg, and 424 assigned to receive fingolimod 0.5 mg, at baseline; 373, 388, and 403 patients, respectively, at 6 months; 356, 376, and 394 patients, respectively, at 12 months; and 332, 343, and 369 patients, respectively, at 24 months. The *P* values for the proportions were obtained with the use of a logistic-regression model, with adjustment for study group, country, and number of lesions at baseline.

Source: Kappos et al., 2010.

Disability

The time to disability progression, with confirmation either after 3 months (the key secondary endpoint) or after 6 months, was longer in the fingolimod groups compared with the placebo group (Table 28 and Figure 5B). Fingolimod reduced the risk of disability progression, confirmed after 3 months, over the 24-month study period (hazard ratios: 0.70 for the fingolimod 0.5-mg group; 0.68 for the fingolimod 1.25-mg group). The cumulative probability of disability progression (confirmed after 3 months) was 17.7% for the fingolimod 0.5-mg group, 16.6% for the fingolimod 1.25-mg group, and 24.1% for the placebo group.

The risk of disability progression that was confirmed after 6 months was reduced with fingolimod over the 24-month study period (hazard ratio: 0.63 for the fingolimod 0.5-mg group; 0.60 for the fingolimod 1.25-mg group). The cumulative probability of progression was 12.5% for the fingolimod 0.5-mg group, 11.5% for the fingolimod 1.25-mg group, and 19% for the placebo group. During the study period, the EDSS and MSFC z scores remained stable or improved slightly in the fingolimod groups and worsened in the placebo group.

In the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, treatment with fingolimod 0.5 mg resulted in a lower rate of disability progression compared with placebo [redacted]; Table 28). Furthermore, in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume greater than 0.5 mL at baseline, treatment with fingolimod 0.5 mg resulted in a lower rate of disability progression compared with placebo [redacted]Table 28).

MRI outcomes

Patients in the fingolimod groups had significantly fewer gadolinium-enhancing lesions than patients in the placebo group at 6, 12, and 24 months, as well as fewer new or enlarged lesions on T_2-weighted MRI scans at 24 months, when compared with placebo (Table 28). In addition, proportionally more patients in the fingolimod groups were free from gadolinium-enhancing or new or enlarging lesions at these time points, when compared with patients in the placebo group (Table 28 and Figure 5C). The median volume of lesions on T_2-weighted scans decreased between baseline and month 24 in the fingolimod groups but increased in the placebo group. Changes in the volume of hypointense lesions on T_1-weighted scans favoured patients in both fingolimod groups over patients in the placebo group during the 24-month study period (Table 28). In addition, reductions in brain volume

were smaller with patients in the fingolimod groups (mean change in brain volume, baseline to 24 months: the fingolimod 0.5-mg group, –0.84 ± 1.31; the fingolimod 1.25-mg group, –0.89 ± 1.39; placebo, –1.31 ± 1.50). There also was a greater proportion of patients free from MRI activity in the fingolimod groups compared with patients in the placebo group (the fingolimod 0.5-mg group, 186 [50.7%], *P* < 0.001; the fingolimod 1.25-mg group, 172 [52.0%], *P* < 0.001; placebo, 69 [21.0%]).

Patient-reported outcomes

[redacted]
(
Table 29).

Table 29 Change from baseline in the EQ-5D in Study D2301 (the FREEDOMS study)

Change in score from baseline, mean ± SD*	n	Placebo	Fingolimod	
			0.5 mg	1.25 mg
EQ-5D utility score	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D VAS score	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D, 5-dimension European Quality of Life survey; HRQL, health-related quality of life; SD, standard deviation; VAS, Visual Analogue Scale.

* A negative score change indicates deterioration; a positive score change indicates improvement in HRQL.

Source: Novartis data on file, 2010.

Long-term clinical outcomes from Study D2201

Study D2201 was a 6-month evaluation of the safety, tolerability, and effect on MRI-lesion parameters of fingolimod 1.25 mg and 5.0 mg compared with placebo in 281 patients with relapsing MS. After 6 months in the core study, patients receiving treatment were continued in that treatment, while those receiving placebo were rerandomised to fingolimod 1.25 mg or fingolimod 5.0 mg. Although fingolimod 0.5 mg was not evaluated in Study D2201, the

results from this study were consistent with those from Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS). Study D2201 demonstrated that long-term use of fingolimod reduced relapse rates, reduced the rate of disease progression, improved MRI measures of disease burden and activity, and provided benefits in terms of patient-reported outcomes. The aggregate ARR at month 60 for the fingolimod 1.25-mg group was 0.17 compared with 0.23 for the placebo/fingolimod 5.0-mg group ($P < 0.01$) and compared with 0.19 for the fingolimod 5.0-mg/1.25-mg group ($P = 0.05$).

The proportion of patients free from relapse after 60 months of fingolimod treatment was relatively high (51%-68%). In groups receiving fingolimod, only a small proportion (5%-16%) of confirmed relapses required hospitalisation during the 60-month study period.

Study D2201 also demonstrated that more than 60% of patients receiving fingolimod were free from disability progression after 5 years of treatment. More than 90% of patients remained free from gadolinium-enhancing lesions, and more than 86% of patients were free from any MRI lesion activity, indicating that fingolimod treatment has long-term benefits on measures of inflammatory disease activity.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, sections 5.3.9 to 5.3.12.

5.6.1 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 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).

Direct meta-analyses combining data from the two relevant fingolimod trials (FREEDOMS and TRANSFORMS) were not performed because the trials did not have a common, non-fingolimod, comparator, i.e., the comparator in FREEDOMS was placebo, whilst in TRANSFORMS the comparator was interferon-beta-1a (30 mcg).

5.6.2 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.

The rationale for not performing direct meta-analyses of the fingolimod trials is given in Section 5.6.1. Critical appraisal of the FREEDOMS and TRANSFORMS trials can be found in Section 5.4. Further details for these two trials are described in Section 5.3 and in Appendix Section **Error! Reference source not found.**. The specific data used from these trials within the mixed-treatment comparisons (MTCs) is given in Section 5.7.4.

5.6.3 If any of the relevant RCTs listed in response to Section 5.2.4 (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.

No relevant fingolimod trials have been excluded from the analyses. Only the fingolimod dose of 0.5 mg has been submitted for regulatory approval; therefore, this is the dose upon which this submission focuses. Both the FREEDOMS and TRANSFORMS trials contained a separate treatment group of fingolimod at a higher dose (1.25 mg), but this data has been excluded because it will not be the licensed dose. Trial D2201 was excluded because it did not include a study arm containing the 0.5 mg dose.

5.7 Indirect- and mixed-treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, sections 5.3.13 to 5.3.22.

5.7.1 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 **Error! Reference source not found.**, Appendix 4.

The proposed indication for fingolimod when it is considered in its entirety is more restricted than the indication of the comparators. However, Novartis believed it would still be of interest to explore whether any of the components of the fingolimod indication could be compared to components of the current comparators via mixed treatment comparisons. In particular, these comparisons could be of interest as inputs into the cost-effectiveness analysis where there is no head-to-head trial data, For example, it allows interferon-beta-1a to be compared to glatiramer acetate.

The strategy used for searching is described in Section 5.1, the study selection criteria is in Section 5.2.1, and the included exclusion of studies is described in Section 5.2.2. More details can be found in Section **Error! Reference source not found.** (Appendix 4).

5.7.2 Please follow the instructions specified in Sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in Section **Error! Reference source not found.**, Appendix 5, a complete quality assessment for each comparator RCT identified.

Section **Error! Reference source not found.** (Appendix 5) covers quality assessment of all RCTs other than fingolimod included in the MTC.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

The 18 trials (numbered 1, 3-19) included in the MTC are shown in Table 30. Where multiple references exist for a given trial, the primary reference used as the primary data source for the meta-analyses is listed. The table presents the within-trial treatment comparisons and indicates whether the given trial presents data for the three outcomes that provide inputs to the economic model. In **Error! Reference source not found.** in Section **Error! Reference source not found.** (Appendix 4), we list all articles (with full references) relevant for the given trials.

Table 30 Summary of the within-trial treatment comparisons

Meta-analysis trial ID*		Data available on:			Treatments in decision problem							Common comparators		
	Trial: primary author (year) [trial name]	Con-firmed disability progres-sion	Annua-lised relapse rate	Treat-ment with-drawals due to AEs	Fingolimod 0.5 mg	Natalizumab 300 mg	Interferon-beta-1a 30 mcg	Interferon-beta-1b 250 mcg	Interferon-beta-1a 22 mcg	Interferon-beta-1a 44 mcg	Glatiramer acetate 20 mg	Placebo	Interferon-beta-1b 50 mcg	Interferon-beta-1b 500 mcg
1	Polman (2006) [AFFIRM]	Yes	Yes	Yes		✓						✓		
3	Panitch (2002) [EVIDENCE]	Yes	Yes	Yes			✓			✓				
4	Kappos (2010) [FREEDOMS]	Yes	Yes	Yes	✓							✓		
5	Durelli (2002) [INCOMIN]	Yes†	Yes	Yes			✓	✓						
6	Jacobs (1996) [MSCRG]	Yes†	Yes	Yes			✓					✓		
7	The IFNB Multiple Sclerosis Study Group (1993) [no trial name]	Yes	Yes	No				✓				✓	✓	
8	PRISMS Study group (1998) [PRISMS]	Yes	Yes	Yes					✓	✓		✓		
9	Cohen (2010a) [TRANSFORMS]	Yes	Yes	Yes	✓		✓							
10	O'Connor (2009b) [BEYOND]	Yes	Yes	Yes				✓			✓			✓
11	Cadavid (2009) [BECOME]	Yes	Yes	Yes				✓			✓			
12	Mikol (2008) [REGARD]	No	Yes	No						✓	✓			
13	Hurwitz (2008) [No trial name]	Yes†	Yes	Yes				✓						✓
14	Etemadifar (2006) [No trial name]	No	No	No			✓	✓		✓				
15	Wroe (2005) [No trial name]	No	No	No				✓				✓		
16	Saida (2005) [No trial name]	No	No	Yes				✓					✓	
17	Johnson (1995) [no trial name]	No	Yes	Yes							✓	✓		

Meta-analysis trial ID*		Data available on:			Treatments in decision problem							Common comparators		
	Trial: primary author (year) [trial name]	Con-firmed disability progres-sion	Annua-lised relapse rate	Treat-ment with-drawals due to AEs	Fingolimod 0.5 mg	Natalizumab 300 mg	Interferon-beta-1a 30 mcg	Interferon-beta-1b 250 mcg	Interferon-beta-1a 22 mcg	Interferon-beta-1a 44 mcg	Glatiramer acetate 20 mg	Placebo	Interferon-beta-1b 50 mcg	Interferon-beta-1b 500 mcg
18	Comi (2001) [no trial name]	No	Yes	Yes							✓	✓		
19	Bornstein (1987) [no trial name]	Yes	Yes	No							✓	✓		

AE, adverse event; ID, identification.

* Meta-analysis trial ID 2 is no longer included in the meta-analyses due to the removal of cladribine from the list of treatment comparators in the fingolimod scope.

† The trials ID 5, 6, and 13 were excluded from the primary confirmed disability progression analysis because the confirmation of disability was required at 6 months rather than the 3-months criteria used in the other trials.

The network diagrams corresponding to three key outcomes for which MTC were performed are shown in Figure 6, Figure 7, and Figure 8. These three outcomes are the clinical efficacy outcomes used in the health economics model. The dashed lines in the confirmed disability progression diagram indicate the trials only included in the sensitivity analysis. The shaded boxes over interferon-beta-1b 50 mcg and 500 mcg indicate that although data are available for these common comparators, only one trial has data for the given endpoint; therefore, those data are excluded because they cannot be used as a 'common comparator' with another trial. Please note that not all of the therapies shown in the network diagram have identical licensed indications so some of the comparisons in the meta-analysis may be considered partially outside the indication of the therapy. For example the proposed licence for fingolimod is not as broad as the licence for interferon-beta-1a.

Figure 6 Network diagram for the confirmed disability progression mixed-treatment comparisons meta-analysis

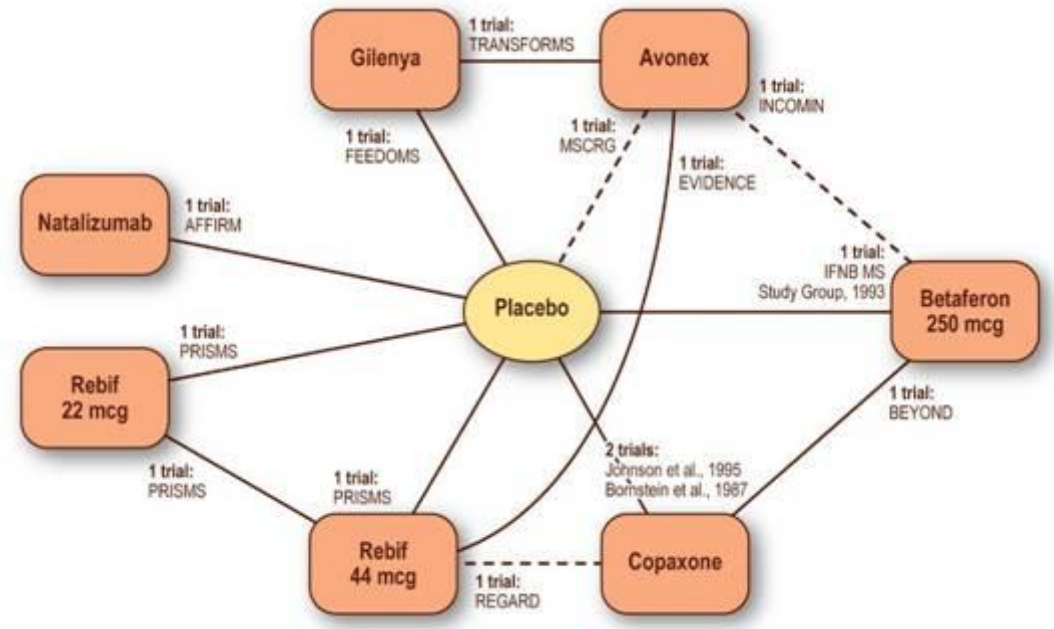


Figure 7 Network diagram for the annualised relapse rate mixed-treatment comparisons meta-analysis

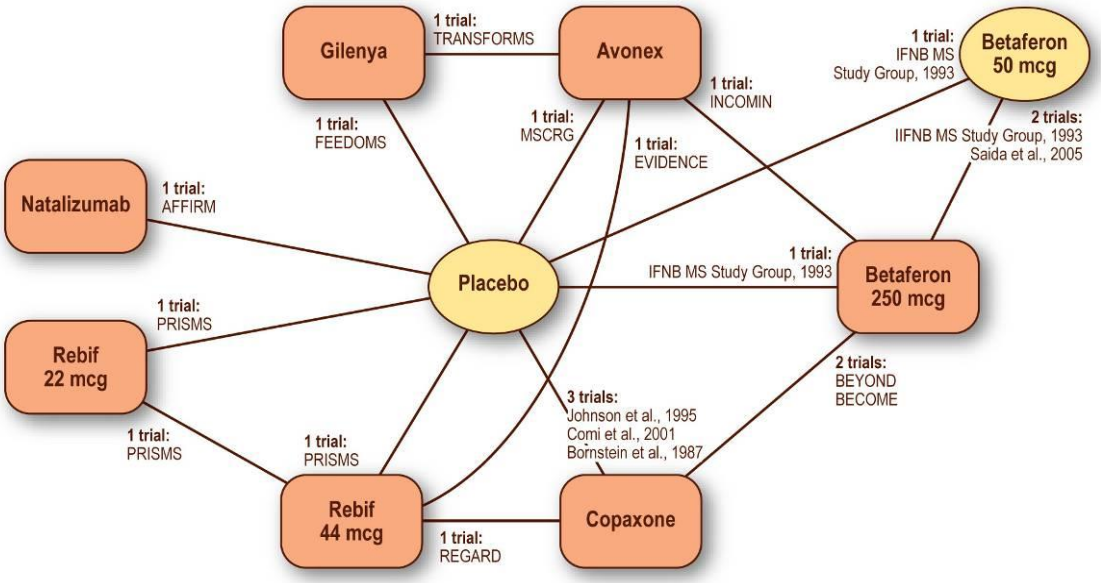
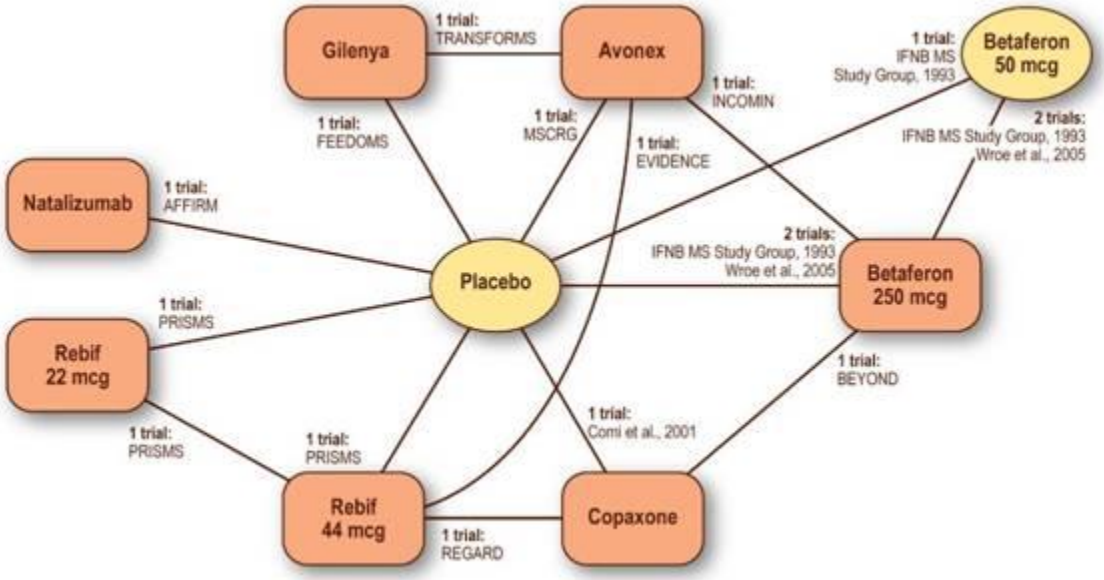


Figure 8 Network diagram for the treatment discontinuations due to adverse events mixed-treatment comparisons meta-analysis



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

Table 31, Table 32, and Table 33 present the underlying treatment estimates used in the MTC for the three outcomes meta-analysed.

- Confirmed disability progression (at 3 months)
- Annualised relapse rate
- Treatment discontinuations due to adverse events

Where appropriate, these tables include information pertaining to the outcome definitions within the specific trials. The tables also include data source details and/or required data imputations where the numbers implied by the articles were not clear. As a general rule for the outcomes, we opted for unadjusted patient numbers and event counts wherever possible, to avoid differences between the trial analyses. The articles used for each trial are the primary data source articles as listed in Table 30 in Section 5.7.3.

Table 31 Confirmed disability progression data used in the mixed-treatment comparison

Meta-analysis trial ID	Confirmed disability progression definition	Patient counts, data source	Timepoint of analysis (years)	Treatment	Group N	Patients with confirmed disability	Risk of confirmed disability
1	Sustained disability progression was defined as an increase of 1.0 point or more in scores on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 points or more from a baseline score of 0 that was sustained for 12 weeks	Patient counts imputed from percentages	2.00	Natalizumab 300 mg	627	107	0.17
				Placebo	315	91	0.29
3	Disability was defined as progression by 1 point on the EDSS scale, confirmed at a visit 3 months later without an intervening EDSS value that would not meet the criteria for progression	Reported	1.00	Interferon-beta-1a 30 mcg	338	49	0.14
				Interferon-beta-1a 44 mcg	339	43	0.13
4	Confirmed disability progression was defined as an increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression	Patient counts imputed from Kaplan-Meier percentages	2.00	Fingolimod 0.5 mg	425	75	0.18
				Placebo	418	101	0.24
5*	Sustained or confirmed progression in disability was defined as an increase in EDSS of at least 1 point sustained for at least 6 months and confirmed at the end of follow-up	Reported	2.00	Interferon-beta-1a 30 mcg	92	28	0.30
				Interferon-beta-1b 250 mcg	96	13	0.14
6*	Sustained worsening in disability was defined as deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months	Patient counts imputed from Kaplan-Meier percentages	2.00	Interferon-beta-1a 30 mcg	158	35	0.22
				Placebo	143	50	0.35

Meta-analysis trial ID	Confirmed disability progression definition	Patient counts, data source	Timepoint of analysis (years)	Treatment	Group N	Patients with confirmed disability	Risk of confirmed disability
7	Sustained disease progression was defined as an increase of at least one full step on the EDSS that persisted for at least 3 months	Patient counts imputed from percentages	2.00	Glatiramer acetate 20 mg	125	27	0.22
				Placebo	126	31	0.25
8	Confirmed disability was defined as two consecutive EDSS scores, separated by 90 days, that were identical, with both showing a 1.0-point increase over baseline	Reported	3.00	Interferon-beta-1b 250 mcg	124	25	0.20
				Placebo	123	34	0.28
9	Progression in disability was defined as an increase in EDSS of at least 1 point sustained over at least 3 months	Patient counts imputed from Kaplan-Meier plot	2.00	Placebo	187	69	0.37
				Interferon-beta-1a 22 mcg	189	55	0.29
				Interferon-beta-1a 44 mcg	184	48	0.26
10	Progression of disability was defined as a 1-point increase in the EDSS score (or a half-point increase for patients with a baseline score of at least 5.5) that was confirmed 3 months later in the absence of relapse	Patient counts imputed from Kaplan-Meier percentages	1.00	Interferon-beta-1a 30 mcg	431	34	0.08
				Fingolimod 0.5 mg	429	25	0.06
11	EDSS progression was defined as a 1-point change in the score that was sustained for 3 months	Reported	2.00	Interferon-beta-1b 250 mcg	897	200[†]	0.22
				Glatiramer acetate 20 mg	448	92	0.21

Meta-analysis trial ID	Confirmed disability progression definition	Patient counts, data source	Timepoint of analysis (years)	Treatment	Group N	Patients with confirmed disability	Risk of confirmed disability
13*	Disability progression at the 6-month follow-up visit was confirmed as follows: if the EDSS score at baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5 to 4.5 at baseline, then a change of 1.0 point or more was required; and if the EDSS at baseline was 5.0 points or more, then the change required was 0.5 points or more	Reported	2.00	Glatiramer acetate 20 mg	378	33	0.09
				Interferon-beta-1a 44 mcg	386	45	0.12
19	Progression was defined as an increase of at least 1 unit in the Krutzke score and maintained for at least 3 months	Reported	2.00	Glatiramer acetate 20 mg	25	5	0.20
				Placebo	23	11	0.48

EDSS, Expanded Disability Status Scale; ID, identification.

* Trials 5, 6, and 13 were not included in the primary confirmed disability analysis as disability was confirmed at the 6-month point rather than at 3 months. They are included in the sensitivity analysis for this endpoint.

† The number of interferon-beta-1b patients with confirmed disability in the BEYOND publication (meta-analysis trial ID 11) were erroneously noted as 244. Following correspondence with the lead author, we found the true value to be 200.

Table 32 Annualised relapse rate data used in the mixed-treatment comparison

Meta-analysis trial ID	Relapse definition	Total relapses, data source	Total person-years, data source	Timepoint of analysis (years)	Treatment	Group N	Total relapses	Total person-years	ARR
1	Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurologic signs found by the examining neurologist	Imputed using person-years and reported unadjusted ARR	Reported	2.00	Natalizumab 300 mg	627	294	1338.00	0.22
					Placebo	315	472	738.00	0.64
3	A relapse was defined as the appearance of a new symptom or worsening of an old symptom, accompanied by an appropriate objective finding on neurologic examination by the blinded evaluator, lasting at least 24 hours in the absence of fever, and preceded by at least 30 days of clinical stability or improvement. An objective finding was defined as an abnormality on examination that was consistent with the reported neurologic symptom. A relapse was recorded only if the blinded evaluator described new findings consistent with the patient's reported symptoms and if the treating physician had excluded the possibility of a pseudo-relapse	Imputed using person-years and reported adjusted (by centre) ARR	Reported (as average weeks)	1.00	Interferon-beta-1a 30 mcg	337	195	304.20	0.64
					Interferon-beta-1a 44 mcg	339	165	304.71	0.54
4	Relapses were verified by the examining neurologist within 7 days after the onset of symptoms. To constitute a confirmed relapse, the symptoms must have been accompanied by an increase of at least 0.5 points in the EDSS score, of 1 point in each of two EDSS functional-system scores, or of 2 points in one EDSS functional-system score (excluding scores for the bowel-bladder or cerebral functional systems)	From CSR	From CSR	2.00	Fingolimod 0.5 mg	425	172	810.30	0.21
					Placebo	418	359	766.30	0.47
5	Relapses were defined as the occurrence of a new neurological symptom or worsening of an old one, with an objective change of at least 1 point in Kurtzke's	Imputed using person-years and ARR	Imputed as (2 years × completers)	2.00	Interferon-beta-1a 30 mcg	92	126	180.00	0.70

Meta-analysis trial ID	Relapse definition	Total relapses, data source	Total person-years, data source	Timepoint of analysis (years)	Treatment	Group N	Total relapses	Total person-years	ARR
	functional system scale score, lasting at least 24 hours, without fever, and which followed a period of clinical stability or of improvement of at least 30 days	(unknown adjustment)	+ (1 year × lost to follow-up)		Interferon-beta-1b 250 mcg	96	95	190.00	0.50
6	On-study exacerbations were defined by the appearance of new neurological symptoms or worsening of preexisting neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days accompanied by objective change on neurological examination (worsening of 0.5 points on the EDSS or a worsening by at least 1.0 point on the pyramidal, cerebellar, brainstem, or visual functional system scores)	Imputed using person-years and unadjusted exacerbation rate	Imputed from follow-up weeks table (drop-outs given half time to that point)	2.00	Interferon-beta-1a 30 mcg	184	220	275.30	0.80
					Placebo	206	250	251.14	1.00
7	A relapse was defined as the appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurological state of at least 30 days. Objective changes on the neurologic examination consistent with an increase of at least half a step on the EDSS, 2 points on one of the seven functional symptoms, or 1 point on two or more of the functional symptoms were used to confirm a relapse	Reported	Imputed using number of relapses and adjusted (by baseline covariates) ARR	2.00	Glatiramer acetate 20 mg	125	161	273.00	0.59
					Placebo	126	210	250.00	0.84
8	An exacerbation was defined as the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by an appropriate new neurologic abnormality; lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days. Documentation of an exacerbation implied that the investigator thought there was at least one new MS lesion or enlargement of an old one	Reported	Reported	2.00	Interferon-beta-1b 250 mcg	115	173	207.00	0.84
					Interferon-beta-1b 50 mcg	111	242	207.00	1.17
					Placebo	112	266	209.20	1.27

Meta-analysis trial ID	Relapse definition	Total relapses, data source	Total person-years, data source	Timepoint of analysis (years)	Treatment	Group N	Total relapses	Total person-years	ARR
9	A relapse was defined according to Schumacher et al. as the appearance of a new symptom or the worsening of an old symptom attributable to MS, accompanied by an appropriate new neurologic abnormality or focal neurologic dysfunction lasting at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days	Imputed from mean relapses per patient	Imputed as (2 years × completers) + (1 year × lost to follow-up)	2.00	Placebo	187	479	364.00	1.32
					Interferon-beta-1a 22 mcg	189	344	366.00	0.94
					Interferon-beta-1a 44 mcg	184	318	363.00	0.88
10	Relapse was defined as new, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and that were accompanied by an increase of at least 0.5 points on the EDSS or an increase of at least 1 point in two functional-systems scores or of at least 2 points in one functional-system score (excluding changes in bowel or bladder function and cognition)	From CSR	From CSR	1.00	Interferon-beta-1a 30 mcg	431	179	415.70	0.43
					Fingolimod 0.5 mg	429	89	424.60	0.21
11	Relapse was defined as new or recurrent neurological abnormalities that were separated by at least 30 days from the onset of the preceding event, that lasted at least 24 hours, and that occurred without fever or infection. A neurological event was deemed as a relapse only if it was associated with an increase in EDSS or functional system scores, as determined by the masked, evaluating physician, that was appropriate to the reported symptoms	Imputed using person-years and ARR (unknown adjustment)	Imputed as (2.75 years × completers) + (1 year × lost to follow-up)	2.00	Interferon-beta-1b 250 mcg	888	814	2260.00	0.36
					Glatiramer acetate 20 mg	445	374	1099.50	0.34

Meta-analysis trial ID	Relapse definition	Total relapses, data source	Total person-years, data source	Timepoint of analysis (years)	Treatment	Group N	Total relapses	Total person-years	ARR
12	All new or worsening neurologic symptoms lasting 24 hours and not explained by fever or infection were considered subjective relapses. Subjective relapses that were confirmed by a blinded examining neurologist using worsening scores on either the SNRS or the EDSS were considered objective relapses. One or more of the following changes compared with baseline was required for relapse confirmation: 1) increase in total EDSS by 0.5 points; 2) increase in the EDSS score for one system by 2 points; 3) increase in the score of two or more EDSS systems by 1 point; 4) decrease in SNRS score by 7 points	Reported	Reported	2.00	Interferon-beta-1b 250 mcg	36	25	68.04	0.37
					Glatiramer acetate 20 mg	39	23	70.59	0.33
13	A qualifying relapse was defined as new or worsening neurological symptoms, without fever, that lasted for 48 hours or more and was accompanied by a change in KFS score	Imputed using 395 total relapses and both ARR (adjusted for centre)	Imputed using 395 total relapses and both ARR (adjusted for centre)	2.00	Glatiramer acetate 20 mg	378	194	669.50	0.29
					Interferon-beta-1a 44 mcg	386	201	669.50	0.30
17	Relapses were defined according to the criteria of Schumacher et al.	Imputed using person-years and unadjusted ARR	Imputed using observation periods and paper-specific ARR equation	2.00	Interferon-beta-1b 250 mcg	95	111	145.50	0.76
					Interferon-beta-1b 50 mcg	93	155	145.00	1.07

Meta-analysis trial ID	Relapse definition	Total relapses, data source	Total person-years, data source	Timepoint of analysis (years)	Treatment	Group N	Total relapses	Total person-years	ARR
18	A relapse was defined as the appearance of one or more new neurological symptoms or the reappearance of one or more previously experienced ones. Patients were instructed to telephone their local center immediately if they perceived that they might be experiencing a relapse. A visit was arranged within 7 days of notification. Neurological deterioration had to last at least 48 hours and be preceded by a relatively stable or improving neurological state in the prior 30 days. An event was counted as a relapse only when a patient's symptoms were accompanied by objective changes in the neurological examination corresponding to an increase of at least 0.5 points on the EDSS, or one grade in the score of two or more FSs, or two grades in one FS. Deterioration associated with fever or infection that can cause transient, secondary impairment of neurological function in MS patients was not considered as a relapse. Nor was a change in bowel, bladder, or cognitive function alone accepted as a relapse. The principal investigator reviewed all exacerbation reports to check their consistency with this relapse definition	Imputed from mean relapses per patient	Imputed using relapse count and ARR (unknown adjustment)	0.75	Glatiramer acetate 20 mg	119	61	75.30	0.81
					Placebo	120	91	75.20	1.21

Meta-analysis trial ID	Relapse definition	Total relapses, data source	Total person-years, data source	Timepoint of analysis (years)	Treatment	Group N	Total relapses	Total person-years	ARR
19	An exacerbation was defined as the rapid onset of new symptoms or a worsening of pre-existing symptoms that existed for 48 hours or more. An event was counted as an exacerbation only when a patient's symptoms were accompanied by observed objective changes during the neurologic examination involving an increase of at least one grade in the score for one of eight functional groups on the Kurtzke Scale. Sensory symptoms unaccompanied by objective findings or transient neurologic worsening were not considered to represent an exacerbation	Reported	Reported in figure	2.00	Glatiramer acetate 20 mg	25	16	47.33	0.34
					Placebo	23	62	45.08	1.38

ARR, annualised relapse rate; CSR, clinical study report; EDSS, Expanded Disability Status Scale; FS, functional system; ID, identification; KFS, Kurtzke functional scale; MS, multiple sclerosis; SNRS, Scripps Neurological Rating Scale.

Table 33 Adverse event treatment discontinuations data used in the mixed-treatment comparison

Meta-analysis trial ID	Timepoint of analysis (years)	Treatment	Group N	Patients with AE-related treatment discontinuation	Risk of AE-related treatment discontinuation
1	2.00	Natalizumab 300 mg	627	15	0.024
		Placebo	312	6	0.019
3	1.00	Interferon-beta-1a 30 mcg	338	14	0.041
		Interferon-beta-1a 44 mcg	339	16	0.047
4	2.00	Fingolimod 0.5 mg	425	15	0.035
		Placebo	418	24	0.057
5	2.00	Interferon-beta-1a 30 mcg	92	1	0.011
		Interferon-beta-1b 250 mcg	96	5	0.052
6	2.00	Interferon-beta-1a 30 mcg	158	7	0.044
		Placebo	143	2	0.014
8	2.00	Interferon-beta-1b 250 mcg	124	10	0.081
		Interferon-beta-1b 50 mcg	125	5	0.040
		Placebo	123	1	0.008
9	2.00	Placebo	187	2	0.011
		Interferon-beta-1a 22 mcg	189	6	0.032
		Interferon-beta-1a 44 mcg	184	9	0.049
10	1.00	Interferon-beta-1a 30 mcg	431	12	0.028
		fingolimod 0.5 mg	429	16	0.037
11	2.00	Interferon-beta-1b 250 mcg	888	13	0.015
		Glatiramer acetate 20 mg	445	8	0.018
13	2.00	Glatiramer acetate 20 mg	375	19	0.051
		Interferon-beta-1a 44 mcg	381	23	0.060
16	2.00	Interferon-beta-1b 250 mcg	65	2	0.031
		Placebo	33	0	0.000

Meta-analysis trial ID	Timepoint of analysis (years)	Treatment	Group N	Patients with AE-related treatment discontinuation	Risk of AE-related treatment discontinuation
17	2.00	Interferon-beta-1b 250 mcg	96	15	0.156
		Interferon-beta-1b 50 mcg	96	5	0.052
18	0.75	Glatiramer acetate 20 mg	119	3	0.025
		Placebo	120	2	0.017

AE, adverse event, ID, identification.

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

Both confirmed disability progression and treatment discontinuations due to AEs were analysed as binomial outcomes, i.e., utilising the number of patients with the “event/outcome” out of the total number of patients. ARR was analysed as a Poisson outcome, i.e., utilising the total number of relapses observed within a treatment group out of the total person-time of follow-up (years) for that treatment group.

Confirmed disability progression naturally lends itself to a survival analysis-type endpoint; however, after exploring the evidence base, we determined that the most consistent reporting of this data was proportion of patients with a confirmed disability progression. Thus, we elected to analyse confirmed disability progression as a binomial outcome in order to maximise the number of contributing trials within the analysis. There were 12 trials with confirmed disability progression data; however, three of these trials only presented data where disability was confirmed after 6 months, rather than after 3 months, as in the other nine trials. To retain the comparability of the data, we chose the nine consistent trials for our primary analysis of this endpoint. We analysed all 12 trials together in a sensitivity analysis.

ARR has a basic definition of total number of relapses divided by the total person-time at risk for relapse. In the evidence base, there was mixture of reporting ARRs in terms of unadjusted and adjusted estimates (using Poisson regression adjusting for selected covariates). We found that the covariates used for adjustment were not consistent throughout the evidence base and that standard errors for estimates of ARRs were not always presented. Thus, we elected to analyse ARRs as Poisson outcomes using the unadjusted estimates of number of relapses and total person-time (wherever possible).

Prior to analysis, we considered several standard but different methods of analysing patient withdrawals, i.e., all study withdrawals, study withdrawals

due to AEs, all treatment discontinuations, and treatment discontinuations due to AEs. As most of the evidence base followed patients for the complete follow-up regardless of treatment course completion, study withdrawals was not an appropriate way to measure the impact of patients not pursuing treatment. Thus, we chose to analyse treatment discontinuations. Furthermore, we elected to analyse just the treatment discontinuations due to AEs because these were consistently reported across all studies; other reasons for treatment discontinuations were allowed to be protocol specific but would not necessarily translate to the real-world setting.

Statistical methods for the binomial outcomes

A mixed log-binomial model was fit for each binomial outcome. A generic version of this type of model, where *i* indicates the study and *j* indicates the treatment, can be written as follows:

- $y_{ij} \sim \text{binomial}(n_{ij}, p_{ij})$,
- $\log(p_{ij}) = t_j + s_i + b \times x_{ij}$,

where y_{ij} and n_{ij} are the number of patients with the outcome and the total number of patients, respectively, in study *i* and on treatment *j*. We assume that

- s_i is a random effect following normal distribution (mean zero and unknown variance),
- x_{ij} is a covariate (or covariate matrix, if more than one) common to all patients in study *i* and on treatment *j* (e.g., mean age within the treatment group),
- t_j is the logarithm of overall event probability for treatment *j* at the mean x_{ij}.

It therefore follows that the relative risk of treatment a versus treatment b is

- pa/pb = exp(ta – tb).

The random effect s_i accounts for the response variables of patients within a given trial being correlated.

The indicative SAS code (PROC GLIMMIX) suitable for binomial MTC is given below (note, *r* = number of patients with the outcome and *n* = total number of patients in that study or treatment arm). It can easily be extended to include more covariates if the data merit their inclusion:

```
proc glimmix data = outcome_data itdetails;
class trt study;
model r/n = trt xcovar / noint link = log solution;
random intercept / subject = study solution;
estimate “trt-a vs trt-b” trt 1 – 1 0 0 … / exp cl;
run
```

Statistical methods for the Poisson outcomes

A mixed Poisson regression was fit for each Poisson distributed outcome. A generic version of this type of model, where *i* indicates the study and *j* indicates the treatment, can be written as follows:

- $y_{ij} \sim \text{Poisson}(n_{ij}p_{ij})$,
- $\log(p_{ij}) = t_j + s_i + b \times x_{ij}$,

where y_{ij} and n_{ij} are the number of events and exposure person-time of patients, respectively, in study *i* and on treatment *j*. We assume that

- s_i is a random effect following normal distribution (mean zero and unknown variance),
- x_{ij} is a covariate (or covariate matrix if more than one) common to all patients in study *i* and on treatment *j* (e.g., mean age within the treatment group),
- t_j is logarithm of overall incidence for treatment *j* at the mean x_{ij}.

It follows that the rate ratio of treatment a versus treatment *b* is

- pa/pb = exp(ta – tb).

The random effect *si* accounts for the response variables of patients within a given trial being correlated.

The indicative PROC GLIMMIX code suitable for Poisson MTCs is given below (note, *r* = total events and *logpy* = log(total person-time for the given study or treatment arm). It can easily be extended to include more covariates and the extra random effect if the data merit their inclusion:

```
proc glimmix data = outcome_data itdetails;
class trt study;
model r = trt xcovar;
/ noint distribution = Poisson offset = logpy;
random intercept / subject = study solution;
estimate “trt-a vs trt-b” trt 1 – 1 0 0 … / exp cl;
run
```

5.7.6 Please present the results of the analysis.

The following three tables (Table 34, Table 35, and Table 36) present the results from the MTC meta-analyses. The results presented show relative treatment effects of each included treatment versus fingolimod 0.5 mg and separately versus placebo. It should be remembered that these comparisons are for the entire trial population. The proposed UK licence for fingolimod and the UK licence for natalizumab are more restricted than their trial population.

Table 34 Confirmed disability progression (at 3 months) mixed-treatment comparison results

	Relative risk (95% confidence interval)	
Relative risk numerator	**Fingolimod 0.5 mg**	**Placebo**
Fingolimod 0.5 mg	N/A	[redacted]

Relative risk numerator	Relative risk (95% confidence interval)	
	Fingolimod 0.5 mg	Placebo
Interferon-beta-1a 22 mcg	[redacted]	[redacted]
Interferon-beta-1a 44 mcg	[redacted]	[redacted]
Interferon-beta-1a 30 mcg	[redacted]	[redacted]
Interferon-beta-1b 250 mcg	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]
Placebo	[redacted]	N/A

N/A, not applicable.

[redacted]

Table 35 Annualised relapse rate mixed-treatment comparison results

Relative rate numerator	Relative rate (95% confidence interval)	
	Fingolimod 0.5 mg	Placebo
Fingolimod 0.5 mg	N/A	[redacted]
Interferon-beta-1a 22 mcg	[redacted]	[redacted]
Interferon-beta-1a 44 mcg	[redacted]	[redacted]
Interferon-beta-1a 30 mcg	[redacted]	[redacted]
Interferon-beta-1b 250 mcg	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]
Placebo	[redacted]	N/A

N/A, not applicable.

[redacted]

[redacted]

Table 36 Treatment discontinuation due to adverse events mixed-treatment comparison results

Relative risk numerator	Relative risk (95% confidence interval)	
	Fingolimod 0.5 mg	**Placebo**
Fingolimod 0.5 mg	N/A	[redacted]
Interferon-beta-1a 22 mcg	[redacted]	[redacted]
Interferon-beta-1a 44 mcg	[redacted]	[redacted]
Interferon-beta-1a 30 mcg	[redacted]	[redacted]
Interferon-beta-1b 250 mcg	[redacted]	[redacted]
Glatiramer Acetate 20 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]
Placebo	[redacted]	N/A

N/A, not applicable.

[redacted]

[redacted]

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The following tables display the patient/trial characteristics that we considered as potential sources of heterogeneity listed by trial/treatment (Table 37) and then summarised by treatment across the trials (Table 38).

For the summaries by treatment, we used averages weighted on the treatment arm sample sizes as appropriate.

Table 37 Trial and baseline patient characteristics

Meta-analysis trial ID	Publi-cation year	Prior treatment allowed?	Treatment	Group (N)	Mean age (years)	Percent females	Disease duration (years)	Relapses in 2 years prior to baseline	Mean EDSS at baseline
1	2006	No	Natalizumab 300 mg	627	35.6	71.6	5.00	2.31*	2.30
			Placebo	315	36.7	67.0	6.00	2.27*	2.30
3	2002	Yes	Interferon-beta-1a 30 mcg	338	37.4	74.6	6.70	2.60	2.30
			Interferon-beta-1a 44 mcg	339	38.3	74.9	6.50	2.60	2.30
4	2010	Yes	Fingolimod 0.5 mg	425	36.6	69.6	8.00	2.10	2.30
			Placebo	418	37.2	71.3	8.10	2.20	2.50
5	2002	No	Interferon-beta-1a 30 mcg	92	34.9	62.0	6.70	2.76	1.96
			Interferon-beta-1b 250 mcg	96	38.8	68.8	5.90	3.04	1.97
6	1996	Yes	Interferon-beta-1a 30 mcg	158	36.7	74.7	6.60	1.81*	2.40
			Placebo	143	36.9	72.0	6.40	1.81*	2.30
7	1995	Yes	Glatiramer acetate 20 mg	125	34.6	70.4	7.30	2.90	2.80
			Placebo	126	34.3	76.2	6.60	2.90	2.40
8	1993	Yes	Interferon-beta-1b 250 mcg	124	35.2	69.4	4.70	3.40	3.00
			Interferon-beta-1b 50 mcg	125	35.3	68.0	4.70	3.30	2.90
			Placebo	123	36.0	71.5	3.90	3.60	2.80
9	1998	No	Placebo	187	34.6	74.9	4.30	3.00	2.40
			Interferon-beta-1a 22 mcg	189	34.8	67.2	5.40	3.00	2.50
			Interferon-beta-1a 44 mcg	184	35.6	65.8	6.40	3.00	2.50
10	2010	Yes	Interferon-beta-1a 30 mcg	431	36.0	68.4	7.40	2.30	2.19
			Fingolimod 0.5 mg	429	36.7	65.7	7.50	2.30	2.24

Meta-analysis trial ID	Publi-cation year	Prior treatment allowed?	Treatment	Group (N)	Mean age (years)	Percent females	Disease duration (years)	Relapses in 2 years prior to baseline	Mean EDSS at baseline
11	2009	No	Interferon-beta-1b 250 mcg	897	35.8	69.9	5.30	2.42*	2.35
			Interferon-beta-1b 500 mcg	899	35.9	70.0	5.40	2.42*	2.33
			Glatiramer acetate 20 mg	448	35.2	68.3	5.10	2.42*	2.28
12	2009	No	Interferon-beta-1a 250 mcg	36	36.0	75.0	0.90	2.72*	2.00
			Glatiramer acetate 20 mg	39	36.0	64.1	1.20	2.87*	2.00
13	2008	No	Glatiramer acetate 20 mg	378	36.8	72.0	6.55	Nr	2.33
			Interferon-beta-1a 44 mcg	386	36.7	69.2	5.93	Nr	2.35
14	2008	Yes	Interferon-beta-1b 250 mcg	38	37.9	71.1	NR	NR	2.80
			Interferon-beta-1b 500 mcg	33	37.8	75.8	NR	NR	2.00
15	2006	Yes	Interferon-beta-1a 30 mcg	30	28.1	80.0	2.90	3.02*	1.90
			Interferon-beta-1b 250 mcg	30	29.9	70.0	3.70	3.32*	1.90
			Interferon-beta-1a 44 mcg	30	27.4	76.7	3.00	3.62*	2.10
16	2005	No	Interferon-beta-1a 250 mcg	65	35.0	73.8	NR	2.66	2.92
			Placebo	33	38.0	72.7	NR	2.47	3.09
17	2005	No	Interferon-beta-1b 250 mcg	96	35.5	71.9	6.30	3.02*	NR
			Interferon-beta-1a 50 mcg	96	36.3	66.7	8.00	2.87*	NR
18	2001	No	Glatiramer acetate 20 mg	119	34.1	NR	7.90	2.80	2.30
			Placebo	120	34.0	NR	8.30	2.50	2.40
19	1987	Yes	Glatiramer acetate 20 mg	25	30.0	56.0	4.90	3.80	2.90
			Placebo	25	31.0	60.0	6.10	3.90	3.20

EDSS, Expanded Disability Status Scale; ID, identification; NR, not reported.

* The relationship between mean relapses in years 1 and 2 (from trials 4 and 10) was used to impute the 2 year relapse rate for 6 trials where only 1 year data were available (trials 1, 6, 11, 12, 15, 17).

Table 38 Summary of trial and baseline patient characteristics by treatment

Treatment	Num-ber of trials	Mean age in years (range)	Mean percent females (range)	Disease duration in years (range)	Mean relapses in 2 years prior to baseline (range)	Mean EDSS at baseline (range)	Median publication year (range)	Number of trials allowing prior use of disease-modifying therapy
Fingolimod 0.5 mg	2	37 (37-37)	68 (66-70)	7.7 (7.5-8.0)	2.2 (2.1-2.3)	2.3 (2.2-2.3)	2010 (2010-2010)	2/2
Interferon-beta-1a 22 mcg	1	35 (n/a)	67 (n/a)	5.4 (n/a)	3.0 (n/a)	2.5 (n/a)	1998 (n/a)	0/1
Interferon-beta-1a 44 mcg	4	37 (27-38)	71 (66-77)	6.1 (3.0-6.5)	2.7 (2.6-3.0)	2.4 (2.1-2.5)	2004 (1998-2008)	2/4
Interferon-beta-1a 30 mcg	5	36 (28-37)	71 (62-80)	6.9 (2.9-7.4)	2.4 (1.8-2.8)	2.2 (1.9-2.4)	2002 (1996-2010)	4/5
Interferon-beta-1b 250 mcg	8	36 (30-39)	70 (69-75)	5.2 (0.9-6.3)	2.6 (2.4-3.4)	2.4 (1.9-3.0)	2006 (1993-2009)	3/8
Glatiramer acetate 20 mg	6	35 (30-37)	69 (56-72)	6.0 (1.2-7.9)	2.6 (2.4-3.8)	2.4 (2.0-2.9)	2005 (1987-2009)	2/6
Natalizumab 300 mg	1	36 (n/a)	72 (n/a)	5.0 (n/a)	2.3 (n/a)	2.3 (n/a)	2006 (n/a)	0/1
Placebo	9	36 (31-38)	71 (60-76)	6.5 (3.9-8.3)	2.5 (1.8-3.9)	2.5 (2.3-3.2)	1998 (1987-2010)	5/9

EDSS, Expanded Disability Status Scale; n/a, not applicable.

The distributions of the trial/patient characteristics are reasonably similar across the treatments within the analyses. The characteristics that exhibit some differences across the treatments are disease duration at baseline, year of publication, and allowance of prior disease modifying therapy.

We explored all the characteristics as covariates separately within the MTC model for each outcome of interest (Table 39). Additionally we explored the inclusion of a covariate to account for the timepoint of analysis (in most cases the length of the study).

Table 39 Effects of trial/patient characteristics used as covariates in mixed-treatment comparison models

Characteristic used as a covariate in mixed treatment comparison	Covariate effect estimate (95% CI) [statistical significance P value]		
	Confirmed disability progression	Annualised relapse rate	Treatment discontinuation due to adverse events
Mean age (years)	[redacted]	[redacted]	[redacted]
Percentage of females	[redacted]	[redacted]	[redacted]
Disease duration (years)	[redacted]	[redacted]	[redacted]
Mean number of relapses in past 2 years	[redacted]	[redacted]	[redacted]
Mean baseline EDSS Score	[redacted]	[redacted]	[redacted]
Year of publication	[redacted]	[redacted]	[redacted]
Prior disease modifying therapy allowed	[redacted]	[redacted]	[redacted]
Timepoint of analysis	[redacted]	[redacted]	[redacted]

CI, confidence interval; EDSS, Expanded Disability Status Scale.

None of the covariates had consistently statistically significant effects across all three endpoints. The statistically significant covariates were age (for confirmed disability progression), baseline EDSS score (for annualised relapse rate), publication year (for annualised relapse rate), and timepoint of analysis (for confirmed disability progression). Of these, the direction of relationship between covariate and endpoint were intuitive apart from age.

The age effect estimate of 0.87 suggests that increased age is negatively correlated with confirmed disability progression, which is clinically counterintuitive. It should be stated however that exploration of heterogeneity via the use of covariates in a meta-regression fashion is far from an exact science and has limitations, most notably of lack of statistical power and the use of summary statistics for covariate and endpoint response for a given treatment arm does not automatically translate into a patient level relationship.

We investigated the actual relative treatment effects with the covariates included in the model and found no material differences in these whether or not we included the covariate, even for those models that had significant covariate effects. Therefore, the final MTC results presented here are from models including no covariates. Ideally, we would investigate the interaction of the treatment effects with the covariates, rather than the additive effect, but this is not possible in our model due to lack of data.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

In the primary analysis, we present the results for confirmed disability progression at 3 months. The definitions of confirmed disability differed slightly among trials, but a key difference in these definitions was the timepoint at which disability progression was confirmed. Ten trials used a timepoint of 3 months to confirm disability progression, and these form the basis of the primary analysis. Three further trials used a timepoint of 6 months to confirm disability progression (Trials 5 [INCOMIN: 188 patients], 6 [MSCRG: 301 patients], and 13 [REGARD: 764 patients]). [redacted] Table 40 [redacted]

Table 40 Confirmed disability progression (at 3 or 6 months) mixed-treatment comparison results

Relative risk numerator	Relative risk (95% confidence interval)	
	Fingolimod 0.5 mg	Placebo
Fingolimod 0.5 mg	N/A	[redacted]
Interferon-beta-1a 22 mcg	[redacted]	[redacted]
Interferon-beta-1a 44 mcg	[redacted]	[redacted]
Interferon-beta-1a 30 mcg	[redacted]	[redacted]
Interferon-beta-1b 250 mcg	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]
Placebo	[redacted]	N/A

N/A, not applicable.

[redacted]

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Table 41 presents the relative (active) treatment effect estimates calculated both head to head within a trial and those estimated in the MTC for each endpoint.

Table 41 Comparison of trial-based treatment effects against mixed-treatment comparison results

Trial name [trial ID]	Treatment comparison	Confirmed disability progression		Annualised relapse rate		Treatment discontinuations due to adverse events	
		Trial RR	MTC RR (95% CI)	Trial RR	MTC RR (95% CI)	Trial RR	MTC RR (95% CI)
EVIDENCE [3]	Interferon-beta-1a 30 mcg vs. interferon-beta-1b 44 mcg	1.14	[redacted]	1.18	[redacted]	0.88	[redacted]
INCOMIN [5]	Interferon-beta-1a 30 mcg vs. interferon-beta-1b 250 mcg	n/a	n/a	1.40	[redacted]	0.21	[redacted]
PRISIMS [9]	Interferon-beta-1a 22 mcg vs. interferon-beta-1a 44 mcg	1.12	[redacted]	1.07	[redacted]	0.65	[redacted]
TRANSFORMS [10]	Interferon-beta-1a 30 mcg vs. fingolimod 0.5 mg	1.35	[redacted]	2.05	[redacted]	0.75	[redacted]
BEYOND [11]	Glatiramer acetate 20 mg vs. interferon-beta-1b 250 mcg	0.92	[redacted]	0.94	[redacted]	1.23	[redacted]

Trial name [trial ID]	Treatment comparison	Confirmed disability progression		Annualised relapse rate		Treatment discontinuations due to adverse events	
		Trial RR	MTC RR (95% CI)	Trial RR	MTC RR (95% CI)	Trial RR	MTC RR (95% CI)
BECOME [12]	Glatiramer acetate 20 mg vs. interferon-beta-1b 250 mcg	NR	NR	0.89	[redacted]	NR	NR
REGARD [13]	Glatiramer acetate 20 mg vs. interferon-beta-1a 44 mcg	N/A	N/A	0.97	[redacted]	0.84	[redacted]

CI, confidence interval; ID, identification; MTC, mixed-treatment comparison; N/A, not applicable; NR, not reported; RR, relative risk/rate.

For the confirmed disability progression endpoint, the MTC-derived relative risks closely match those derived from the head to head trials, with the slight exception of TRANSFORMS (interferon-beta-1a 30 mcg vs. fingolimod). Inspecting the data more closely, we found that contributing data from both interferon-beta-1a 30 mcg trials had follow-up of 1 year, compared with the "standard" follow-up of 2 years for most other trials. Although analysis timepoint was not statistically significant in the covariate investigations, this highlights the lack of statistical power to fully assess the impact of covariates in this analysis. Exclusion of trials with only 1 year of follow-up is not a sensible option in this case because this endpoint is the only source of interferon-beta-1a 30 mcg data. It should be noted, however, that the MTC's relative risk confidence interval for interferon-beta-1a versus fingolimod ([redacted]) comfortably contained the trial estimate of relative risk (1.35). Thus, we accept the potential limitation of the interferon-beta-1a 30 mcg data in this analysis and acknowledge that the wide confidence interval reflects the uncertainty of the estimate.

For the ARR endpoint, the MTC-derived relative rates closely match those derived from the head to head trials.

For the treatment discontinuations due to adverse events endpoint, there appears to be several inconsistencies between the MTC results and the head to head results, although most head to head point estimates lay within the MTC estimate confidence limits. On further inspection, the most likely reason for these inconsistencies stem from inconsistent direction of treatment effects across all trials (including placebo controlled ones). For example, there is contradictory evidence between placebo, interferon-beta-1a 30 mcg and fingolimod; the MSCRG trial has interferon-beta-1a 30 mcg with a higher risk of adverse event related treatment discontinuation compared to placebo, the FREEDOMS trial has placebo with a higher risk of discontinuation compared to fingolimod and the TRANSFORMS trial has fingolimod with a higher risk of discontinuation compared to interferon-beta-1a 30 mcg. Without evidence to exclude any of the contradictory trials, we assume the MTC consolidates the different treatment effects as well as possible.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see Section 5.2.7), please repeat the instructions specified in Sections 5.1 to 5.5 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 **Error! Reference source not found.** and **Error! Reference source not found.**, Appendices 6 and 7.

The systematic review (described in Appendix 2, Section **Error! Reference source not found.**) identified no relevant non-RCT articles.

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 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 **Error! Reference source not found.** and **Error! Reference source not found.**, Appendices 8 and 9.

None of the fingolimod trials were designed to assess safety as a primary outcome.

5.9.2 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. A suggested format is shown below.

The adverse reactions in Study D2302 (TRANSFORMS, a 1-year study) and Study D2301 (FREEDOMS, a 2-year study) were generally similar to each other, taking into account the differences in study duration (Novartis, draft SPC, 2011). In both studies, the most serious adverse events in patients receiving fingolimod 0.5 mg were infections, macular oedema, and transient atrioventricular block at treatment initiation (Novartis, draft SPC, 2011). The pooled number, percentages, and relative risks of these adverse events at 12 months are detailed in Table 42.

Table 42 Most frequent serious adverse events in patients receiving fingolimod 0.5 mg at 12 months in pooled data from Study D2302 (the TRANSFORMS study) and Study D2301 (the FREEDOMS study)

Adverse event	**Fingolimod 0.5 mg (n = 854) n (%)**	**Beta interferon (n = 431) n (%)**	**Relative risk: fingolimod vs. beta-interferon (95% CI)**	**Placebo (n = 418) n (%)**	**Relative risk: fingolimod vs. placebo (95% CI)**
Severe infections and infestations	10 (1.2)	6 (1.4)	0.84 (0.31, 2.30)	8 (1.9)	0.61 (0.24, 1.54)
Macular oedema	2 (0.2)	1 (0.2)	1.01 (0.09, 11.10)	0 (0.0)	
Atrio-ventricular block, first degree	1(0.1)	0 (0.0)		0 (0.0)	
Atrio-ventricular block, second degree	1 (0.1)	0 (0.0)		0 (0.0)	

CI, confidence interval.

The number, percentages, and relative risks of the most frequent adverse reactions (incidence ≥ 5%) at 12 months in patients receiving fingolimod 0.5 mg are detailed in Table 43.

Table 43 The most frequent adverse reactions (incidence ≥ 5%) at 12 months in patients receiving fingolimod 0.5 mg in pooled data from Study D2302 (the TRANSFORMS study) and Study D2301 (the FREEDOMS study)

Adverse event	Fingolimod 0.5 mg (n = 854) n (%)	Beta interferon (n = 431) n (%)	Relative risk: fingolimod vs. beta-interferon (95% CI)	Placebo (n = 418) n (%)	Relative risk: fingolimod vs. placebo (95% CI)
Headache	195 (22.8)	88 (20.4)	1.12 (0.89, 1.40)	79 (18.9)	1.21 (0.96, 1.53)
Naso-pharyngitis	166 (19.4)	88 (20.4)	0.95 (0.76, 1.20)	81 (19.4)	1.00 (0.79, 1.27)
Upper respiratory tract infection	86 (10.1)	27 (6.3)	1.61 (1.06, 2.44)	58 (13.9)	0.73 (0.53, 0.99)
Fatigue	86 (10.1)	45 (10.4)	0.96 (0.69, 1.36)	36 (8.6)	1.17 (0.81, 1.69)
Nausea	75 (8.8)	29 (6.7)	1.31 (0.86, 1.97)	30 (7.2)	1.22 (0.81, 1.84)
Diarrhoea	67 (7.8)	21 (4.9)	1.61 (1.00, 2.59)	26 (6.2)	1.26 (0.81, 1.95)
Influenza	64 (7.5)	32 (7.4)	1.01 (0.67, 1.52)	30 (7.2)	1.04 (0.69, 1.59)
Back pain	62 (7.3)	23 (5.3)	1.36 (0.86, 2.16)	24 (5.7)	1.26 (0.80, 2.00)
ALT increased	61 (7.1)	8 (1.9)	3.85 (1.86, 7.97)	11 (2.6)	2.71 (1.44, 5.10)
Cough	53 (6.2)	16 (3.7)	1.67 (0.97, 2.89)	23 (5.5)	1.13 (0.70, 1.81)
Dizziness	49 (5.7)	21 (4.9)	1.18 (0.72, 1.94)	19 (4.5)	1.26 (0.75, 2.12)
Urinary tract infection	48 (5.6)	22 (5.1)	1.10 (0.67, 1.80)	36 (8.6)	0.65 (0.43, 0.99)
Depression	47 (5.5)	33 (7.7)	0.72 (0.47, 1.10)	17 (4.1)	1.35 (0.79, 2.33)

ALT, alanine aminotransferase; CI, confidence interval.

Adverse reactions reported at 12 months in patients receiving fingolimod 0.5 mg at an incidence of ≥ 1% or higher than with placebo in Study D2301 (the FREEDOMS study) or with beta interferon in Study D2302 (the TRANSFORMS study) are shown in Table 44. Some of these adverse reactions have been reported in Table 42 and Table 43; for completeness, these adverse reactions are reiterated in Table 44.

Table 44 Adverse reactions reported in patients at 12 months receiving fingolimod 0.5 mg at an incidence of ≥ 1% or higher than with placebo in Study D2301 (the FREEDOMS study) or interferon in Study D2302 (the TRANSFORMS study)[*,†]

Primary system organ class/ preferred term	Fingolimod 0.5 mg (n = 854) n (%)	Beta interferon (n = 431) n (%)	Relative risk: fingolimod vs. beta-interferon (95% CI)	Placebo (n = 418) n (%)	Relative risk fingolimod vs. placebo (95% CI)
Infections and infestations					
Upper respiratory tract	86 (10.1)	27 (6.3)	1.61 (1.06, 2.44)	58 (13.9)	0.73 (0.53, 0.99)
Bronchitis	39 (4.6)	11 (2.6)	1.79 (0.93, 3.46)	11 (2.6)	1.74 (0.90, 3.35)
Tinea infections	10 (1.2)	6 (1.4)	0.84 (0.31, 2.30)	1 (0.2)	4.89 (0.63, 38.11)
Pneumonia	2 (0.2)	1 (0.2)	1.01 (0.09, 11.10)	1 (0.2)	1.01 (0.09, 11.10)
Blood and lymphatic system disorders					
Leucopenia	14 (1.6)	1 (0.2)	7.07 (0.93, 53.55)	1 (0.2)	6.85 (0.90, 51.93)
Psychiatric disorders					
Depression	47 (5.5)	33 (7.7)	0.72 (0.47, 1.10)	17 (4.1)	1.35 (0.79, 2.33)
Nervous system disorders					
Headache	195 (22.8)	88 (20.4)	1.12 (0.89, 1.40)	79 (18.9)	1.21 (0.96, 1.53)
Dizziness	49 (5.7)	21 (4.9)	1.18 (0.72, 1.94)	19 (4.5)	1.26 (0.75, 2.12)
Paraesthesia	32 (3.7)	16 (3.7)	1.01 (0.56, 1.82)	11 (2.6)	1.42 (0.73, 2.80)
Migraine	24 (2.8)	7 (1.6)	1.73 (0.75, 3.98)	3 (0.7)	3.92 (1.19, 12.93)
Eye disorders					
Vision blurred	19 (2.2)	13 (3.0)	0.74 (0.37, 1.48)	4 (1.0)	2.32 (0.80, 6.79)
Metabolism					
Hypercholesterolaemia	24 (2.8)	3 (0.7)	4.04 (1.22, 13.33)	19 (4.5)	0.62 (0.34, 1.12)
Ear and labyrinth disorders					
Vertigo	23 (2.7)	3 (0.7)	3.87 (1.17, 12.81)	16 (3.8)	0.70 (0.38, 1.32)
Vascular disorders					

Primary system organ class/ preferred term	Fingolimod 0.5 mg (n = 854) n (%)	Beta interferon (n = 431) n (%)	Relative risk: fingolimod vs. beta-interferon (95% CI)	Placebo (n = 418) n (%)	Relative risk fingolimod vs. placebo (95% CI)
Hypertension	36 (4.2)	9 (2.1)	2.02 (0.98, 4.15)	11 (2.6)	1.60 (0.82, 3.11)
Respiratory, thoracic, and mediastinal disorders					
Cough	53 (6.2)	16 (3.7)	1.67 (0.97, 2.89)	23 (5.5)	1.13 (0.70, 1.81)
Dyspnoea	36 (4.2)	7 (1.6)	2.60 (1.16, 5.78)	17 (4.1)	1.04 (0.59, 1.82)
Gastrointestinal disorders					
Nausea	75 (8.8)	29 (6.7)	1.31 (0.86, 1.97)	30 (7.2)	1.22 (0.81, 1.84)
Diarrhoea	67 (7.8)	21 (4.9)	1.61 (1.00, 2.59)	26 (6.2)	1.26 (0.81, 1.95)
Skin and subcutaneous tissue disorders					
Eczema	14 (1.6)	2 (0.5)	3.53 (0.81, 15.47)	5 (1.2)	1.37 (0.50, 3.78)
Alopecia	21 (2.5)	6 (1.4)	1.77 (0.72, 4.34)	7 (1.7)	1.47 (0.63, 3.43)
Musculoskeletal and connective tissue disorders					
Back pain	62 (7.3)	23 (5.3)	1.36 (0.86, 2.16)	24 (5.7)	1.26 (0.80, 2.00)
General disorders and administration site conditions					
Fatigue	86 (10.1)	45 (10.4)	0.96 (0.69, 1.36)	36 (8.6)	1.17 (0.81, 1.69)
Pyrexia	24 (2.8)	77 (17.9)	0.16 (0.10, 0.25)	7 (1.7)	1.68 (0.73, 3.86)
Influenza-like illness	21 (2.5)	159 (36.9)	0.07 (0.04, 0.10)	2 (0.5)	5.14 (1.21, 21.81)
Asthenia	19 (2.2)	6 (1.4)	1.60 (0.64, 3.97)	4 (1.0)	2.32 (0.80, 6.79)
Investigations					
ALT increased	61 (7.1)	8 (1.9)	3.85 (1.86, 7.97)	11 (2.6)	2.71 (1.44, 5.10)
GGT increased	28 (3.3)	1 (0.2)	14.13 (1.93, 103.51)	3 (0.7)	4.57 (1.40, 14.94)
Hepatic enzyme increased	30 (3.5)	3 (0.7)	5.05 (1.55, 16.44)	1 (0.2)	14.68 (2.01, 107.30)
Liver function test abnormal	8 (0.9)	2 (0.5)	2.02 (0.43, 9.47)	0 (0.0)	
Weight decreased	17 (2.0)	3 (0.7)	2.86 (0.84, 9.71)	11 (2.6)	0.76 (0.36, 1.60)

Primary system organ class/ preferred term	Fingolimod 0.5 mg (n = 854) n (%)	Beta interferon (n = 431) n (%)	Relative risk: fingolimod vs. beta-interferon (95% CI)	Placebo (n = 418) n (%)	Relative risk fingolimod vs. placebo (95% CI)
Weight increased	12 (1.4)	0 (0.0)		18 (4.3)	0.33 (0.16, 0.67)
Blood cholesterol increased	10 (1.2)	0 (0.0)		11 (2.6)	0.44 (0.19, 1.04)

AE, adverse event; ALT, alanine transaminase; CI, confidence interval; GGT, gamma-glutamyl transferase.

* A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

† Data is from the pooled safety population of Study D2302 (the TRANSFORMS study) and Study D2301 (the FREEDOMS study).

Source: Novartis, data on file, 2010.

Discontinuations due to adverse events were reported in the patient subgroups of interest for the indication in this submission. In Study 2302 (TRANSFORMS), the frequency of discontinuations due to adverse events were low in non-responder patients who had received any prior DMT in the year before the study and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year, both in those receiving fingolimod 0.5 mg (3.1%) or interferon-beta-1a (1.6%). Also in Study 2302 (TRANSFORMS), there was a low discontinuation rate due to adverse events both in patients receiving fingolimod 0.5 mg (3.2%) and in those receiving interferon-beta-1a (1.6%) for the subgroups of patients receiving any prior DMT in the year before the study, patients with ≥ 1 relapse while on therapy, and patients with either ≥ 1 gadolinium-enhancing lesions or a T2 lesion volume of ≥ 500 mm^2.

In Study 2301 (FREEDOMS), the discontinuation rate due to adverse events was lower in patients receiving fingolimod 0.5 mg (2.2%) when compared with placebo (7.6%) in non-responder patients who had received any prior DMT in the year before the study and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year. Also in Study 2301 (FREEDOMS), the discontinuation rate due to adverse events was lower in patients receiving fingolimod 0.5 mg (2.3%) compared with placebo (9.1%) in the subgroups of patients receiving any prior DMT in the year before the study, patients with ≥ 1 relapse while on therapy, and patients with either ≥ 1 gadolinium-enhancing lesions or a T2 lesion volume of ≥ 500 mm^2.

In Study 2302 (TRANSFORMS), there were no deaths reported with fingolimod 0.5 mg or interferon-beta-1a in this study. Two deaths were reported during the trial, both in the fingolimod 1.25-mg group. One death was caused by disseminated primary Varicella-Zoster infection in a patient with no history of chicken pox during an 8-day course of corticosteroids (intravenous and then oral methylprednisolone) for a relapse of MS. Fingolimod was discontinued after 317 days of therapy and intravenous antiviral therapy was started, but the patient died 3 days later. The other death was caused by

herpes simplex encephalitis; the patient had received 339 days of therapy. A 3-day course of methylprednisolone was administered intravenously for suspected relapse of MS, followed by antiviral therapy starting 1 week after presentation. The patient died approximately 2 months later.

In addition, two patients who received fingolimod 1.25 mg died after the study ended. One patient, with a baseline EDSS score of 5.0 at 3 years after disease onset, discontinued fingolimod after 11 months because of neurologic deterioration. The patient's condition continued to decline, aspiration pneumonia developed, and the patient died 6 months after study discontinuation. The other patient died from metastatic breast cancer 10 months after discontinuing fingolimod.

In Study 2301 (FREEDOMS), there were no deaths reported with fingolimod 0.5 mg in this study, although two deaths were reported in the placebo group. The causes of death for these patients were pulmonary embolism and traffic accident. One death also was reported in the fingolimod 1.25-mg group, the cause of which was suicide.

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

Overview of fingolimod safety

Phase II and Phase III studies have provided data for more than 5,000 patient-years of exposure to fingolimod. Fingolimod 0.5 mg has a more favourable safety profile than that of fingolimod 1.25 mg. In total, the Phase III studies included 1,703 patients receiving fingolimod, 854 of which were receiving fingolimod 0.5 mg.

Oral fingolimod was generally well tolerated in patients in the Phase II and Phase III studies, with a similar rate of AEs with fingolimod 0.5 mg compared with placebo and a lower rate of AEs compared with beta-interferon.

The overall incidence of infection was similar between treatment groups in both Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS), and

infections were mostly mild or moderate in severity. The incidence of serious infection was low in Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS) and comparable to beta-interferon or placebo.

Warnings, precautions, and contraindications

The following warnings and precautions are issued for fingolimod (Novartis, draft SPC, 2011):

- Since fingolimod suppresses the immune system, and increases the risk of infection, strategies should be employed in patients with infection while on treatment. Vigilance is required to monitor infection for 2 months after discontinuation of therapy because fingolimod may still remain in the blood. Patients receiving fingolimod should report signs of infection to their physician. Treatment may be suspended if a patient develops a serious infection.
- Before initiating fingolimod treatment, a recent CBC (i.e., within 6 months) should be available. Assessments of CBC also are recommended periodically during treatment and in case of signs of infection. If an absolute lymphocyte count of less than 0.2×10^9/l is confirmed, fingolimod treatment should be interrupted until recovery.
- Patients with a history of chickenpox or without a vaccination for Varicella-Zoster virus (VZV) should be tested for VZV antibodies. VZV vaccination of antibody-negative patients should be considered before commencing therapy with fingolimod. After vaccination, initiation of fingolimod treatment should be postponed for 1 month to allow full vaccination effect.
- Antineoplastic, immunosuppressive, or immune-modulating therapies should be co-administered with caution because of potential additive effects on the immune system.
- Substances that reduce heart rate (e.g., beta blockers, class Ia and class III antiarrhythmics, calcium channel blockers like verapamil or diltiazem, digoxin, anticholinesteratic agents, or pilocarpine) should be administered with caution.

- Substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, and some macrolides such as clarithromycin or telithromycin) should also be administered with caution.
- Vaccination may be less effective during and for up to 2 months after fingolimod treatment initiation. As such, the use of live attenuated vaccines may carry a risk of infection and should be avoided.
- An ophthalmological examination is recommended at 3 to 4 months after fingolimod treatment initiation because of the risk of macular oedema. Also, if patients report visual disturbance, evaluation of the fundus should be carried out.
- Patients with uveitis and diabetes are at increased risk for macular oedema and should undergo an ophthalmological examination before receiving fingolimod.
- All patients should be observed for any serious changes in heart rate for 6 hours after treatment initiation. This will need to be carried out in a hospital capable of immediate treatment should there be a severe case of bradycardia or atrioventricular block.
- Fingolimod should not be co-administered with class Ia (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol) anti-arrhythmic medicinal products.
- Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.
- In the absence of clinical symptoms, liver transaminases should be monitored at 1, 3, and 6 months on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase measurement. With repeated confirmation of liver transaminases above 5 times the ULN, fingolimod treatment should be interrupted and only re-commenced once liver transaminase levels have normalised.

- Patients who develop symptoms suggestive of hepatic dysfunction (such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, and/or dark urine) should have liver enzymes checked, and treatment should be discontinued if significant liver injury is confirmed (e.g., liver transaminases greater than 5 times the ULN and/or serum bilirubin elevations).
- Fingolimod should be used with caution in patients with pre-existing liver abnormalities; these patients should be monitored regularly for signs of liver toxicity.
- Fingolimod should be used with caution in patients with mild or moderate hepatic impairment at treatment initiation of fingolimod (although no dose adjustments are needed).
- If a decision is made to discontinue fingolimod treatment, a 6-week interval without therapy is required to clear fingolimod from the circulation. Use of immunosuppressants soon after the discontinuation of fingolimod may lead to an additive effect on the immune system, and caution is indicated.
- Caution is required when switching patients from long-acting therapies with immune effects, such as natalizumab, mitoxantrone, azathioprine, cyclophosphamide, and mycophenolate mofetil, because of the risk of additive immune suppressing effects.
- Fingolimod should be used with caution in patients aged 65 year and older.
- Fingolimod should not be used in women who are breastfeeding (these patients should stop breastfeeding before treatment with fingolimod is initiated).
- Fingolimod should not be used in pregnant women (discontinuation of fingolimod is recommended in women who become pregnant while receiving fingolimod).
- Fingolimod should be used with caution in women of childbearing potential. Before fingolimod treatment is initiated, a negative pregnancy test result must be available. Contraception is recommended in women who are

receiving fingolimod, or who have received fingolimod within the previous 2 months.

- Blood pressure should be regularly monitored during treatment with fingolimod.
- Patients should not take fingolimod if they (Novartis, draft SPC, 2011):
  - Are hypersensitive to fingolimod or any of the excipients,
  - Have known active malignancies (except cutaneous basal-cell carcinoma),
  - Have known immunodeficiency syndrome,
  - Have severe active infection or active chronic infections, such as hepatitis and tuberculosis,
  - Have severe hepatic impairment (Child-Pugh class C),
  - Are at increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).

Overview of comparator safety

Table 45 summarises adverse events associated with all the comparator interventions.

Table 45 Summary list of adverse events, by comparator

Intervention	Key adverse events
Interferon-beta-1a (Avonex)	Flu-like symptoms following injection, which lessen over time for many Less common: depression, mild anaemia, liver abnormalities*, allergic reactions, heart problems
Interferon-beta-1a (Rebif)	Flu-like symptoms following injection, which lessen over time for many; injection-site reactions Less common: liver abnormalities*, depression, allergic reactions, and low red or white blood-cell counts
Interferon-beta-1b (Betaferon)	Flu-like symptoms following injection, which lessen over time for many; injection-site reactions, about 5% of which need medical attention Less common: allergic reactions, depression, liver abnormalities*, low white blood-cell counts

Intervention	Key adverse events
Interferon-beta-1b (Extavia)	Flu-like symptoms following injection, which lessen over time for many; injection site reactions, about 5% of which need medical attention Less common: allergic reactions, depression, liver abnormalities*, low white blood-cell counts
Glatiramer acetate (Copaxone)	Injection-site reactions Less common: vasodilation (dilation of blood vessels); chest pain; a reaction immediately after injection, which includes anxiety, chest pain, palpitations, shortness of breath, and flushing. This lasts 15-30 minutes, passes without treatment, and has no known long-term effects
Natalizumab (Tysabri)	Headache, fatigue, urinary tract infections, depression, lower respiratory tract infections, joint pain, and chest discomfort Less common: allergic or hypersensitivity reactions within 2 hours of infusion (dizziness, fever, rash, itching, nausea, flushing, low blood pressure, difficulty breathing, chest pain), liver abnormalities*. Patients must be monitored for PML.

PML: progressive multifocal leukoencephalopathy.

* It is recommended that patients taking interferon-beta-1a, interferon-beta-1b, or natalizumab receive baseline liver-function testing at the start of treatment and periodic testing thereafter.

Source: National Multiple Sclerosis Society, 2009.

5.10 Interpretation of clinical evidence

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

Summary of efficacy: primary evidence for fingolimod

Fingolimod 0.5 mg reduces relapse frequency and severity and improves disability-related outcomes in patients with relapsing forms of MS, compared with a current first-line DMT, interferon-beta-1a, as reported in Study D2302 (TRANSFORMS). Fingolimod also reduces brain atrophy and improves MRI measures of inflammatory disease activity compared with interferon-beta-1a.

- The primary endpoint, ARR, was 0.16 (95% confidence interval [CI], 0.12-0.21) for fingolimod versus 0.33 (95% CI: 0.26-0.42) for interferon-beta-1a ($P < 0.001$). The ARR was significantly lower for fingolimod 0.5 mg compared with interferon-beta-1a in patients who received a DMT in the

previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year (ARR ratio of 0.50; *P* < 0.001), and in patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume > 0.5 mL at baseline (ARR ratio of 0.48; *P* < 0.001). The ARR was significantly lower for fingolimod compared with interferon-beta-1a in patients who had no previous DMT (0.15 [0.10-0.23] vs. 0.31 [0.22-0.41]; *P* < 0.001) and in patients who had received previous DMT (0.26 [0.19-0.34] vs. 0.53 [0.43-0.65]; *P* < 0.001).

- The proportion of patients with no confirmed relapse was greater with fingolimod 0.5 mg compared with interferon-beta-1a (82.6% vs. 69.3%; *P* < 0.001).
- Many MRI outcomes showed significant improvements with fingolimod 0.5-mg treatment compared with interferon-beta-1a.
- Treatment with fingolimod showed a smaller reduction in brain volume compared with interferon-beta-1a (–0.31 vs. –0.45; *P* < 0.001).
- A larger proportion of patients receiving fingolimod 0.5 mg showed no confirmed disability progression, compared with those patients receiving interferon-beta-1a, although the difference was not significant (94.1% vs. 92.1%; *P* = 0.25). Treatment with fingolimod resulted in a lower rate of disability progression, compared with interferon-beta-1a, in the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year ([redacted]) and in the subgroups of patients who received a DMT in the previous year, patients who had at least one relapse in the previous year, and patients with either at least one gadolinium-enhancing lesion or a T2 volume > 0.5 mL at baseline ([redacted]).

In Study D2301 (FREEDOMS), fingolimod 0.5 mg administered daily for 24 months was associated with a significant reduction in the ARR, the proportion of patients with confirmed relapse, and significant changes in MRI outcomes, disability progression, and brain volume when compared with placebo.

- The primary endpoint, ARR, was 0.18 (95% CI: 0.15-0.22) for fingolimod 0.5 mg versus 0.40 (95% CI: 0.34-0.47) for placebo ($P < 0.001$). The ARR was significantly lower for fingolimod 0.5 mg compared with placebo in patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year (ARR ratio of 0.38; $P < 0.001$), and in patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume > 0.5 mL at baseline (ARR ratio of 0.52; $P = 0.005$).
- The proportion of patients with an absence of relapse during the study was significantly greater with fingolimod 0.5 mg compared with placebo (70.4% vs. 45.6%; $P < 0.001$).
- The proportion of patients with an absence of disability progression, confirmed after 3 months, was greater in patients treated with fingolimod 0.5 mg compared with placebo (82.3% vs. 75.9%; $P = 0.03$). Treatment with fingolimod resulted in a lower rate of disability progression, when compared with placebo, in the subgroup of patients who received a DMT in the previous year and who had an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year ([redacted])and in the subgroup of patients who received a DMT in the previous year and who had at least one relapse in the previous year and either at least one gadolinium-enhancing lesion or a T2 volume > 0.5 mL at baseline ([redacted])
- Patients treated with fingolimod 0.5 mg reported significant improvements in all reported disability outcomes ($P \leq 0.03$) and MRI outcomes ($P < 0.001$) compared with placebo.

- Treatment with fingolimod 0.5 mg showed a smaller reduction in brain volume compared with placebo (–0.84 vs. –1.31; $P < 0.001$).

Summary of efficacy: indirect comparisons and mixed-treatment comparisons

Indirect treatment comparisons using MTC methodology were performed to compare fingolimod with the important comparators not otherwise studied in head to head trials against fingolimod. A separate MTC model was used for each of the endpoints of interest, the results of which ultimately provided inputs to the economic evaluation; there were 2 efficacy endpoints, confirmed disability progression and annualised relapse rate, and 1 safety endpoint, treatment discontinuations due to adverse events.

[redacted]

[redacted]

Summary of safety

From studies totalling more than 5,000 years of patient exposure, fingolimod is generally safe and well tolerated, with a similar incidence of adverse events compared with beta-interferon. A similar rate of infection was reported with fingolimod 0.5 mg and beta-interferon, with most infections reported being mild to moderate in severity. Fingolimod is not associated with injection-site reactions, which are associated with all currently approved, parenterally-administered treatments. The incidence of serious adverse events was low across Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS). In both studies, the most serious AEs in patients receiving fingolimod 0.5 mg were infections, macular oedema, and transient atrioventricular block at treatment initiation (Novartis, draft SPC, 2011). Treatment with fingolimod 1.25 mg in both Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS) resulted in an increased risk of macular oedema, although this was reversible on discontinuation of treatment. Fingolimod requires a 2-month wash-out period and may benefit patients who wish to stop or change treatment at short notice, such as those who are planning a family. This wash-out period is shorter than that required for natalizumab but longer than that required for either beta-interferon or glatiramer acetate. However, interferons have the potential to impair male and female fertility (Bayer, 2006).

Summary of HRQL

Patients with RRMS receiving fingolimod 0.5 mg showed significantly less deterioration in their ability to perform daily activities compared with patients

receiving interferon-beta-1a, in Study D2302 (TRANSFORMS). Furthermore, a slight, non-significant improvement in HRQL has been observed with fingolimod 0.5 mg, while a slight but non-significant improvement was observed in patients receiving interferon-beta-1a, as measured on the PRIMUS-QoL scale. Also, after 6 months of treatment with fingolimod 0.5 mg, patients showed significant improvement in the UFIS score, compared with interferon-beta-1a; although at 12 months, this improvement was no longer significantly different between groups.

Furthermore, because of its simple and convenient once-daily oral regimen, fingolimod is likely to have a greater patient adherence rate compared with the other injectable DMTs currently available.

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

Strengths

The primary efficacy and safety evidence for fingolimod is based on two large, randomised clinical trials in which data on the ARRs, patients with relapse, MRI outcomes, and disability outcomes were collected compared with interferon-beta-1a and placebo (in Study D2302 [TRANSFORMS]) and with placebo (in Study D2301 [FREEDOMS]).

In both Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS), randomisation and concealment of treatment allocation were adequate and the groups were similar in terms of baseline characteristics. The primary endpoint (ARR) was determined by means of a blinded examination by an examining neurologist. Multiplicity of the primary and secondary endpoints was controlled for using a pre-specified statistical testing strategy.

The efficacy of fingolimod has been demonstrated versus interferon-beta-1a and versus placebo, using endpoints that are directly relevant to the clinical benefits experienced by patients in practice, i.e., ARRs. Additional endpoints were tested for, including inflammatory MRI markers, measures of disability

progression, and brain volume. Brain atrophy has been used as a potential surrogate endpoint and may be preferential to other commonly used MRI markers because it appears more closely correlated with the progression of physical and cognitive disability. As such, it is believed by some to be more useful for predicting long-term physical disability than inflammatory MRI markers (Zivadinov, 2009). Furthermore, the specific method (brain parenchymal fraction) used to assess brain atrophy in the fingolimod studies has widely been shown to correlate with markers of the disease course (Gauthier et al., 2009; Benedict et al., 2004; Kassubek et al., 2003).

Safety data for fingolimod were available for more than 5,000 patient-years of exposure. Fingolimod has shown a manageable and predictable safety profile, with a similar overall incidence of adverse events in patients with RRMS between fingolimod 0.5 mg and interferon-beta-1a after 1 year and between fingolimod 0.5 mg and placebo after 2 years. The long-term safety of fingolimod 1.25 mg and 5.0 mg also has been assessed over 5 years in a well-controlled RCT (Study D2201). Fingolimod 1.25 mg was reported to be well tolerated in patients with RRMS over a 5-year period, with most reported adverse events (79.8%) being of mild or moderate severity.

Limitations

There are no head-to-head studies between fingolimod 0.5 mg and interferon-beta-1b, glatiramer acetate, or natalizumab. These comparisons are based on indirect comparisons. As with any indirect comparison, differences in the methodology, outcome measurement, and the populations included in the underlying studies must be carefully considered. It is also worth noting that not all of the comparators have the same licensed indication so some of the comparisons are partially off-label.

A clear limitation is the lack of consistency throughout the endpoint definitions, most notably in the confirmed disability progression. The timepoint at which disability was confirmed varied across trials, most trials (including fingolimod) using a 3 month criteria, but 3 trials used a 6-month criteria. We analysed this

endpoint using the trials with 3 month data alone (base case analysis), then separately using the combined data for trials with 3 or 6 month data (sensitivity analysis). It is unfortunate that one of the trials excluded from the base case analysis was the REGARD study, a fairly large phase 3 trial comparing glatiramer acetate 20 mg (n = 378) with Rebif 44 mcg (n = 386). The timepoint for confirmation of disability for this study was 3 months, but because progression data were only collected at 6-month intervals, the prespecified analysis could not be fulfilled.

We explored heterogeneity across the trials in the form of patient characteristics, and found only a small number of differences, but we acknowledge the lack of statistical power in assessing covariates.

A potentially important source of heterogeneity between the trials is with the allowance of prior disease-modifying therapy for some trials, but not others. We assessed the statistical significance of this study exclusion criteria (as a dichotomous variable), but it would have been stronger to analyse this covariate using the percentage of patients who received prior disease-modifying therapy, which unfortunately was seldom reported in the articles.

Finally, we made no adjustment for multiple comparisons made both with the number of pairwise comparisons for a given endpoint, and for the fact we analysed more than one endpoint. Accordingly, borderline statistical significance should be viewed cautiously, but the confidence intervals are valid to use for quantifying the magnitude and precision of the relative treatment effects from the MTC.

5.10.3 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 evidence base for fingolimod addresses all aspects of the decision problem. Both Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS) investigated fingolimod at the licensed dose (0.5 mg per day)

in patients with RRMS. The outcome measures included ARRs, MRI markers, brain volume, markers of disability progression, adverse effects of treatment, and HRQL. The primary endpoint in both these trials directly measured the clinical benefits experienced by patients in clinical practice (i.e., the ARR). In Study D2302 (TRANSFORMS), fingolimod 0.5 mg was compared directly with the most relevant comparator, beta-interferon.

Inflammatory markers as measured by MRI and markers of disability progression are commonly used outcomes measured in trials in RRMS patients. However, both Study D2302 (TRANSFORMS) and Study D2301 (FREEDOMS) also reported changes in brain volume after treatment. Brain atrophy may be used as an additional surrogate endpoint, since this has been shown to be more closely correlated with the progression of physical disability compared with inflammatory MRI markers (Zivadinov, 2009). As such, brain atrophy is more useful for predicting long-term physical disability. Furthermore, the specific method of brain parenchymal fraction, used to assess brain atrophy in the fingolimod studies has widely been shown to correlate with markers of the disease course (Gauthier et al., 2009; Benedict et al., 2004; Kassubek et al., 2003).

For measuring changes in HRQL with fingolimod treatment, both disease-specific (PRIMUS-QoL and PRIMUS-Activities) and generic instruments (the EQ-5D and EQ-5D Visual Analogue Scale) were used. Although relatively new instruments, the PRIMUS scales have been validated (Doward et al., 2009).

5.10.4 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?

Fingolimod dose and frequency in the trials

In the key Phase III fingolimod trials (Study D2302 [TRANSFORMS] and Study D2301 [FREEDOMS]) included in the submission, fingolimod was administered at the same dose and frequency as the licensed dose that will be used in clinical practice (0.5 mg daily) (Novartis, draft SPC, 2011).

Generalisability of fingolimod trial results to the UK RRMS population

Table 46 compares the baseline characteristics of the population randomised to fingolimod 0.5 mg in Study D2302 (TRANSFORMS) with those for patients with RRMS treated with DMTs in observational studies in the UK. Of 431 patients randomised to fingolimod 0.5 mg in Study D2302 (TRANSFORMS), 8 (1.9%) were enrolled in the UK. Patients were aged between 18 and 55 years. The mean age and median age were both 37 years. The median time from onset of symptoms to randomisation was 6 years, and patients had experienced a mean of 2.3 and a median of 2 relapses in the previous 2 years. Patients in Study D2302 (TRANSFORMS) had a mean EDSS score of 2.24 and a median score of 2.0.

Data from two observational studies for patients with RRMS treated with DMTs in the UK (Boggild et al., 2009; Lily et al., 2006) suggest a similar mean (36 years) and median age (38 years) to those patients in Study D2302 (TRANSFORMS). Boggild et al. (2009) reported a wider age range (18-73 years) compared with patients in Study D2302 (TRANSFORMS) (18-55 years). A higher proportion of patients in the observational studies were female (75%) compared with 65% of those in Study D2302 (TRANSFORMS). The median time between symptom onset and treatment was similar between Study D2302 (TRANSFORMS) and the study by Boggild et al. (2009) (6 vs. 5.7 years). The smaller observational study by Lily et al. (2006) reported a longer duration of MS (9 years), although this was not reported as time from symptoms onset. Patients with RRMS in the observational studies reported a similar number relapses in the previous 2 years as those reported in Study D2302 (TRANSFORMS), with a mean of 2.5 (Lily et al., 2006) and a

median of 3 relapses (Boggild et al., 2009). The extent of disability, as measured by the EDSS scale, was slightly higher in the observational studies compared with Study D2302 (TRANSFORMS), with a mean of 3.07 (Boggild et al., 2009) and a median of 2.5 (Lily et al., 2006).

Table 46 Characteristics of patients treated for RRMS in the UK compared with Study D2302 (the TRANSFORMS study) population

Characteristic	Patients randomised to fingolimod 0.5 mg (n = 431)	Patients treated for RRMS in England and Wales	
		Boggild et al., 2009* (interferon-beta or glatiramer acetate) (n = 4,293)	Lily et al., 2006† (DMTs) (N = 182)
Age, years			
Mean (SD)	36.7 (8.8)	NR	36.3 (NR)
Median (range)	37 (18-55)	38 (18-73)	NR
Females, number (%)	282 (65.4)	3,233 (75.3)	NR (75)
Time from onset of symptoms to randomisation, years			
Median (range)	6 (0-34)	5.7 (0-48)	9 (NR)‡
Number of relapses in previous 2 years			
Mean (SD)	2.3 (2.2)	NR	2.5 (NR)
Median (range)	2 (1-40)	3 (0-21)	NR
EDSS score			
Mean (SD)	2.24 (1.33)	3.07 (1.52)	NR
Median (range)	2.0 (0-5.5)	NR (0-6.5)	2.5 (NR)

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NR, not reported; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; UK, United Kingdom.

* Data for a prospective cohort of patients who started treatment between May 2002 and April 2005, under the UK risk-sharing scheme, recruited from specialist MS clinics in 70 centres in the UK.

† Data for a cohort of patients entering the open-label observational study, the MS Treatment Programme, based at St James University Hospital in Leeds. Patients were allowed to choose their own DMT with no randomisation or blinding.

‡ Reported as median MS duration.

The eligibility criteria for Study D2302 (TRANSFORMS) excluded the following groups: patients with documented relapse or corticosteroid treatment within 30 days before randomisation; active infection; macular oedema; immunosuppression (either drug or disease induced); or clinically significant co-existing systemic disease. Most of these groups are listed in the draft SPC as populations that require special care when considering the administration of fingolimod (Novartis, draft SPC, 2011).

In summary, the efficacy of fingolimod observed in Study D2302 (TRANSFORMS) is expected to be generalisable to effectiveness in the eligible population in clinical practice. However, it is worth noting that the likely UK licence for fingolimod is narrower than RRMS.

Conclusion

The external validity of the results of Study D2302 (TRANSFORMS) to patients in routine clinical practice is expected to be high. Fingolimod was used in the trial, as it will be in clinical practice; no significant patient groups were excluded, and the trial population characteristics are generally comparable with patients treated for RRMS in the UK.

As a result of tolerability issues, particularly injection-site reactions, the currently used injectable DMTs, including beta-interferon and glatiramer acetate, are expected to have suboptimal adherence and compliance (Costello et al., 2008). As a result, effectiveness of DMTs in clinical practice is expected to be inferior to the efficacy demonstrated in trials.

6 Cost-effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 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 **Error! Reference source not found.**, Appendix 10.

A systematic literature review was performed in accordance with a pre-specified protocol. The primary objective of this review was to systematically search and identify all existing economic evaluations of fingolimod for the treatment of adults with RRMS.

Searches encompassed electronic medical databases and specified Internet sites. The following electronic databases were searched:

- The Cochrane Library, including the following:
  - The Cochrane Database of Systematic Reviews;
  - The Cochrane Central Register of Controlled Trials;
  - Database of Abstracts of Reviews of Effectiveness;
  - Health Technology Assessment database;
- MEDLINE and MEDLINE In-Process (using PubMed platform);
- EMBASE (using Dialog Platform);
- EconLit;
- National Health Services' Economic Evaluation Database.

No time limits or language restrictions were used in the search strategy. Search terms included combinations of free text and Medical Subject Headings (MeSHs).

- Population: terms relating to the health condition of interest (e.g., “Multiple Sclerosis, Relapsing-Remitting” [MeSH], Demyelinating Diseases [MeSH], etc.);
- Study type:
    - Terms for economic evaluations (e.g., pharmacoeconomic*[Text Word], “modelling” [Text Word], “Costs and Cost Analysis” [MeSH], “resource utilization” [Text Word], etc.).

Section **Error! Reference source not found.** presents full listing of the search terms used.

The following Web sites were searched to identify conference abstracts and unpublished studies:

- Conference abstracts published from 2007 to present on the Web sites of the following organisations:
    - International Society for Pharmacoeconomics and Outcomes Research,
    - American Academy of Neurology,
    - Americas Committee for Treatment and Research in Multiple Sclerosis,
    - European Committee for Treatment and Research in Multiple Sclerosis,
    - European Charcot Foundation.

In addition, the NICE Web site was searched to identify any relevant Health Technology Assessment reports. Bibliographic reference lists of the seminal papers also were searched for relevant studies.

The inclusion and exclusion criteria used to identify studies of interest were based on a strategy that identified study types of interest within the population and disease condition of interest for the intervention of interest. The inclusion and exclusion criteria were as follows:

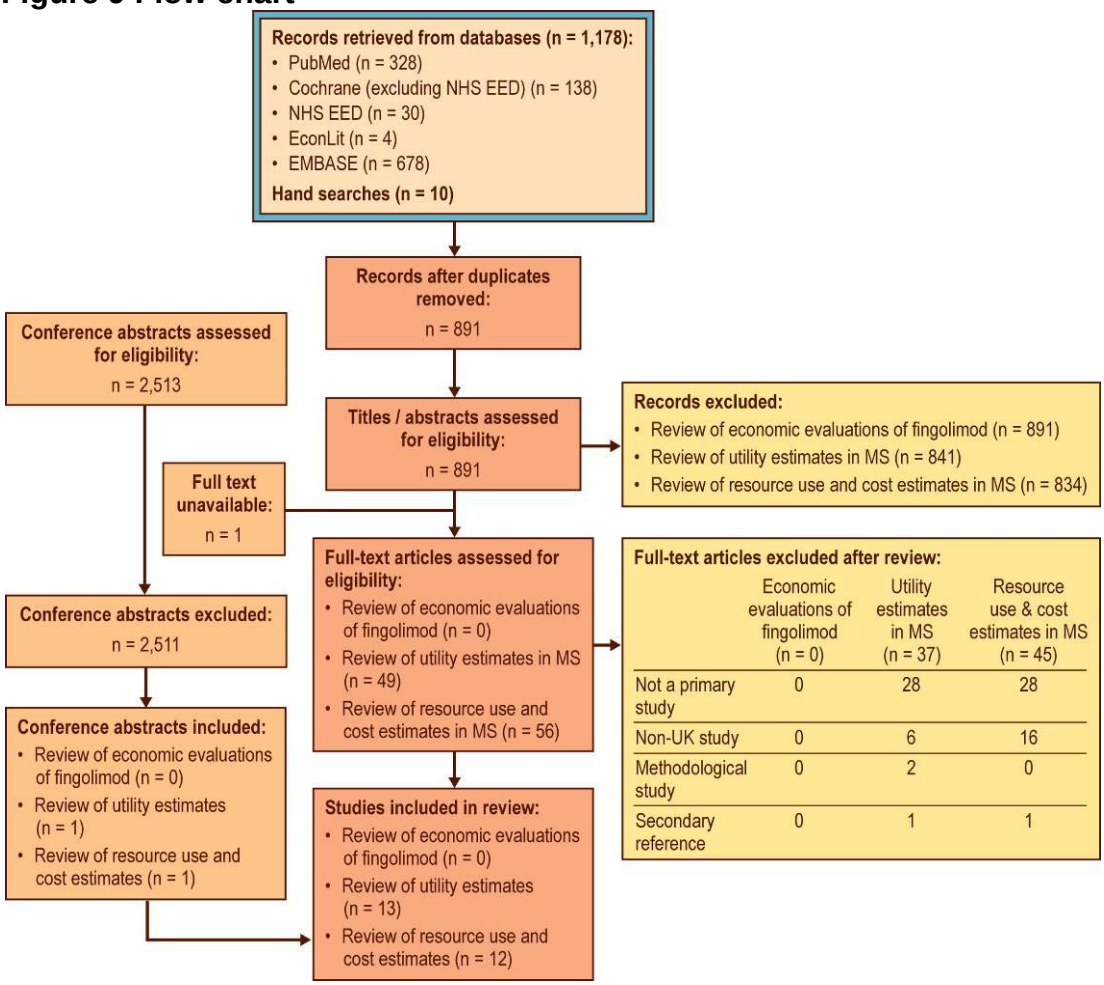
- Inclusion criteria:
  - Population: patients with RRMS or patients with secondary progressive multiple sclerosis (SPMS);
  - Interventions: fingolimod;
  - Study type: economic evaluation studies, e.g., studies based on models, cost analyses performed alongside clinical trials, and budget-impact analyses;
  - Outcomes: cost-effectiveness results for fingolimod in MS.
- Exclusion criteria:
  - Population: patients with primary progressive multiple sclerosis (PPMS) or progressive-relapsing multiple sclerosis (PRMS);
  - Interventions: any other interventions in MS;
  - Study type: retrospective observational studies, reviews, letters, comment articles, or any sources that discuss costs but where no formal economic analysis has been undertaken; general cost-of-illness or economic-burden studies that do not estimate incremental cost-effectiveness or cost-utility ratios for fingolimod.

In the first-level screen, titles and abstracts of studies that were identified from the electronic databases and Internet searches were reviewed using the inclusion and exclusion criteria. In the second-level screen, full texts of the studies selected in the first-level screen were obtained for further review, and the same inclusion and exclusion criteria were applied to identify relevant studies.

Figure 9 presents results of the systematic literature searches for published fingolimod cost-effectiveness, utility, and cost studies in MS and of the study

selection process in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Moher et al., 2009).

Figure 9 Flow chart



	Economic evaluations of fingolimod (n = 0)	Utility estimates in MS (n = 37)	Resource use & cost estimates in MS (n = 45)
Not a primary study	0	28	28
Non-UK study	0	6	16
Methodological study	0	2	0
Secondary reference	0	1	1

EED, Economic Evaluation Database; NHS, National Health Service; MS, multiple sclerosis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UK, United Kingdom.

Description of identified studies

6.1.2 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. If more than one study is identified, please present in a table as suggested below.

No economic evaluations of fingolimod for the treatment of adults with RRMS were identified.

6.1.3 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)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see Section **Error! Reference source not found.**, Appendix 11.

No economic evaluations of fingolimod for the treatment of adults with RRMS were identified.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/cost-effectiveness (CE) marking or the population from the trials in Sections 1.4 and 5.3.3, 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.

On 20 January 2011, the EMA recommended the granting of a marketing authorisation for fingolimod for the treatment of adult patients with relapsing-remitting MS with high disease activity (EMA, 2011a). Novartis decided to consider the approved indication for Gilenya in three parts:

[1] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Br Med J 1996;313(7052):275-83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2003;8:36.

- Part 1: Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy and have had at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion (Part 1a). A non-responder also could be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year (Part 1b).
- Part 2: Patients with rapidly evolving, severe, relapsing-remitting MS, defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.

Below is a summary of identified subgroups from the TRANSFORMS and FREEDOMS study that had the closest fit to each of the descriptions in the indication. The three subgroups partially overlap, which is why the percentages do not add up to 100% (Table 47).

Table 47 Approved indication and subgroups of TRANSFORMS and FREEDOMS trial

	Description in approved fingolimod indication	**Description of closest subgroup in FREEDOMS or TRANSFORMS**	**Percentage of subjects from FREEDOMS and TRANSFORMS who fit into the subgroup**

	Description in approved fingolimod indication	Description of closest subgroup in FREEDOMS or TRANSFORMS	Percentage of subjects from FREEDOMS and TRANSFORMS who fit into the subgroup
Part 1a	Highly active RRMS adult patients with high disease activity despite treatment with a beta-interferon, defined as those who have failed to respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy and have had at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion.	Previously treated and have had at least 1 relapse in prior year and either at least 1 gadolinium-enhancing lesion or a T2 volume of > 0.5 mL at baseline	32%
Part 1b	Highly active RRMS adult patients with high disease activity despite treatment with a beta-interferon and with an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year.	Previously treated and have had equal or more relapses in year 1 than year 2	32%
Part 2	Highly active RRMS adult patients with rapidly evolving, severe RRMS, defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.	2 or more relapses and 1 or more gadolinium-enhancing T1 lesions	15%

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Score; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting MS.

For Part1a, T2 volume of ≥ 500 mm^3 was used instead of ≥ 9 T2 lesions for the following reason: T2 lesion volume, but not T2 lesion count, was obtained at baseline. Novartis have now acquired T2 lesion count data, but this information has not yet been incorporated into the study database. Novartis have evaluated the correlation between baseline lesion burden that is in the

database with the recently collected baseline T2 lesion count that is not yet incorporated into the database. Novartis have determined that the T2 volume cut-off of ≥ 500 mm^3 includes 99% of patients with ≥ 9 T2 lesions, while including 8% of patients who have < 9 T2 lesions, demonstrating a strong positive correlation between these two MRI measures ($P < 0.001$). Thus, this assumption closely approximates the actual findings related to T2 lesion count. As Novartis cannot integrate the newly acquired T2 lesion count data into the database, we used this approximation in the analyses for Part 1a.

For Parts 1a and 1b, the SPC specifically states with regard to the previous treatment: "despite treatment with a beta-interferon". The FREEDOMS and TRANSFORMS studies used a broader criterion for "previously treated", which was the closest subgroup in these trials. We have used this broader criterion because the EPAR states that "intolerance to alternative MS therapy should also include Copaxone being tried", implying that the definition of previous treatment can be generalised to DMTs. Using this broader definition means that the subgroup can include a larger number of trial subjects, thus providing more robust confidence intervals.

Part 1a and Part 1b are the largest subgroups, so Novartis believe these are the best places to start the cost-effectiveness analysis. In addition, this area of focus is the area of greatest clinical unmet need because there is no current therapy available for patients who have had an inadequate treatment response to DMTs and who do not quite qualify for natalizumab treatment per the NICE TA 127. TA 127 specifically does not recommended natalizumab for this population. This means that this is clinically the strongest case, as there is nothing else available for these patients.

Novartis suggest that it is best to start with the population with the highest clinical efficacy, i.e., patients who fit Part 1b, since this definition is the more likely to be the cost-effective population. The base-case economic analysis therefore is based on non-responder patients with high disease activity despite treatment with a beta-interferon, in line with Part 1b of the approved indication.

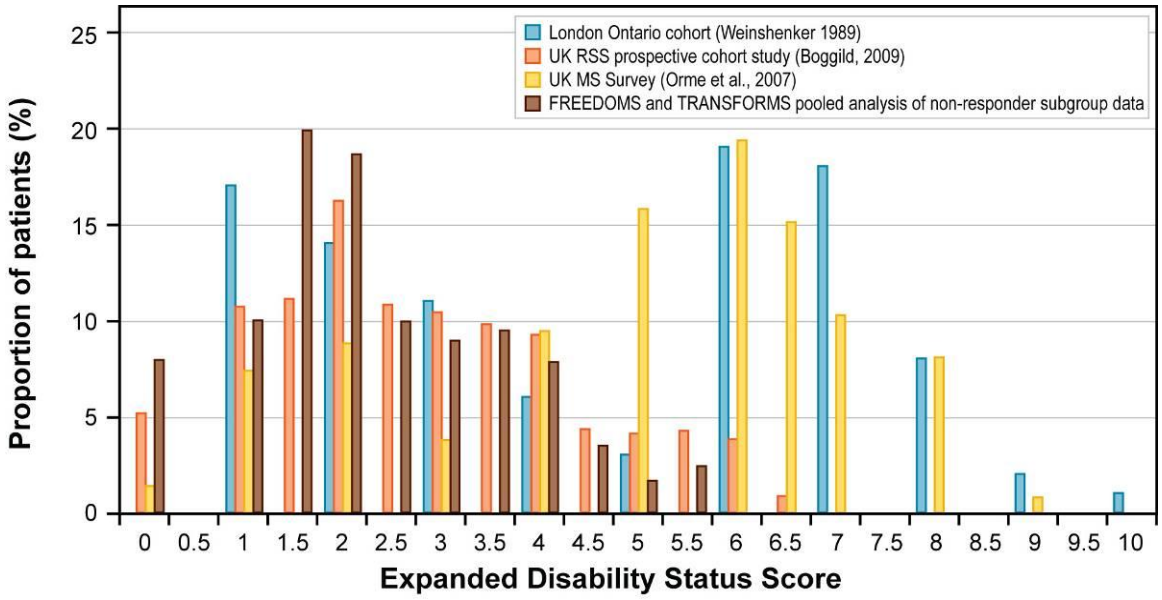
The current model is designed so that the user may define various characteristics of the patients who populate the model. These characteristics include age at treatment initiation, female-to-male ratio, years since diagnosis, and initial distribution of patients between EDSS states. Table 48 and Figure 10 present these characteristics for populations from a number of relevant studies.

Table 48 Baseline patient characteristics

Characteristic	FREEDOMS and TRANSFORMS pooled analysis of non-responder subgroup data	UK MS Survey (Orme et al., 2007; Tyas et al., 2007)	UK RSS prospective cohort study (Boggild et al., 2009)	London, Ontario, cohort (Weinshenker et al., 1989)
Age, years	37.3 (mean)	51.4 (mean)	38 (median)	NR
Female-to-male ratio	2.3:1	3:1	3:1	2:1
Time since first diagnosis, years	6.25 (mean)	12.6 (mean)	2.6 (median)	11.9 (mean)
Cohort size, n	603	2048	4293	1099
Type of MS	RRMS: 100%	RRMS: 35.3% SPMS: 37.2% PPMS: 27.3%	RRMS: 100%	RRMS: 65.8% RPMS: 14.8% CPMS: 18.7% Unavailable: 0.9%

MS, multiple sclerosis; NR, not reported; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; RSS, risk-sharing scheme; SPMS, secondary progressive multiple sclerosis; UK, United Kingdom.

Figure 10 Distribution of patients across EDSS states



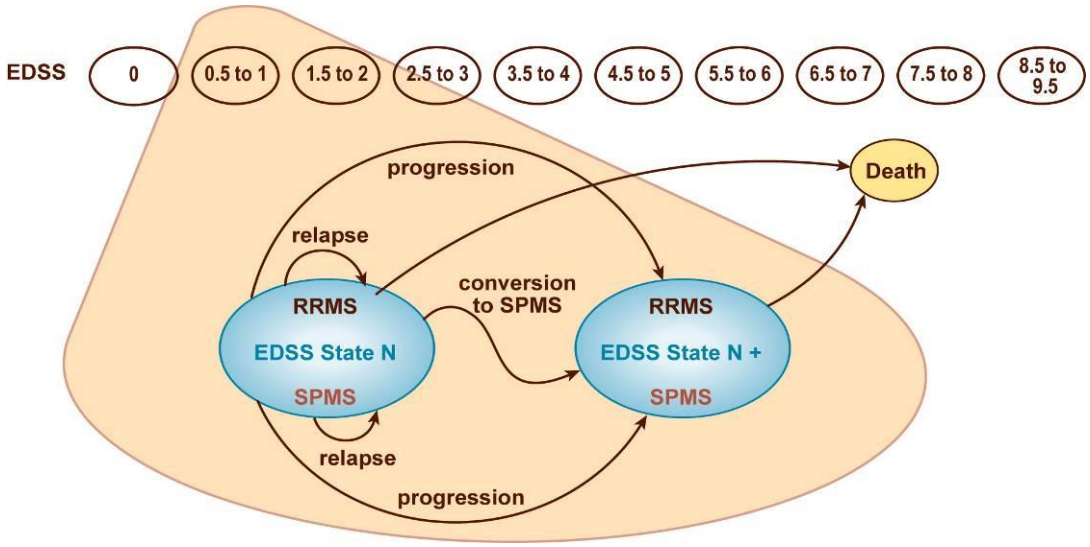
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RSS, risk sharing scheme; UK, United Kingdom.

In the base case, the model utilises patient characteristics for age, female-to-male ratio, and years since diagnosis from a pooled analysis of non-responder subgroup data from the FREEDOMS and TRANSFORMS trials. The pooled analysis also is used for the initial distribution of patients between EDSS states. The model's population appears to be reflective of the population eligible to receive DMTs in England and Wales (as shown by the UK RSS cohort in Figure 10).

Model structure

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

Figure 11 Schematic of the model



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

Source: Biogen Idec UK and Elan Pharma International, 2007.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in Section 2.4.

The model has been designed to capture health service costs and health consequences arising from disease progression and disease activity (i.e., rate of relapse) over time. The model is based on a Markov cohort approach previously used to estimate the cost-effectiveness of beta interferons and glatiramer acetate (Tappenden et al., 2001) and natalizumab (Biogen Idec UK and Elan Pharma International, 2007). The model uses a transition matrix to estimate progression through 21 disability states, which are defined by EDSS score and account for disability for patients with RRMS (10 states), patients with SPMS (10 states), and death. Patients enter the model from a baseline RRMS disease-course state, from which they can progress to a higher or lower EDSS state or remain in the same state. Patients can also convert from an RRMS disease course to an SPMS disease course, and then once converted to SPMS progress to a higher EDSS state or remain in the same disability state. As per clinical definition and understanding of SPMS, once a patient has become an SPMS patient, conversion back to RRMS is not

possible in the model. Disability progression rates are defined in a natural history transition matrix and were derived from a longitudinal data set of patients with MS from London, Ontario, Canada (Weinshenker et al., 1989). The London Multiple Sclerosis Clinic (London Health Sciences Centre, Canada), established in 1972, provides long-term care for patients with multiple sclerosis from its referral area of south-western Ontario. Clinic and database characteristics have been extensively outlined (Weinshenker et al., 1989; Cottrell, 1999; Kremenchutzky, 2006). Patients were evaluated annually or semi-annually regardless of clinical course. Disability was assessed using the Disability Status Scale (DSS) (Kurtzke, 1955). Data collection was performed through separate research charts containing data forms completed at patient visits, with the observation period ending in 2000.

Previous models in MS have utilised this longitudinal data set for modelling the natural history transitions across EDSS states (Tappenden et al., 2001; Biogen Idec UK and Elan Pharma International, 2007). For this submission a re-analysis of the London Ontario data set was undertaken to provide updated transition matrices for patients who have not received DMT treatment for their MS (i.e., focusing on a treatment naive group); the matrix for RRMS utilised in the submission model is presented in Table 49.

Table 49 Natural history transition matrix: active RRMS

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

The DSS stages can be modelled as a homogeneous, continuous-time Markov process with a transition matrix *Q*, e.g., a transition matrix for a three-stage disease with one absorbing stage:

$$Q = \begin{pmatrix} -(q_{01} + q_{02}) & q_{01} & q_{02} \\ 0 & -q_{12} & q_{12} \\ 0 & 0 & 0 \end{pmatrix}.$$

A common way to interpret a transition matrix is by calculating the transition probability matrix *P(t)* for transitions after time *t*, using the matrix exponential:

$$P(t) = Exp(t \cdot Q).$$

Incorporating a covariate *k* is accomplished by estimating *Q(k)*. A proportional hazards model can be used to estimate *Q(k)*:

$$q_{rs}(k(t)) = q_{rs}^{(0)} \cdot exp(\beta_{rs}^{T} \cdot k(t))$$

.

All calculations were made using R software with the MSM package.

Two major enhancements have been made to the transition matrices used in previous NICE submissions. Firstly, the transition matrices include a more complete data set enhancing the long-term predictive quality of the model. Secondly, the model includes an adjustment for active forms of relapsing MS alongside primary progressive (PPMS, not applicable for this analysis), secondary progressive (SPMS) and benign relapsing forms of MS (benign RRMS). As a result, the model includes transition matrices for patients who reported 2 or more relapses during the first two years of MS, representing a

patient population typical of active relapsing MS (active RRMS), and therefore would be applicable for treatment with DMTs in the UK in accordance with the guidelines of the Association of British Neurologists (Association of British Neurologists 2009).

In previous analyses, the London Ontario transition matrices did not include adjustments for active or benign forms of relapsing MS and, as a result, may have under- or over-estimated the cost-effectiveness of DMT treatment. By excluding patients who have less progressive forms of relapsing MS we have adjusted the natural history transition matrices to fully represent patients who are eligible for DMT treatment.

Progression probabilities are assumed to be independent of initial DSS state and the duration at a particular DSS state. The cycle length in the model is 1 year; a half-cycle correction is applied to reflect the occupancy of the health states at mid-cycle. Treatment dropouts are modelled in terms of the rate of discontinuation due to AEs.

Natural history conversion rates from RRMS to SPMS also were included in the Markov model. In the London, Ontario, Canada, data set (Weinshenker et al., 1989), conversion from RRMS to SPMS was observed in 509 (65.2%) of the RRMS patients during follow-up. The annual probabilities of converting from RRMS to SPMS (Table 50) were calculated from this data set using an exponential curve for DSS 1, parameterized by the median time to conversion, and adjusted for all other DSS states based on a Cox proportional hazards model. This is considered appropriate for the base case because the relationship between the DSS 1 state and all other states in terms of conversion to SPMS was found to be consistent and highly statistically significant.

Table 50 Annual conversion rates from RRMS to SPMS

DSS	Hazard	Probability
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]

DSS	Hazard	Probability
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]

DSS, Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

The exponential survival curve for progression to SPMS from RRMS can be parameterized by the relationship between the single parameter in the survivor function and the median time to progression. This relationship is defined as follows:

$$m[X] = \frac{ln[2]}{\lambda},$$

where *λ* is the parameter of the exponential curve. This equation can be rearranged, and parameters for each curve can be estimated. The Cox proportional hazards model is fitted to DSS as a continuous value and defines the relationship between covariates (DSS in this case) and the hazard ratio of progression between the base-case DSS 1 state and all other DSS states. This can be formulated in the following way:

$$ln[\frac{H(t)}{H(t)_{DSS1}}] = \beta \times X.$$

This provides the relationship between the DSS state and the log of the hazard ratio between the hazard rate of DSS *X* and DSS 1, the reference case in this setting. The model calculates the annual probability of progression to SPMS, given that the patient is in DSS state 1, by using the lambda (*λ*) value in the following equation:

$$P = 1 - e^{(-\lambda)}.$$

To estimate the probability of progression for all other DSS states, the model calculates the hazard rates based on the following equation:

$$H(t) = \lambda \times e^{\beta \times X},$$

where *X* is the DSS state and lambda (*λ*) is the hazard rate (or lambda value for DSS 1) for progression from DSS 1.

The model also included a set of EDSS transition probabilities for patients who have converted to SPMS (Table 51), which were also derived from the London, Ontario data set. No transitions from SPMS 0, 1 or 9 were observed in the dataset and this is reflected in the matrix.

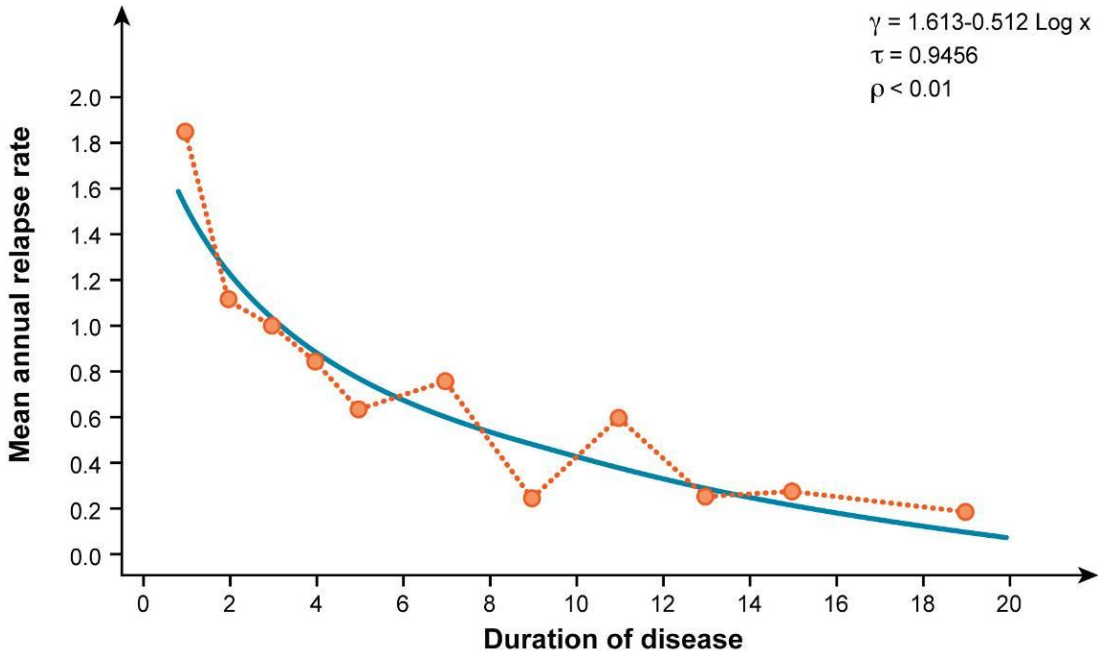
Table 51 Natural history transition matrix: SPMS

EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

A combination of the three sets of transition and conversion data (RRMS progression, SPMS conversion, and SPMS progression) resulted in an overall natural history Markov transition matrix being calculated for the economic model.

The relapsing-remitting nature of MS is incorporated in the model via inclusion of a probability of relapse in each model cycle. The London, Ontario, Canada, study did not capture much data on relapses beyond the first 2 years and could not be used as a data source for the natural history of relapses. The model uses the Patzold and Pocklington (1982) data on relapse rates, together with the UK MS Survey (Orme et al., 2007; Tyas et al., 2007) to estimate the natural history of relapses by disease type and EDSS stage. Data from Patzold and Pockington (1982) on the relapse rates since year of diagnosis are shown in the original form in Figure 12, along with the regression curve fitted to the data as part of the analysis. Despite some outliers, the data clearly demonstrate an inverse correlation between the years since diagnosis and annual rate of relapses.

Figure 12 Individual relapse rate correlated to the duration of the disease



Data points were estimated from this graphic and are presented in Table 52.

Table 52 Number of relapses, by year since diagnosis

Years since diagnosis	Relapse rate per person
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

Source: Patzold and Pockington, 1982.

The data from the UK MS Survey (Orme et al., 2007; Tyas et al., 2007) provided the numbers of patients for each EDSS state, further categorised by the numbers of years since diagnosis (Table 53 and Table 54).

Table 53 Number of individuals per RRMS EDSS group, by time since diagnosis

	Years since diagnosis: data from the UK MS Cohort										
EDSS	**1**	**2**	**3**	**4**	**5**	**6-7**	**8-9**	**10-11**	**12-13**	**14-15**	**16+**
0	2	2	1	2	6	6	3	2	0	1	3
1	11	16	18	11	16	22	15	10	3	10	18
2	11	16	7	17	14	13	19	19	9	5	22
3	6	4	4	5	7	9	4	1	5	6	6
4	6	15	7	12	13	24	8	13	6	2	17
5	2	5	12	9	13	18	11	10	4	7	23
6	2	3	3	5	2	6	11	2	2	6	20
6.5	1	0	2	0	3	3	4	1	2	2	9
7	1	0	0	0	0	0	1	1	1	0	3
8	0	0	0	0	1	2	1	0	0	0	1
9	1	0	0	0	0	0	0	0	0	0	1
6.5-9 (pooled)	3	0	2	0	4	5	6	2	3	2	14

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; UK, United Kingdom.

Source: UK MS Survey, 2005 (Orme et al., 2007; Tyas et al., 2007).

Table 54 Number of individuals per SPMS EDSS group, by time since diagnosis

	Years since diagnosis: data from the UK MS cohort										
EDSS	**1**	**2**	**3**	**4**	**5**	**6-7**	**8-9**	**10-11**	**12-13**	**14-15**	**16+**
0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	0	0	0	1	2	2	0	0	0	0	5
3	2	0	1	1	0	4	0	1	1	0	1
4	1	2	3	3	0	6	6	2	6	1	7
5	6	6	5	6	7	14	17	15	10	11	35
6	3	5	8	14	11	20	23	21	17	14	74
6.5	2	1	3	4	5	18	16	11	19	12	78
7	0	1	0	0	3	8	10	9	7	8	63
8	0	0	0	0	3	5	4	7	4	5	46
9	0	0	0	0	0	1	2	1	2	0	2
6.5-9 (pooled)	2	2	3	4	11	32	32	28	32	25	189

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis; UK, United Kingdom.

Source: UK MS Survey, 2005 (Orme et al., 2007; Tyas et al., 2007).

The numbers of patients in each of the EDSS states were multiplied by the corresponding relapse rate from Patzold and Pocklington (1982) for each of the years-since-diagnosis categories. To obtain the rate of relapses for each of the EDSS states, the number of relapses in each of the states were summed up across all of the years-since-diagnosis groups and then divided by the total number of patients in each EDSS state (Table 55).

Table 55 Natural history relapse rates, by EDSS

	Relapse Rate	
EDSS Scale	**RRMS**	**SPMS**
0	0.709	0
1	0.729	0
2	0.676	0.465
3	0.720	0.875
4	0.705	0.545
5	0.591	0.524
6	0.490	0.453
7	0.508	0.340
8	0.508	0.340
9	0.508	0.340

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

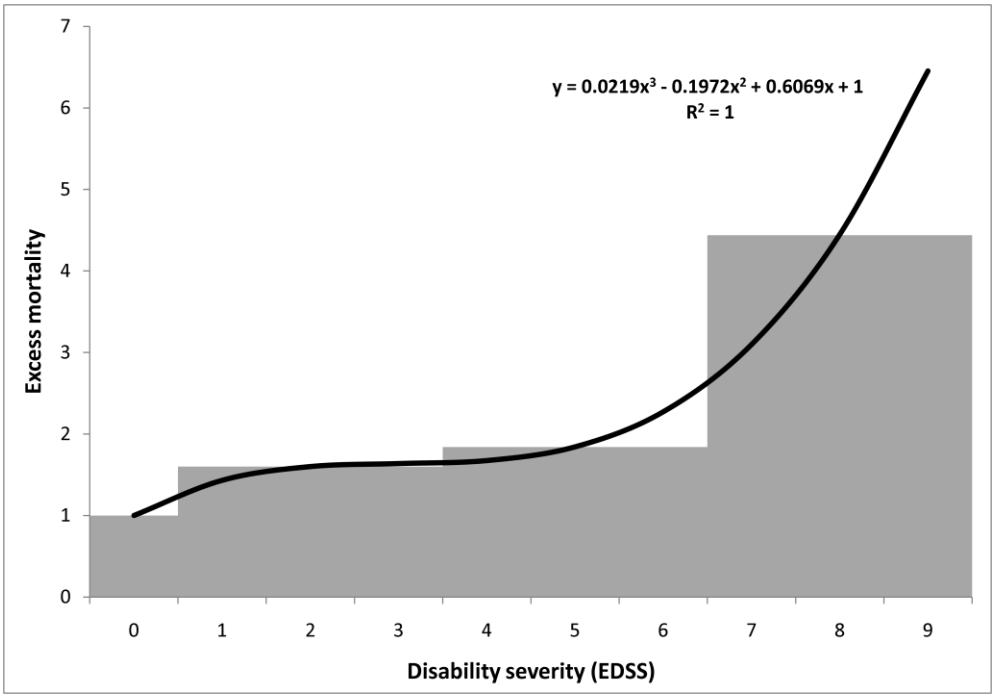
Progression and relapses are applied separately in the model so that progression has no influence on relapse events and relapses do not have a direct impact on the disease severity or the disease progression. The rates of relapse are driven by the severity of the disease, i.e., the EDSS score, and the time since diagnosis.

All patients are individually followed through the model from the age of treatment initiation for up to a maximum of 50 years (the time horizon for the primary economic analysis). NICE recommends that the model time horizon should reflect the period of time over which the main differences between technologies (in terms of their cost and health effects) are expected. In view of NICE recommendations, the base-case model time horizon is 50 years.

Alternative time horizons, including 10 and 20 years, are investigated in the sensitivity analyses.

Probabilities for all-cause mortality for the general population are derived from age- and gender-specific mortality rates for England and Wales (ONS, 2010). The probabilities are adjusted for the MS population, using the mortality ratios reported by Pokorski (1997). Pokorski (1997) presented mortality experience of MS by mild, moderate and severe degrees of disability. To add more granularity to these mortality ratios, analysis by Sadovnick and colleagues (1992) was used to generate an equation to predict excess mortality for individual EDSS scores (Figure 13).

Figure 13 Effect of EDSS score on mortality



EDSS, Expanded Disability Status Scale.

An important consequence of applying this mortality factor to MS patients is the resulting redundancy of the EDSS state 10, therefore avoiding double-counting MS-related mortality. Mortality multipliers are applied to both RRMS and SPMS populations (Table 56).

Table 56 Multiplier to standard mortality rate used in the model

EDSS score	Multiplier on standard mortality rate
0	1.000
1	1.432
2	1.600
3	1.637
4	1.674
5	1.842
6	2.273
7	3.097
8	4.447
9	6.454

EDSS, Expanded Disability Status Scale.

The main outcome measure adopted in the economic model is the ICER, measured in terms of the incremental cost per quality-adjusted life-year (QALY) saved. The primary objective of the model was to quantify the expected costs and benefits of using fingolimod in clinical practice and to compare these with the expected costs and benefits of alternative treatment options.

The model structure captures both the disability associated with MS and the relapsing nature of MS. In addition, it encapsulates the probability of change from RRMS to SPMS and to mortality. Changes in the EDSS scores are most commonly used to define disability progression. A Markov structure was selected to model transitions through the health states defined by the EDSS scores. Evidence of relapses, quality of life, costs, and treatment decisions also is typically based on the EDSS scores. The EDSS-based Markov structure has been adopted in previous economic evaluations in MS (Tappenden et al., 2001; Biogen Idec UK and Elan Pharma International, 2007). Therefore, a Markov structure was deemed appropriate for this economic evaluation.

In considering appropriate comparators for the model we need to take note of current clinical practice and of available evidence of clinical efficacy and effectiveness in the selected patient population. In this case, we are

concerned with RRMS non-responder patients with high disease activity despite treatment with a beta-interferon.

There is direct evidence available from the TRANSFORMS study for fingolimod in this patient group compared directly with interferon-beta-1a 30 mcg (intramuscular) Avonex. There is also similar evidence available comparing fingolimod with best supportive care, from the FREEDOMS study.

In reviewing the evidence for the original MTC analysis conducted for all RRMS patients (reported in Section 5) we found no published trials of additional comparators (Betaferon, Copaxone, Rebif 22, Rebif 44) which provided reported efficacy data in this specific patient group. We have therefore excluded these as comparators in the economic analysis, focusing specifically on Avonex. It may be possible to consider the use of the "all RRMS" relative risk data (from the MTC) as a proxy for "highly active RRMS non-responder" data.

As stated in the natalizumab submission (Biogen Idec UK and Elan Pharma International, 2007), the underlying model structure addresses many of the key criticisms originally made against the original ScHARR model.

- Natural history has been model using data from observational studies with impact of DMT modelled as the impact on the natural history.
- Mortality included based both on age and disability severity.
- Model includes transition from RRMS to SPMS.
- Disutility and costs due to adverse events for all DMTs included.
- Treatment dropouts included in the model whereby they have the same progression and relapse rates as those not on DMTs (i.e., return to natural history).
- Assume that efficacy and progression rates are non-linear since the probability of transition between health states follows an exponential distribution (as the ScHARR model).

- Extended time horizons to 50 years.
- Disutility of relapse rates is by EDSS state and based on UK utility measures and severity measurements.
- Extensive univariate sensitivity is undertaken with adverse event rates, efficacy, costs and utility varied during the PSA.

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

The health states in the model are defined by the EDSS scale, which measures the progression of the disease in terms of impairment and disability. The EDSS scale ranges from 0 (normal neurological examination) to 10 (death due to MS). The model includes the EDSS states for both the RRMS and SPMS patients. The disease activity represented by the frequency of relapses is modelled as state-dependent, given the available evidence. The model therefore consists of 21 health states designed to capture the important health-service costs and health consequences arising from disability progression and incidence of relapse.

6.2.5 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.

The model structure is based on a series of health states and clinical events that reflect the key aspects of MS, namely progression through disease severity stages (defined using EDSS) and the risk of relapse. The fuller detail of the model structure is covered in Sections 6.2.2 and 6.2.3.

Natural history was based on the best supportive care experience of patients as represented through the London Ontario data set, for patients who have not received DMT treatment for their MS.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Key features of analysis are presented in Table 57.

Table 57 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	50 years	NICE recommends a time horizon to reflect costs and health-effect differences between therapies. In order to reflect the life-long nature of MS, the base case model time horizon is 50 years	Section 6.2.3
Cycle length	1 year	Consistent with previous economic models in MS	Section 6.2.3
Half-cycle correction	Half-cycle correction included	NICE reference case criteria	Section 6.2.3
Were health effects measured in QALYs; if not, what was used?	QALYs employed	NICE reference case criteria	Section 6.2.3
Discount of 3.5% for utilities and costs	Discount of 3.5% included	NICE reference case criteria	Section 6.5.1
Perspective (NHS/PSS)	NHS/PSS perspective	NICE reference case criteria	Section 6.5.1

MS, multiple sclerosis; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PSS, Personal Social Services; QALY, quality-adjusted life-year.

Technology

6.2.7 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?

Fingolimod does not yet have a UK marketing authorisation for the indication detailed in this submission. Fingolimod is modelled according to its anticipated marketing authorisation (see Section 1.5). The comparators have been modelled as per their UK marketing authorisations.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? 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. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The model assumes that only RRMS patients with an EDSS score of 6 or less may receive a DMT. All SPMS patients and RRMS patients with an EDSS score of greater than 6 receive BSC. This is in line with the assumption made by Biogen Idec Ltd. (2007) in the NICE submission for natalizumab. In addition, guidelines from the Association of British Neurologists (2009) recommend DMTs for patients who can walk independently, i.e., those with an EDSS of 6 or less. The threshold is applied as a DMT stopping rule in the model. The threshold can be varied by the user to allow analyses of alternative treatment rules.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (Section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

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

Natural history disability progression rates for patients with RRMS or SPMS were derived from a large 25-year cohort study undertaken in London, Ontario, Canada (Weinshenker et al., 1989). The methodology used is discussed in Section 6.2.3. The results of this analysis form the baseline risks for disability progression. The natural history of relapses was estimated using a different study because the London, Ontario, cohort study collected very little data on relapses beyond the first 2 years of follow-up (methodology described in Section 6.2.3). The effect of treatment on disease progression is modelled as a relative risk of confirmed disability progression. The effect of treatment on the mean number of relapses is modelled as a relative ARR. The probabilities of annual relapse rate and disability progression for fingolimod were calculated from the absolute incidences of these endpoints reported in the FREEDOMS trial (Kappos et al., 2010), allowing a relative risk for fingolimod versus BSC to be derived directly from the FREEDOMS study. The

corresponding placebo relative risk value for interferon-beta-1a (Avonex) was calculated indirectly from the TRANSFORMS trial (Cohen et al., 2010a), which directly compared fingolimod with interferon beta-1a, by using the adjusted indirect comparison method (Bucher et al., 1997). The following calculations were performed:

- If Avonex is represented as *A*, placebo as *P*, and the common comparator (fingolimod) as *F*;
- Estimates of RR are represented as follows:

$$\text{Avonex vs. fingolimod: } RR_{AF}$$

$$\text{Placebo vs. fingolimod: } RR_{PF}.$$

- Then, using the Bucher method, the RR for Avonex vs. placebo (RR_{AP}) is given by the following:

$$\ln RR_{AP} = \ln RR_{AF} - \ln RR_{PF},$$

and the variance of RRAP is given by the following:

$$\text{Var}(\ln RR_{AP}) = \text{Var}(\ln RR_{AF}) + \text{Var}(\ln RR_{PF}).$$

- Assuming that In RR is normally distributed, then the upper 95% confidence interval (*UCI*) and lower 95% confidence interval (*LCI*) may be estimated as follows:

$$\ln UCI_{AP} = \ln RR_{AP} + 1.96 \times \text{Var}(\ln RR_{AP}),$$

$$\ln LCI_{AP} = \ln RR_{AP} - 1.96 \times \text{Var}(\ln RR_{AP}).$$

Probabilities of ARR and disability progression for Avonex versus placebo were then applied to the incidence of each endpoint for placebo.

The discontinuations due to AEs are applied in the model throughout the on-treatment period. The data on discontinuations due to AEs also were obtained from the head-to-head trial; however, the discontinuation data for the whole

trial population are applied. The analyses versus BSC use the data from FREEDOMS trial.

6.3.2 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.

The model applies relative risks to the individual natural history transitions in the RRMS. The relative risk for fingolimod versus BSC is derived directly from the FREEDOMS study. The corresponding placebo relative risk value for Avonex is calculated indirectly using the standard adjusted method (Bucher et al., 1997) based on the TRANSFORMS trial, which directly compared fingolimod with Avonex. In the base case analysis the model does not apply any DMT treatment effect to the conversion rate from RRMS to SPMS. However, the model is capable of varying this effect and this is explored in the sensitivity analyses. The relative risks for disease progression are not applied in SPMS EDSS transitions, as treatment is not indicated in this type of MS, therefore all patients follow a natural history path once converted to SPMS.

6.3.3 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.

The model assumes that the relative risks of disability progression and relapse remain constant over time while remaining on treatment. The model assumes that there is no remaining treatment effect once DMT is stopped.

6.3.4 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?

The model is based directly on a health states structure based on the progression along the EDSS states assessed using direct clinical evidence. Therefore, there was no need to include any intermediate outcome measures.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- The criteria for selecting the experts,
- The number of experts approached,
- The number of experts who participated,
- Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought,
- The background information provided and its consistency with the totality of the evidence provided in the submission,
- The method used to collect the opinions,
- The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?),
- The questions asked,
- Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two UK clinicians specializing in MS were asked to provide a review of the entire submission from a UK MS clinical perspective. The clinicians represented different geographies within the UK and were selected because of their willingness and availability to take part in the review. Neither of the clinicians is employed by Novartis. Both experts were given the entire draft submission to review as a stand-alone document and were asked to provide their feedback as written comments. This was followed up by telephone interviews. The feedback from the clinicians did not contradict one another, so

[1] Adapted from Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

no iteration was used in the collation of opinions. In addition, the assumptions used in developing the model were tested with the clinicians, and their feedback was incorporated.

Summary of selected values

6.3.6 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 58 Summary of variables applied in the economic model

Variable	Value	Distribution	Reference
Population			
Age at treatment start	37.3 years	Deterministic	Section 6.2.1
Female-to-male ratio	2.3:1	Deterministic	Section 6.2.1
Years since diagnosis	6.25 years	Deterministic	Section 6.2.1
Initial EDSS distribution	State dependant	Deterministic	Section 6.2.1
Cohort size	1000	Deterministic	Section 6.2.1
Utility			
Health state utilities	State dependant	Multinomial distribution	Section 6.4.9
Years since diagnosis	0.002	Multinomial distribution	Section 6.4.9
Male	0.017	Multinomial distribution	Section 6.4.9
Disutility of relapse	–0.071	Multinomial distribution	Section 6.4.9
Disutility of treatment	Therapy dependent	Deterministic	Section 6.4.9
Disutility of AE	AE dependant	Deterministic	Section 6.4.9
Costs			
Drug therapy costs	Therapy dependent	Deterministic	Section 6.5
Health-state costs	State dependant	Lognormal	Section 6.5
Cost of relapse	£3,039	Lognormal	Section 6.5
Cost of macula oedema	£179	Deterministic	Section 6.5.7
Cost of atrioventricular block, first degree	£427	Deterministic	Section 6.5.7
Cost of atrioventricular block, second degree	£427	Deterministic	Section 6.5.7
Clinical			
Relative risk of confirmed progression (for non-responders)*	[redacted]	Lognormal	Section 5.7

Variable	Value	Distribution	Reference
	[redacted]		

Variable	Value	Distribution	Reference
Relative rate of relapse (for non-responders)*	FREEDOMS (direct) Fingolimod vs. placebo = 0.559 TRANSFORMS (indirect) Avonex vs. placebo = 0.933	Lognormal	Section 5.7
Discontinuations due to AEs (for non-responders)*	TRANSFORMS Fingolimod = 6/191 Avonex = 3/183	Deterministic	Section 5.7
Mortality	Age/health-state dependant	Deterministic	Section 6.2.3
Modelling horizon	50 years	Deterministic	Section 6.2.3
Discount rates			
Costs	3.5%	Deterministic	Section 6.5.1
Benefits	3.5%	Deterministic	Section 6.5.1

AE, adverse event; EDSS, Expanded Disability Status Scale; MTC, mixed-treatment comparison.

* Please note that the values presented here are different to those in Table 26, which reports the hazard ratios rather than the relative risks presented above (both use the same patient numbers and definition, i.e., non-responder patients with high disease activity despite prior treatment with a beta-interferon). The economic model required the relative risks to be applied to the underlying natural history.

The key data used to populate the economic model are presented in Table 58. The table shows those parameters and data items included in the probabilistic sensitivity analysis, using associated distributions. The table also links to the description of the data in the appropriate sections of the submission document.

6.3.7 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 model assumes that the treatment effect risk reduction is maintained over the long-term whilst the patient remains in the treatable EDSS range. In the

sensitivity analysis the model explores the reduction in effect beyond the trials follow-up period.

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

The economic analysis makes the following key assumptions:

- Average age of cohort at start of treatment is 37.3 years, the female-to-male ratio is 2.3:1, and the time since diagnosis is 6.25 years, as reflected in the pooled analysis of non-responder subgroups from FREEDOMS and TRANSFORMS.
- The initial distribution of patients across the EDSS states is based upon the pooled analysis of non-responder subgroups from FREEDOMS and TRANSFORMS.
- Transitions within the model are assumed to be progressive only.
- The model assumes that only RRMS patients with an EDSS score of 6 or less may receive a DMT. Prior to reaching an EDSS score of 7 or greater, patients may continue on DMTs until they discontinue due to AEs or until death. All SPMS and RRMS patients with an EDSS score of 7 or greater receive BSC. The guidelines of the Association of British Neurologists (2009) recommend DMTs for patients who can walk independently, i.e., those with an EDSS score of 6 or less.
- The model assumes that the relative risks associated with progression and relapses are maintained for the time horizon of 50 years.
- Utility decrements attributable to AEs are applied over the total treatment duration period. Previous models have assumed that these disutilities do not persist for the whole duration of the treatment period. However, since those studies were conducted, substantial evidence has been published to suggest that disutilities actually do persist over the long term (Herndon et al., 2005; Gold et al., 2005; Rio et al., 2005). We therefore apply these disutility rates each year to treated patients in the model.

- Mortality multipliers linked to EDSS are applied to both RRMS and SPMS populations; the multipliers are not differentiated between treatments.
- The treatment effects are assumed to be fixed, i.e., relative risks associated with disease progression or relapses will not increase or decrease over time.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

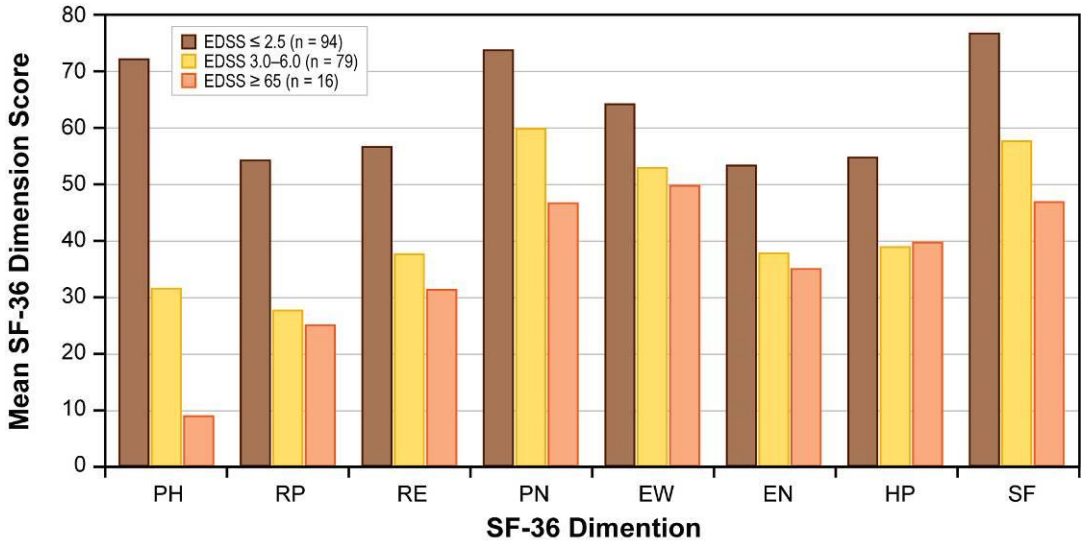
All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

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

Disability progression and relapses in MS have a considerable effect on patient's HRQL, with decline seen across many domains with increasing levels of EDSS disability (Figure 14).

Figure 14 Health-related quality of life and disability levels*



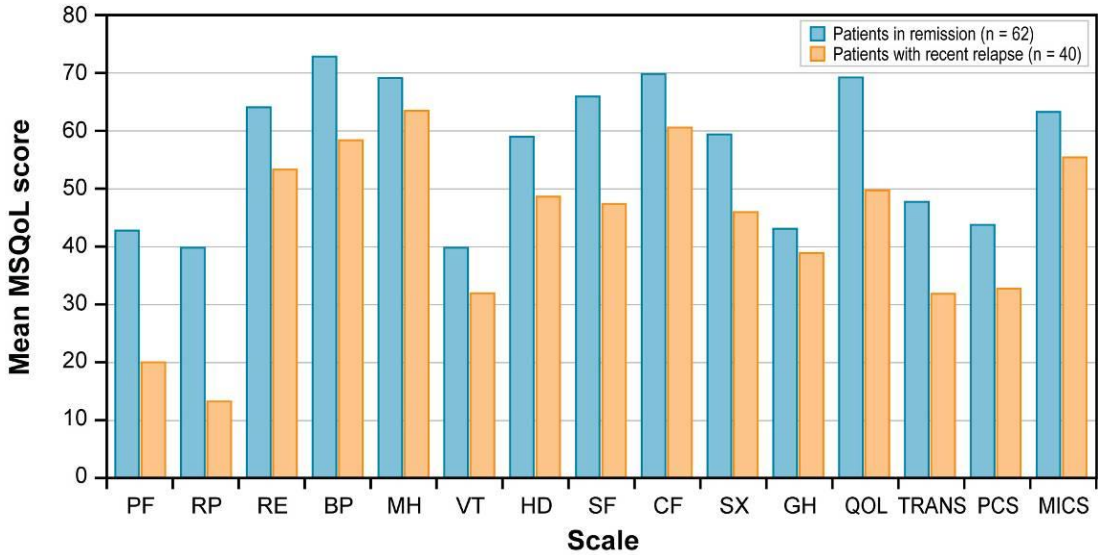
EDSS, Expanded Disability Status Scale; HP, Health Perceptions; HRQL, health-related quality of life; EN, Energy; EW, Emotional Well-Being; PH, Physical Health; PN, Pain; RE, Emotional Role Limitations; RP, Physical Role Limitations; SF, Social Function.

* A higher score indicates increasing disability. The SF-36 Health Survey measures HRQL, with higher scores indicating better HRQL.

Source: Miller et al., 2006.

Relapses also have an impact of patient's HRQL (Figure 15).

Figure 15 Relapses and quality of life



BP, Bodily pain; CF, Cognitive function; GH, General health; HD, Health distress; MH, Mental Health; MICS, Mental health composite score; PCS, Physical health composite score; PF, Physical function; QOL, Overall quality of life; RE, Role emotional; RP, Role physical; VT, Energy/vitality; SF, Social function; SX, Sexual function; TRANS, Change in health.

Source: Parkin et al., 2000.

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

The evidence suggests that people with MS have a quality of life that deteriorates as the disease progresses until severe disability occurs in what some have described as a state worse than death at EDSS 8 (Table 59) (Orme et al., 2007). SPMS and relapses are also indicators of further utility loss (Orme et al., 2007). It has also been observed that the number of years since diagnosis has a positive effect on utility, with an approximate utility gain of 0.01 for every 5-year period with MS (Orme et al., 2007). This utility gain based on time since diagnosis, as observed in the UK MS Survey, is applied in the economic model.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in Section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive:

- Method of elicitation,
- Method of valuation,
- Point when measurements were made,
- Consistency with reference case,
- Appropriateness for cost-effectiveness analysis,
- Results with confidence intervals.

HRQL data were collected in Study D2302 (TRANSFORMS) using the PRIMUS-QoL, PRIMUS-Activities, EQ-5D, and the UFIS instruments. In addition, Study D2301 (FREEDOMS) collected HRQL data using the EQ-5D.

The disease-specific PRIMUS scales have only been recently developed (in 2009) in the UK and are not currently in wide use (Doward et al., 2009). Data from these scales are not consistent with the reference case. The EQ-5D data for fingolimod is presented in Section 5.5. One non-RCT in patients treated with interferon-beta-1a reported change in EQ-5D from baseline (Putzki et al., 2009).

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information:

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D;
- Details of the methodology used;
- Details of validation of the mapping technique.

Appropriate EQ-5D data were identified from secondary sources. Hence, mapping from one instrument to another was not undertaken in the current model.

HRQL studies

6.4.5 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 **Error! Reference source not found.**, Appendix 12.

A systematic review of the HRQL data was undertaken using the same electronic medical databases and additional sources as presented in Section 6.1.1. Full details of the systematic review methods have been detailed in Section **Error! Reference source not found.**, Appendix 12. The

full systematic review report is embedded at the end of Section **Error! Reference source not found.**, Appendix 10.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive:

- Population in which health effects were measured,
- Information on recruitment,
- Interventions and comparators,
- Sample size,
- Response rates,
- Description of health states,
- Adverse events,
- Appropriateness of health states, given condition and treatment pathway,
- Method of elicitation,
- Method of valuation,
- Mapping,
- Uncertainty around values,
- Consistency with reference case,
- Appropriateness for cost-effectiveness analysis,
- Results with confidence intervals,
- Appropriateness of the study for cost-effectiveness analysis,

The details of the included studies are summarised in the full systematic review report embedded at the end of Section **Error! Reference source not found.**, Appendix 10. Table 59 presents utility values by EDSS score reported in the identified studies.

Table 59 Summary of identified studies presenting utility data by EDSS score

EDSS state	Utility estimate						
	Parkin et al., 1998*	Orme et al., 2007*		Biogen Idec UK and Elan Pharma International, 2007		Evidence Review Group Report TA No. 127	
		RRMS	SPMS	RRMS	SPMS	RRMS	SPMS
0	—	0.870	0.825	0.91	0.87	0.959	0.874
1	—	0.799	0.754	0.84 (EDSS 0.5-1)	0.8 (EDSS 0.5-1)	0.688 (EDSS 1)	0.603 (EDSS 1)
2	—	0.705	0.660	0.74 (EDSS 1.5-2)	0.7 (EDSS 1.5-2)	0.688 (EDSS 1.5-2)	0.603 (EDSS 1.5-2)
3	0.71	0.574	0.529	0.61 (EDSS 2.5-3)	0.57 (EDSS 2.5-3)	0.645 (EDSS 2.5-3)	0.560 (EDSS 2.5-3)
4	0.66	0.610	0.565	0.65 (EDSS 3.5-4)	0.61 (EDSS 3.5-4)	0.610 (EDSS 3.5-4)	0.527 (EDSS 3.5-4)
5	0.52	0.518	0.473	0.56 (EDSS 4.5-5)	0.51 (EDSS 4.5-5)	0.581 (EDSS 4.5-5)	0.496 (EDSS 4.5-5)
6	0.49	0.460	0.415	0.49 (EDSS 5.5-6)	0.45 (EDSS 5.5-6)	0.538 (EDSS 5.5-6)	0.453 (EDSS 5.5-6)
7	0.35	0.297	0.252	0.44 (EDSS 6.5-7)	0.39 (EDSS 6.5-7)	0.477-0.343 (EDSS 6.5-7)	0.392-0.258 (EDSS 6.5-7)
8	—	–0.049	–0.094	–0.01 (EDSS 7.5-8)	–0.05 (EDSS 7.5-8)	0.343-0.232 (EDSS 7.5-8)	0.258-0.147 (EDSS 7.5-8)
9	—	–0.195	–0.240	–0.15 (EDSS 8.5-9.5)	–0.19 (EDSS 8.5-9.5)	0.232 to –0.135 (EDSS 8.5-9.5)	0.147 to –0.220 (EDSS 8.5-9.5)

EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal.

* Data not presented in full text publication.

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

The comparison between the utility values derived from the literature and those collected in the fingolimod trials was not drawn.

Adverse events

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

Refer to Section 6.4.9.

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

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

UK utility weights by EDSS score were derived from Orme et al. (2007), which used data from the 2005 UK MS Survey. Orme and colleagues (2007) presented data for patients with RRMS, and the authors assumed that patients with SPMS had a lower utility than patients with RRMS (−0.045) (Table 60).

Orme et al. (2007) reported a utility of 0.002 (95% CI: 0.001-0.003; *P* < 0.001) per year since diagnosis of MS. The authors reported that male gender was associated with a utility of 0.017 (95% CI: −0.007 to 0.041; *P* not stated). Orme et al. (2007) also presented a disutility for recent relapse of −0.071 (95% CI: −0.096 to −0.046; *P* < 0.001).

Table 60 Coefficients from regression analysis for utility derived from EQ-5D

EDSS state	Coefficient	95% CI (lower, upper)	*P* value
Reference case	0.870	(0.782, 0.958)	*
EDSS 1-1.5	–0.071	(–0.165, 0.023)	0.138

EDSS state	Coefficient	95% CI (lower, upper)	*P* value
Reference case	0.870	(0.782, 0.958)	*
EDSS 2-2.5	–0.165	(–0.259, –0.072)	*
EDSS 3-3.5	–0.296	(–0.398, –0.195)	*
EDSS 4-4.5	–0.260	(–0.354, –0.167)	*
EDSS 5-5.5	–0.352	(–0.444, –0.260)	*
EDSS 6	–0.412	(–0.505, –0.319)	*
EDSS 6.5	–0.408	(–0.502, –0.314)	*
EDSS 7-7.5	–0.573	(–0.670, –0.477)	*
EDSS 8-8.5	–0.919	(–1.017, –0.820)	*
EDSS 9-9.5	–1.065	(–1.210, –0.919)	*
Resent relapse	–0.071	(–0.096, –0.046)	*
SPMS	–0.045	(–0.076, –0.014)	0.005
Sex: male	0.017	(–0.007, 0.041)	0.165
Years since diagnosis	0.002	(0.001, 0.003)	*

CI, confidence interval; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

* $P < 0.001$.

Source: Orme et al., 2007.

MS imposes a significant burden on caregivers. The model incorporates caregivers' disutility in the base-case analysis (Table 61), in line with previous STA submissions to NICE (Biogen Idec UK and Elan Pharma International, 2007).

Table 61 Disutilities of caregivers by EDSS score

EDSS state	Average hrs of care per patient per day	Average % of day that friends/family spend caring	Weighting relative to maximum disutility*	Disutility of caregivers per patient
0	0.0	0%	0%	0.00
1	0.1	1%	1%	0.00
2	0.3	1%	2%	0.00
3	1.0	45	7%	0.01
4	1.0	4%	6%	0.01
5	2.1	9%	14%	0.02
6	2.9	12%	19%	0.03
7	5.6	23%	38%	0.05

EDSS state	Average hrs of care per patient per day	Average % of day that friends/family spend caring	Weighting relative to maximum disutility*	Disutility of caregivers per patient
8	11.3	47%	76%	0.11
9	14.8	61%	100%	0.14

Source: Biogen Idec UK and Elan Pharma International, 2007

* The maximum disutility for a caregiver of a person with MS is assumed to be 0.14 (Biogen Idec UK and Elan Pharma International, 2007).

Disutility values from AEs associated with interferon-beta and glatiramer acetate have been estimated using the standard gamble technique as part of a study by Prosser et al. (2003). These disutility values (Table 62) have been used to parameterise a number of economic evaluations estimating the cost-effectiveness of interferon-beta and glatiramer acetate in MS patients (Biogen Idec UK and Elan Pharma International, 2007; Prosser et al., 2004). The disutility per patient is calculated by multiplying the disutility of an event by the frequency of this event. The incidence of AEs is assumed to be 30%, which is in line with the original appraisal of interferon-beta and glatiramer acetate (Tappenden et al., 2001).

Previous models have assumed that these disutilities do not persist for the whole duration of the treatment period. However, since these studies were conducted, substantial evidence has been published to suggest that they actually do persist over the long-term (Herndon et al., 2005; Gold et al., 2005). We therefore apply these disutility rates each year to treated patients in the model.

Table 62 Utility decrements for adverse events

Events	Interferon-beta-1a	Interferon-beta-1b	GA
Disutility per event	0.115	0.204	0.066
Frequency of event	0.30	0.30	0.30
Disutility per patient	0.0345	0.0612	0.0198

GA, glatiramer acetate.

Table 63 presents disutilities for SAEs associated with fingolimod.

Table 63 Estimated decrease in utility per SAE

Condi-tion	Decrease in utility across year	Duration of condition	Assumed annual QALY loss per patient experiencing AE	Source*
Macular oedema	ARMD decrement: –0.04	3 months	0.01	Espallargues et al., 2005; Petrou and Hockley, 2005
Atrioven-tricular block, first degree	CIHD decrement: –0.289	24 hours	0.001	Currie et al., 2005; Petrou and Hockley, 2005
Atrioven-tricular block, second degree	CIHD decrement: –0.289	24 hours	0.001	Currie et al., 2005; Petrou and Hockley, 2005

AE, adverse event; ARMD, age-related macular degeneration; CIHD, chronic ischemic heart disease; EQ-5D, EuroQol 5-dimension survey; QALY, quality-adjusted life-year; SAE, serious adverse event.

* Espallargues et al., 2005, reports a mean EQ-5D for age-related macular degeneration of 0.72; Petrou and Hockley, 2005, reports a general population utility value of 0.882 (for age group 35-44); Currie et al., 2005, reports mean EQ-5D for chronic ischemic heart disease of 0.558.

Table 64 summarises the quality-of-life values for the cost-effectiveness analysis.

Table 64 Summary of quality-of-life values for the cost-effectiveness analysis

Item description	Mean value (CI)		Justification
	RRMS	SPMS	
Utility by health state			
EDSS 0	0.870 (0.782, 0.958)	0.825	Estimates taken from Orme et al., 2007, which was identified by the systematic review as the most appropriate source of the health state utility values for the UK. Utility data were collected via a postal survey using EuroQoL, with utilities assigned using the EQ-5D UK value set, obtained from a representative sample of the UK population using the time-trade-off method.
EDSS 1	0.799	0.754	
EDSS 2	0.705	0.660	
EDSS 3	0.574	0.529	
EDSS 4	0.610	0.565	
EDSS 5	0.518	0.473	
EDSS 6	0.460	0.415	
EDSS 7	0.297	0.252	
EDSS 8	–0.049	–0.094	

Item description	Mean value (CI)		Justification
	RRMS	SPMS	
EDSS 9	–0.195	–0.240	The pattern of decline represented by this data is comparable to other utility datasets (Table 59)
Other utility			
Years since diagnosis	0.002 (0.001, 0.003)	0.002 (0.001, 0.003)	The study by Orme et al., 2007, reported the effects on utility of the number of years since diagnosis and gender. The systematic review of the literature concluded that this study was the most appropriate source of these utility values.
Male	0.017 (–0.007, 0.041)	0.017 (–0.007, 0.041)	
Disutility of caregivers by health state			
EDSS 0	0.00	0.00	The systematic review of the literature identified only one source of the MS caregivers' disutilities, i.e., previous STA submission to NICE (Biogen Idec UK and Elan Pharma International, 2007).
EDSS 1	0.00	0.00	
EDSS 2	0.00	0.00	
EDSS 3	0.01	0.01	
EDSS 4	0.01	0.01	
EDSS 5	0.02	0.02	
EDSS 6	0.03	0.03	
EDSS 7	0.05	0.05	
EDSS 8	0.11	0.11	
EDSS 9	0.14	0.14	
Disutility of relapse			
Relapse	–0.071 (–0.096, –0.046)	–0.071 (–0.096, –0.046)	The systematic review of the literature concluded that the study by Orme et al., 2007, was the most appropriate source of the utility decrement associated with relapse.
Disutility of treatment			
Disutility per patient on Avonex	–0.0345	N/A	The systematic review of the literature concluded that the study by Prosser et al., 2003 was the most appropriate source of the treatment disutility data.
Disutility per patient on fingolimod	0.0000	N/A	Fingolimod is an oral drug and is not associated with the utility decrements applied to the injectable DMTs.
Disutility of adverse events			
Macular oedema	0.01	N/A	Macular oedema is one of the serious adverse events of fingolimod and the disutility associated with this event is included using the published disutility of age-related macular degeneration as a proxy.

Item description	Mean value (CI)		Justification
	RRMS	SPMS	
Atrioventricular block, second degree	0.001	N/A	Atrioventricular block, first and second degree, oedema is one of the serious adverse events of fingolimod and the disutility associated with this event is included using the published disutility of chronic ischemic heart disease as a proxy.

CI, confidence interval; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; N/A, not applicable; NICE, National Institute for Health and Clinical Excellence; STA, single technology appraisal.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:[1]

- The criteria for selecting the experts,
- The number of experts approached,
- The number of experts who participated,
- Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought,
- The background information provided and its consistency with the totality of the evidence provided in the submission,
- The method used to collect the opinions,
- The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?),
- The questions asked,
- Whether iteration was used in the collation of opinions and, if so, how it was used (for example, the Delphi technique).

The same clinicians and process detailed in Section 6.3.5 were used to provide a general review of all utility values used in the model. No clinical opinions were used to elicit utility values.

[1] Adapted from Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

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

The most widely used tools for measuring disability progression in MS are Kurtzke's DSS and the EDSS, developed by adding half points to Kurtzke's original 10-point DSS. A description of the EDSS is provided in Table 65.

Table 65 Summary of patient experience by health state

Health state (DSS)	Description
2.5	Minimal disability in 2 FSs (2 FSs grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in 3 or 4 FSs (3 or 4 FS grade 2, others 0 or 1) though fully ambulatory.
	Fully ambulatory but with moderate disability in one FS (1 grade 3) and 1 or 2 FSs grade 2; or 2 FSs grade 3; or 5 FSs grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of 1 FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 500 metres.
	Fully ambulatory without aid, up and about much of the day, able to work a fully day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability, usually consisting of 1 FS grade
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to preclude full daily activities (usual FS equivalents are 1 grade 5 alone, others 0 to 1, or combinations of lesser grades usually exceeding specifications for step 4.0).
	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities (usual FS equivalents are 1 grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding those for steps 4.0).
6.0	Intermittent or unilateral constant assistance (cane, crutch, or braces) required to walk about 100 metres with or without resting (usual FS equivalents are combinations with more than 2 FSs grade 3+).
	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 metres without resting (usual FS equivalents are combinations with more than 2 FSs grade 3+).

DSS, Disability Status Scale; FS, functional system.

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

None specifically excluded—the model focused on progression and relapses.

6.4.13 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?

The baseline HRQL was based on the utility data linked to EDSS states—based on data reported by Orme et al., 2007—which then were applied to the distribution of patients across the EDSS states.

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

HRQL was assumed to remain constant over time for each EDSS score – with a single adjustment made to reflect time since diagnosis (based on a small 0.01 utility gain for each 5-year period with MS) based on data reported by Orme et al., 2007.

6.4.15 Have the values in Sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

In most cases the utility data were taken directly from the published literature.

We derived the disutility associated with adverse events for Avonex, using the utility of being on interferon-beta-1a (reported in the Prosser et al., 2003, study) and subtracting from a value of perfect health set equal to 1.

Given that fingolimod is an oral drug we did not include any treatment-related disutilities associated with injectable DMTs as reported in the literature (Prosser et al., 2003).

6.5 Resource identification, measurement, and valuation

This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

National Health Service costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the National Health Service (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.

Therapy management

NHS costs for RRMS drug therapy management include the following:

- Initial consultation (e.g., specialist visit),
- Pharmaceutical therapies,
- Drug administration,
- Ongoing monitoring (e.g., subsequent specialist visits, etc.).

The current DMTs are made available in the UK via the MS Risk Sharing Scheme (RSS). Within this, the cost of drug therapy for interferons and glatiramer acetate are specified (Department of Health, 2005).

Cost data has been sourced from the National Schedule of Reference Costs 2009-2010 NHS Trusts and Primary Care Trusts (PCTs) combined schedule (Department of Health, 2010) and 2010-2011 National Tariff (Department of Health, 2011) (Table 66).

Table 66. National Schedule of Reference Costs 2009-2010 NHS Trusts and PCTs combined and 2010-2011 National Tariffs

Currency code	Currency description	National average unit cost	Lower quartile unit cost	Upper quartile unit cost	Average length of stay (days)	Indexed live value
Physician Visits						
TPCTCLFASFF – 400	Neurology – First attendance	£207	£151	£234	—	£207
TPCTCLFASFF – 130	Ophthalmology – First attendance	£105	£82	£123	—	£105
TPCTCLFUSFF – 130	Ophthalmology – Follow up attendance	£74	£61	£83	—	£74
Test/Imaging						
Diagnostic Imaging: Outpatient – RA01Z	Magnetic resonance imaging scan, one area, no contrast	£174	£117	£199	—	£174
Pathology Services – DAP823	Haematology [excluding anti-coagulant services]	£3.06	£1.86	£3.90	—	£3.06
Pathology Services – DAP841	Biochemistry[s]	£1.29	£0.78	£1.57	—	£1.29
Pathology Services – DAP830	Immunology	£7.25	£4.32	£8.75	—	£7.25
Other						
Day Cases HRG Data – AA30Z	Medical care of patients with multiple sclerosis	£501	£269	£547	—	£501
Elective Inpatient HRG Data – AA30Z	Medical care of patients with multiple sclerosis – Elective inpatient	£2,079	£1,259	£2,116	4.15	£2,079
Non-elective Inpatient (Short Stay) HRG Data – EB07H	Arrhythmia or conduction disorders with CC*	£427	£295	£471	1.00	£427
Admitted Patient Care and Outpatient Procedure Tariff –	Multiple sclerosis – Combined day case/elective tariff**	£1,293	-	-	—	£1,293

Currency code	Currency description	National average unit cost	Lower quartile unit cost	Upper quartile unit cost	Average length of stay (days)	Indexed live value
AA30Z						
Admitted Patient Care and Outpatient Procedure Tariff – AA30Z	Multiple sclerosis – Non-elective spell tariff	£3,039	-	-	—	£3,039

CC, complications; CNS, central nervous system; HRG, Healthcare Resource Group.

§ Used for the costs of liver function, basic metabolism, and pregnancy tests.

* Used as a proxy for atrioventricular block, first degree, and atrioventricular block, second degree.

** TA127 Multiple sclerosis – natalizumab: costing template (NICE, 2008) used A18 Multiple Sclerosis or other CNS Demyelinating conditions 2007/08 elective in-patient tariff, uplifted by average market forces factor. The A18 HRG code is superseded by AA30Z in 2010-11 National Tariffs (Department of Health, 2010), and this new code is used to obtain the cost of natalizumab administration.

Both the costs and benefits are discounted at the rate of 3.5%.

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

The NHS reference costs included in the analysis are believed to be appropriate for the costing of the intervention and comparators being appraised.

Resource identification, measurement and valuation studies

6.5.3 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 **Error! Reference source not found.**, Appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- Country of study,

- Date of study,
- Applicability to UK clinical practice,
- Cost valuations used in study,
- Costs for use in economic analysis,
- Technology costs.

A systematic review of resource use and cost data in RRMS was undertaken, using the same electronic medical databases and additional sources as presented in Section 6.1.1. Full details of the systematic review methods and the inclusion and exclusion criteria have been detailed in Section **Error! Reference source not found.**, Appendix 13.

The details of the included studies are summarised in the full systematic review report embedded at the end of Section **Error! Reference source not found.**, Appendix 10. Table 67 presents costs by EDSS score reported in the identified studies.

Table 67 Summary of identified studies presenting cost data by EDSS score

EDSS state	Mean (SE) annual costs									
	Parkin et al., 1998		Tyas et al., 2007					Biogen Idec UK and Elan Pharma International, 2007		
	Direct costs									
	Relapsed patients	Remission patients	DMG	DNMG	DMOP	DNMOP	IOP	NHS and PSS	Govt.	Societal
0	£163	—	£250 (£1,975)	£2,536 (£2,183)	£22 (£135)	£1,780 (£1,223)	£11,509 (£1,633)	£638	£2,682	£16,541
1	£208	£974 (EDSS 1.5)	£85 (£889)	£3,462 (£3,462)	£77 (£63)	£1,214 (£518)	£12,857 (£1,034)	£927	£3,242	£17,949
2	£426	£1,518	£213 (£868)	£4,414 (£1,314)	£110 (£56)	£1,035 (£470)	£17,068 (£1,010)	£883	£4,288	£23,176
3	£369	£1,631	£850 (£1,237)	£6,212 (£1,585)	£214 (£82)	£1,527 (£730)	£19,450 (£1,191)	£2,753	£6,849	£28,958
4	£425	£2,002	£806 (£884)	£4,028 (£1,320)	£241 (£56)	£1,200 (£462)	£16,049 (£1,013)	£1,756	£4,753	£22,657
5	£784	£1,370	£1,419 (£823)	£6,333 (£1,338)	£245 (£44)	£1,344 (£357)	£21,116 (£1,029)	£2,543	£7,452	£30,598
6	£794	£1,490	£2,162 (£851)	£6,580 (£1,338)	£286 (£41)	£1,358 (£323)	£21,338 (£1,042)	£3,146	£8,604	£32,166
7	£2,296 (EDSS 6.5-7)	£5,574 (EDSS 6.5-7)	£6,583 (£995)	£10,808 (£1,485)	£371 (£53)	£1,944 (£439)	£22,736 (£1,161)	£7,384	£14,217	£39,322
8	—	—	£10,761 (£1,069)	£15,339 (£1,514)	£409 (£57)	£1,498 (£498)	£23,088 (£1,169)	£17,370	£27,153	£52,686
9	—	—	£15,121 (£2,656)	£10,161 (£2,837)	£821 (£175)	£288 (£1,610)	£23,583 (£2,107)	£16,307	£26,439	£52,039

DMG, direct governmental medical costs; DMOP, direct medical out-of-pocket costs; DNMG, direct governmental non-medical costs; DNMOP, direct non-medical out-of-pocket costs; EDSS, Expanded Disability Status Scale; IOP, indirect costs; SE, standard error.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:[1]

- The criteria for selecting the experts,
- The number of experts approached,
- The number of experts who participated,
- Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought,
- The background information provided and its consistency with the totality of the evidence provided in the submission,
- The method used to collect the opinions,
- The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?),
- The questions asked,
- Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

See Section 6.3.5.

Intervention and comparators' costs

6.5.5 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 6.2.2.

Treatment costs are summarised in Table 68. The resource use for each therapy was taken from the appropriate Summary of Product Characteristics

[1] Adapted from Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

(SPC) for the therapy and from the Association of British Neurologist 2009 MS guidelines.

Table 68 Costs associated with the technology in the economic model*

Items (first year/subsequent year)	Fingolimod (Gilenya)	Interferon-beta-1a (Rebif) 22	Interferon-beta-1a (Rebif) 44	Interferon-beta-1a (Avonex)	Interferon-beta-1b (Betaferon)	Glatiramer acetate (Copaxone)	Natalizumab (Tysabri)
Technology cost	£1,470	£52.06	£67.77	£163.50	£39.78	£18.73	£1130.30
Dosing description	1 x 0.5 mg once daily	1 × 22 mg three times a week	1 × 44 mg three times a week	1 × 30 mg once a week	1 × 300 mg every other day	1 × 20 mg once daily	1 × 300 mg every four weeks
Mean cost per year (without risk-share)	£19,175	£8,161	£10,623	£8,531	£7,265	£6,841	£14,740
Mean cost per year (risk-sharing)	—	£7,513	£8,942	£8,502	£7,279	£5,823	
Route of administration	Oral	Injection	Injection	IM Injection	SC Injection	SC Injection	IV Infusion
Administration cost	£0	£78	£78	£78	£78	£78	£16,861
Physician visits							
Neurology visit	£414 / £207	£828 / £207	£828 / £207	£828 / £207	£828 / £207	£828 / £207	£207 / £207
Ophthalmology (treatment initiation)	£106 / —	—	—	—	—	—	—
Ophthalmology (follow-up visit)	£74 / —	—	—	—	—	—	—
Tests/imaging							
MRI	—	—	—	—	—	—	£174 / £174
Full blood count	£12.24 / £6.12	£12.24 / £6.12	£12.24 / £6.12	£12.24 / £6.12	£12.24 / £6.12	—	—
Liver function test	£5.16 / £2.58	£5.16 / £2.58	£5.16 / £2.58	£5.16 / £2.58	£5.16 / £2.58	—	—
Basic metabolism	£2.58 / £2058	—	—	—	—	—	—
Pregnancy test	£0.89 / —	—	—	—	—	—	—
Test for prior exposure to chicken pox	£0.73 / —	—	—	—	—	—	—
Other							
Patient observation following 1st administration	£501 / —	—	—	—	—	—	—
Protocol Mandated Hospitalisation	£41.57 / —	—	—	—	—	—	—
Evaluation of the fundus	£3.69 / —	—	—	—	—	—	—

Items (first year/subsequent year)	Fingolimod (Gilenya)	Interferon-beta-1a (Rebif) 22	Interferon-beta-1a (Rebif) 44	Interferon-beta-1a (Avonex)	Interferon-beta-1b (Betaferon)	Glatiramer acetate (Copaxone)	Natalizumab (Tysabri)
Total cost per first year (Risk sharing)	—	£8,435	£9,864	£9,424	£8,181	£6,727	£31,986
Total cost per subsequent year (Risk-sharing)	—	£7,728	£9,157	£8,717	£7,474	£6,030	£31,986

BNF, British National Formulary; CI, confidence interval; MRI, magnetic resonance imaging.

* Primary comparator is Avonex (based on the direct trial comparison with fingolimod in non-responder patients with high disease activity despite treatment with a beta-interferon).

Health-state costs

6.5.6 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 6.2.4.

NHS and Personal Social Services costs by EDSS score were derived from the Biogen Idec UK and Elan Pharma International joint STA submission for natalizumab, which used data from the 2005 UK MS Survey. Costs were updated to 2010 values, using inflation indices derived from Curtis, 2010 (Table 69). Societal costs were incorporated in the model but were not used in the base-case analysis.

Table 69 NHS and PSS costs, by EDSS score

	Annual cost			
EDSS State	**NHS and PSS (£, Year 2005)**	**NHS and PSS (£, Year 2010)***	**Societal (£, Year 2005)**	**Societal (£, Year 2010)***
0	638	746	16,541	19,332
1	927	1,083	17,949	20,978
2	883	1,032	23,176	27,087
3	2,758	3,223	28,958	33,845
4	1,756	2,052	22,657	26,480
5	2,543	2,972	30,598	35,761
6	3,146	3,677	32,166	37,594
7	7,384	8,630	39,322	45,957
8	17,370	20,301	52,686	61,577
9	16,307	19,059	52,039	60,820

EDSS, Expanded Disability Status Scale; NHS, National Health Service; PSS, Personal Social Services.
Source: Biogen Idec UK and Elan Pharma International, 2007.
* Inflated to 2010 values using inflation indices derived from Curtis (2010).

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in Section 5.9 (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 6.2.2.

Adverse events included in the model and their associated costs are listed in Table 70. The base case analysis incorporates only the costs of adverse events associated with fingolimod. The inclusion of the costs of adverse events associated with Avonex is explored in the sensitivity analysis.

Table 70 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Unit cost
Macular oedema	Visit to ophthalmologist (1 first attendance)	£105
	Visit to ophthalmologist (1 follow-up attendance)	£74
	Total per event	**£179**
Atrio-ventricular block, first degree	Non-elective inpatient stay*	£427
	Total per event	**£427**
Atrio-ventricular block, second degree	Non-elective inpatient stay*	£427
	Total per event	**£427**

* Based on arrhythmia or conduction disorders with complications.

Miscellaneous costs

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

Cost of relapse was obtained from the 2010-2011 National Tariff (Department of Health, 2010): “Admitted Patient Care & Outpatient Procedure Tariff, AA30Z Multiple sclerosis non-elective tariff” was used, and the cost incorporated in the model was £3,039.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 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.

For this section of the sensitivity analysis we considered variation in the following structural assumptions:

- Waning of treatment effect after 2-years,
- Reduced time horizon (10-year and 20-year),
- Inclusion of a partial treatment effect on conversion from RRMS to SPMS,
- Discontinuation due to AEs limit to the first 10-year treatment period.

6.6.2 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 6.3.6 (summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic one-way sensitivity analysis has been conducted on the following variables, representing the key clinical and economic inputs into the economic model (as set out in Table 58):

- Relative risk of progression for fingolimod (95% CI)
- Relative risk of relapse for fingolimod (95% CI)
- Relative risk of progression for Avonex (95% CI)
- Relative risk of relapse for Avonex (95% CI)
- Discontinuation rates (95% CI)
- Cost of relapse (± 20%)
- Cost of disease by EDSS stages (± 20%)
- Utility of EDSS stages (95% CI)
- Utility adjustment from years since diagnosis (95% CI)
- Utility adjustment for males (95% CI)
- Disutility of relapse (95% CI)
- Disutility of treatment (95% CI)
- Discounting rates (0%-6%)

6.6.3 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 6.3.6, 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).

A fully comprehensive PSA analysis was undertaken based on the distribution assumptions and variables as detailed in Table 58. The model allows the user to consider a range of user selected variables for the PSA, but the reported PSA is based on the full available variable list.

When sampling PSA data for progression and relapse effect, it is theoretically possible for the model to generate extreme RR values, which would result in a set of infeasible absolute transition rates (where the transition matrix would include negative values to force a sum to 1 in the matrix rows). To counter this effect, the model has been programmed to ignore such infeasible PSA samples and to re-sample the data.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000-£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see Section 4), 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 outcomes from the model were not compared with the corresponding clinical outcomes reported in the trials due to the fact that the model uses natural history transitions derived from the London, Ontario, data set and does not apply natural history transitions based on the FREEDOMS placebo-arm.

6.7.2 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.

The primary economic analysis is based on a comparison of fingolimod versus Avonex in non-responder patients with high disease activity despite prior treatment with a beta-interferon (i.e., Part 1b of approved indication: patients with an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year).

The analysis is based on a scenario using drug costs for fingolimod based on 13 packs per year at standard pricing.

The following tables provide the Markov trace data for fingolimod (Table 71 and Table 72) and Avonex (Table 73 and Table 74) over a 50-year time horizon. The data is shown separately for RRMS and SPMS health states, defined using EDSS states. The data presents a breakdown of 1000 patients at the start of the model.

The tables show the slower progression of patients through the EDSS health states, and eventual conversion to SPMS, for fingolimod over Avonex. The

data can be seen directly in the Entire Cohort tables in the Mid-Yr Est sheet in the model.

Table 71 Summary of Markov trace: RRMS health states (fingolimod)

Year	0	1	2	3	4	5	6	7	8	9	10
1	47.05	218.53	298.05	192.70	128.66	55.54	17.71	1.29	0.95	0.01	0.00
2	29.15	188.44	269.88	191.38	99.30	49.72	46.76	3.76	3.19	0.03	0.00
3	17.95	160.09	241.11	186.48	78.67	43.10	64.74	5.87	5.83	0.06	0.00
4	11.01	134.47	213.09	178.70	63.99	36.86	74.70	7.48	8.39	0.08	0.00
5	6.73	111.98	186.67	168.80	53.31	31.42	79.03	8.58	10.60	0.10	0.00
6	4.11	92.64	162.31	157.43	45.31	26.87	79.56	9.22	12.34	0.11	0.00
7	2.51	76.24	140.24	145.20	39.11	23.12	77.59	9.49	13.58	0.12	0.00
8	1.53	62.48	120.51	132.61	34.13	20.02	74.05	9.47	14.35	0.12	0.00
9	0.93	51.04	103.05	120.04	29.99	17.44	69.59	9.25	14.69	0.12	0.00
10	0.56	41.58	87.74	107.81	26.44	15.26	64.64	8.87	14.68	0.12	0.00
11	0.34	33.79	74.41	96.14	23.34	13.39	59.48	8.40	14.39	0.12	0.00
12	0.21	27.40	62.86	85.15	20.59	11.76	54.30	7.86	13.88	0.11	0.00
13	0.13	22.18	52.93	74.98	18.13	10.33	49.25	7.28	13.21	0.11	0.00
14	0.08	17.93	44.43	65.65	15.91	9.07	44.40	6.69	12.42	0.10	0.00
15	0.05	14.47	37.19	57.19	13.93	7.94	39.80	6.11	11.57	0.09	0.00
16	0.03	11.67	31.04	49.59	12.14	6.93	35.50	5.54	10.68	0.08	0.00
17	0.02	9.39	25.84	42.81	10.55	6.03	31.51	4.99	9.78	0.08	0.00
18	0.01	7.55	21.45	36.80	9.13	5.23	27.83	4.47	8.89	0.07	0.00
19	0.01	6.07	17.77	31.50	7.87	4.53	24.47	3.98	8.03	0.06	0.00
20	0.00	4.87	14.68	26.87	6.76	3.90	21.42	3.53	7.20	0.06	0.00
21	0.00	3.90	12.11	22.84	5.78	3.35	18.67	3.11	6.42	0.05	0.00
22	0.00	3.12	9.96	19.35	4.93	2.86	16.20	2.73	5.69	0.04	0.00
23	0.00	2.50	8.18	16.33	4.19	2.44	14.01	2.38	5.02	0.04	0.00
24	0.00	1.99	6.70	13.74	3.55	2.07	12.06	2.07	4.40	0.03	0.00
25	0.00	1.59	5.47	11.53	2.99	1.75	10.33	1.79	3.83	0.03	0.00
26	0.00	1.27	4.46	9.63	2.52	1.48	8.81	1.54	3.32	0.03	0.00
27	0.00	1.01	3.63	8.02	2.11	1.24	7.49	1.32	2.85	0.02	0.00
28	0.00	0.80	2.94	6.66	1.76	1.04	6.33	1.12	2.44	0.02	0.00
29	0.00	0.63	2.38	5.51	1.46	0.86	5.33	0.95	2.08	0.02	0.00
30	0.00	0.50	1.92	4.55	1.21	0.72	4.47	0.80	1.76	0.01	0.00
31	0.00	0.40	1.55	3.74	1.00	0.59	3.73	0.67	1.48	0.01	0.00
32	0.00	0.31	1.24	3.06	0.82	0.49	3.10	0.56	1.23	0.01	0.00
33	0.00	0.25	0.99	2.50	0.67	0.40	2.56	0.47	1.02	0.01	0.00
34	0.00	0.19	0.79	2.03	0.55	0.33	2.11	0.38	0.84	0.01	0.00
35	0.00	0.15	0.63	1.64	0.45	0.27	1.73	0.31	0.69	0.01	0.00
36	0.00	0.12	0.50	1.32	0.36	0.22	1.40	0.26	0.56	0.00	0.00
37	0.00	0.09	0.39	1.06	0.29	0.17	1.13	0.21	0.45	0.00	0.00
38	0.00	0.07	0.31	0.84	0.23	0.14	0.91	0.17	0.36	0.00	0.00
39	0.00	0.05	0.24	0.67	0.18	0.11	0.72	0.13	0.28	0.00	0.00
40	0.00	0.04	0.19	0.52	0.14	0.09	0.57	0.10	0.22	0.00	0.00
41	0.00	0.03	0.14	0.41	0.11	0.07	0.45	0.08	0.16	0.00	0.00
42	0.00	0.02	0.11	0.32	0.09	0.05	0.34	0.06	0.12	0.00	0.00
43	0.00	0.02	0.08	0.24	0.07	0.04	0.26	0.05	0.09	0.00	0.00
44	0.00	0.01	0.06	0.18	0.05	0.03	0.20	0.03	0.07	0.00	0.00
45	0.00	0.01	0.05	0.14	0.04	0.02	0.15	0.03	0.05	0.00	0.00
46	0.00	0.01	0.03	0.10	0.03	0.02	0.11	0.02	0.03	0.00	0.00
47	0.00	0.01	0.02	0.07	0.02	0.01	0.08	0.01	0.02	0.00	0.00

Year	0	1	2	3	4	5	6	7	8	9	10
48	0.00	0.00	0.02	0.05	0.01	0.01	0.05	0.01	0.01	0.00	0.00
49	0.00	0.00	0.01	0.04	0.01	0.01	0.04	0.01	0.01	0.00	0.00
50	0.00	0.00	0.01	0.03	0.01	0.00	0.02	0.00	0.01	0.00	0.00

RRMS, relapsing-remitting multiple sclerosis.

Table 72 Summary of Markov trace: SPMS health states (fingolimod)

Year	0	1	2	3	4	5	6	7	8	9	10
1	0.00	0.00	5.28	11.47	9.02	8.68	4.37	0.00	0.00	0.00	0.00
2	0.00	0.00	12.26	30.36	26.14	22.02	20.13	4.25	0.80	0.29	0.00
3	0.00	0.00	14.08	41.51	40.23	29.80	45.93	14.64	4.85	1.31	0.00
4	0.00	0.00	13.62	46.34	49.85	34.98	75.75	27.36	14.50	3.23	0.00
5	0.00	0.00	12.25	46.81	55.05	38.09	106.14	40.18	30.44	6.09	0.00
6	0.00	0.00	10.62	44.61	56.61	39.31	134.63	51.87	52.42	9.81	0.00
7	0.00	0.00	9.00	40.97	55.50	38.94	159.50	61.80	79.68	14.29	0.00
8	0.00	0.00	7.52	36.68	52.64	37.37	179.74	69.74	111.18	19.39	0.00
9	0.00	0.00	6.23	32.27	48.72	35.00	194.90	75.64	145.78	24.97	0.00
10	0.00	0.00	5.13	28.02	44.29	32.15	205.04	79.61	182.39	30.89	0.00
11	0.00	0.00	4.20	24.09	39.71	29.10	210.47	81.79	219.92	37.04	0.00
12	0.00	0.00	3.43	20.54	35.21	26.02	211.70	82.39	257.30	43.28	0.00
13	0.00	0.00	2.79	17.41	30.94	23.04	209.37	81.63	293.77	49.52	0.00
14	0.00	0.00	2.26	14.69	27.00	20.24	204.14	79.77	328.60	55.68	0.00
15	0.00	0.00	1.83	12.33	23.41	17.65	196.61	77.00	361.19	61.66	0.00
16	0.00	0.00	1.48	10.32	20.19	15.31	187.36	73.54	391.13	67.42	0.00
17	0.00	0.00	1.19	8.60	17.33	13.21	176.89	69.57	417.99	72.88	0.00
18	0.00	0.00	0.96	7.15	14.81	11.34	165.61	65.25	441.48	77.97	0.00
19	0.00	0.00	0.77	5.93	12.61	9.70	153.89	60.73	461.45	82.63	0.00
20	0.00	0.00	0.62	4.90	10.69	8.26	142.03	56.11	477.73	86.82	0.00
21	0.00	0.00	0.50	4.04	9.04	7.01	130.28	51.51	490.43	90.52	0.00
22	0.00	0.00	0.40	3.33	7.62	5.93	118.84	47.00	499.67	93.72	0.00
23	0.00	0.00	0.32	2.73	6.40	5.00	107.84	42.65	505.35	96.34	0.00
24	0.00	0.00	0.26	2.24	5.36	4.20	97.35	38.48	507.48	98.34	0.00
25	0.00	0.00	0.20	1.83	4.47	3.52	87.43	34.52	505.75	99.54	0.00
26	0.00	0.00	0.16	1.49	3.72	2.94	78.12	30.80	500.32	99.94	0.00
27	0.00	0.00	0.13	1.21	3.09	2.44	69.47	27.34	491.58	99.58	0.00
28	0.00	0.00	0.10	0.98	2.55	2.03	61.49	24.14	479.58	98.39	0.00
29	0.00	0.00	0.08	0.80	2.11	1.68	54.18	21.21	464.77	96.46	0.00
30	0.00	0.00	0.06	0.64	1.73	1.38	47.51	18.54	447.22	93.74	0.00
31	0.00	0.00	0.05	0.52	1.42	1.13	41.47	16.12	427.09	90.24	0.00
32	0.00	0.00	0.04	0.41	1.16	0.93	36.03	13.95	404.84	86.05	0.00
33	0.00	0.00	0.03	0.33	0.94	0.76	31.14	12.01	380.73	81.21	0.00
34	0.00	0.00	0.02	0.26	0.76	0.61	26.78	10.28	354.93	75.75	0.00
35	0.00	0.00	0.02	0.21	0.62	0.50	22.90	8.74	327.55	69.70	0.00
36	0.00	0.00	0.02	0.17	0.49	0.40	19.45	7.38	298.74	63.09	0.00
37	0.00	0.00	0.01	0.13	0.39	0.32	16.41	6.18	269.07	56.12	0.00
38	0.00	0.00	0.01	0.10	0.31	0.25	13.73	5.14	238.84	48.90	0.00
39	0.00	0.00	0.01	0.08	0.25	0.20	11.39	4.23	208.49	41.60	0.00

Year	0	1	2	3	4	5	6	7	8	9	10
40	0.00	0.00	0.01	0.06	0.19	0.16	9.36	3.44	178.61	34.44	0.00
41	0.00	0.00	0.00	0.05	0.15	0.12	7.61	2.77	149.69	27.62	0.00
42	0.00	0.00	0.00	0.04	0.12	0.09	6.12	2.20	122.54	21.40	0.00
43	0.00	0.00	0.00	0.03	0.09	0.07	4.85	1.72	97.51	15.90	0.00
44	0.00	0.00	0.00	0.02	0.07	0.05	3.79	1.33	75.18	11.27	0.00
45	0.00	0.00	0.00	0.02	0.05	0.04	2.91	1.00	55.96	7.58	0.00
46	0.00	0.00	0.00	0.01	0.04	0.03	2.19	0.74	39.89	4.77	0.00
47	0.00	0.00	0.00	0.01	0.03	0.02	1.62	0.54	27.07	2.78	0.00
48	0.00	0.00	0.00	0.01	0.02	0.02	1.17	0.38	17.34	1.48	0.00
49	0.00	0.00	0.00	0.00	0.01	0.01	0.82	0.26	10.41	0.71	0.00
50	0.00	0.00	0.00	0.00	0.01	0.01	0.56	0.17	5.86	0.31	0.00

SPMS, secondary progressive multiple sclerosis.

Table 73 Summary of Markov trace: RRMS health states (Avonex)

Year	0	1	2	3	4	5	6	7	8	9	10
1	43.37	215.21	297.36	195.89	125.81	56.18	23.66	1.73	1.27	0.01	0.00
2	21.42	178.46	266.30	199.11	93.09	50.58	61.74	5.22	4.47	0.04	0.00
3	10.56	144.39	232.91	195.55	72.39	43.11	83.88	8.42	8.43	0.08	0.00
4	5.19	115.11	200.46	186.89	58.80	36.20	94.84	10.85	12.28	0.12	0.00
5	2.55	90.93	170.53	174.76	49.40	30.48	98.38	12.43	15.53	0.15	0.00
6	1.25	71.41	143.77	160.53	42.45	25.92	97.20	13.26	17.98	0.16	0.00
7	0.61	55.86	120.34	145.29	36.97	22.26	93.13	13.48	19.60	0.17	0.00
8	0.30	43.59	100.12	129.88	32.41	19.27	87.40	13.25	20.46	0.18	0.00
9	0.15	33.94	82.88	114.88	28.44	16.76	80.78	12.71	20.66	0.17	0.00
10	0.07	26.40	68.29	100.68	24.92	14.62	73.80	11.97	20.33	0.17	0.00
11	0.04	20.51	56.05	87.52	21.77	12.74	66.78	11.11	19.61	0.16	0.00
12	0.02	15.91	45.83	75.53	18.92	11.08	59.92	10.18	18.59	0.15	0.00
13	0.01	12.34	37.35	64.76	16.36	9.60	53.36	9.23	17.37	0.14	0.00
14	0.00	9.56	30.34	55.20	14.08	8.28	47.20	8.30	16.03	0.13	0.00
15	0.00	7.40	24.57	46.80	12.05	7.12	41.49	7.40	14.64	0.12	0.00
16	0.00	5.72	19.85	39.49	10.27	6.08	36.26	6.56	13.25	0.10	0.00
17	0.00	4.42	15.99	33.17	8.70	5.18	31.51	5.77	11.88	0.09	0.00
18	0.00	3.42	12.86	27.74	7.34	4.39	27.23	5.04	10.57	0.08	0.00
19	0.00	2.64	10.31	23.10	6.17	3.70	23.41	4.38	9.34	0.07	0.00
20	0.00	2.03	8.25	19.17	5.16	3.11	20.03	3.79	8.19	0.06	0.00
21	0.00	1.57	6.58	15.85	4.30	2.60	17.05	3.26	7.14	0.05	0.00
22	0.00	1.21	5.24	13.06	3.57	2.16	14.46	2.79	6.18	0.05	0.00
23	0.00	0.93	4.17	10.73	2.95	1.80	12.20	2.37	5.33	0.04	0.00
24	0.00	0.71	3.31	8.78	2.43	1.48	10.25	2.01	4.56	0.03	0.00
25	0.00	0.55	2.62	7.17	1.99	1.22	8.57	1.69	3.88	0.03	0.00
26	0.00	0.42	2.06	5.83	1.63	1.00	7.13	1.42	3.28	0.02	0.00
27	0.00	0.32	1.63	4.72	1.33	0.82	5.91	1.18	2.75	0.02	0.00
28	0.00	0.25	1.28	3.81	1.08	0.67	4.87	0.98	2.30	0.02	0.00
29	0.00	0.19	1.00	3.07	0.87	0.54	4.00	0.81	1.91	0.01	0.00
30	0.00	0.14	0.78	2.46	0.70	0.44	3.27	0.66	1.57	0.01	0.00
31	0.00	0.11	0.61	1.97	0.56	0.35	2.66	0.54	1.29	0.01	0.00

Year	0	1	2	3	4	5	6	7	8	9	10
32	0.00	0.08	0.47	1.57	0.45	0.28	2.15	0.44	1.05	0.01	0.00
33	0.00	0.06	0.37	1.25	0.36	0.22	1.74	0.36	0.85	0.01	0.00
34	0.00	0.05	0.28	0.98	0.29	0.18	1.39	0.29	0.68	0.01	0.00
35	0.00	0.04	0.22	0.78	0.23	0.14	1.11	0.23	0.54	0.00	0.00
36	0.00	0.03	0.17	0.61	0.18	0.11	0.88	0.18	0.43	0.00	0.00
37	0.00	0.02	0.13	0.47	0.14	0.09	0.69	0.14	0.33	0.00	0.00
38	0.00	0.01	0.10	0.37	0.11	0.07	0.54	0.11	0.26	0.00	0.00
39	0.00	0.01	0.07	0.28	0.08	0.05	0.42	0.09	0.20	0.00	0.00
40	0.00	0.01	0.05	0.22	0.06	0.04	0.32	0.07	0.15	0.00	0.00
41	0.00	0.01	0.04	0.16	0.05	0.03	0.24	0.05	0.11	0.00	0.00
42	0.00	0.00	0.03	0.12	0.04	0.02	0.18	0.04	0.08	0.00	0.00
43	0.00	0.00	0.02	0.09	0.03	0.02	0.14	0.03	0.06	0.00	0.00
44	0.00	0.00	0.02	0.07	0.02	0.01	0.10	0.02	0.04	0.00	0.00
45	0.00	0.00	0.01	0.05	0.01	0.01	0.07	0.01	0.03	0.00	0.00
46	0.00	0.00	0.01	0.04	0.01	0.01	0.05	0.01	0.02	0.00	0.00
47	0.00	0.00	0.01	0.02	0.01	0.00	0.04	0.01	0.01	0.00	0.00
48	0.00	0.00	0.00	0.02	0.01	0.00	0.02	0.00	0.01	0.00	0.00
49	0.00	0.00	0.00	0.01	0.00	0.00	0.02	0.00	0.00	0.00	0.00
50	0.00	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.00	0.00

RRMS, relapsing-remitting multiple sclerosis.

Table 74 Summary of Markov trace: SPMS health states (Avonex)

Year	0	1	2	3	4	5	6	7	8	9	10
1	0.00	0.00	5.28	11.47	9.02	8.68	4.37	0.00	0.00	0.00	0.00
2	0.00	0.00	12.11	30.31	26.44	21.68	20.23	5.38	0.90	0.39	0.00
3	0.00	0.00	13.56	41.17	41.07	29.02	46.00	18.19	5.69	1.80	0.00
4	0.00	0.00	12.67	45.35	50.96	34.16	75.50	33.25	17.15	4.53	0.00
5	0.00	0.00	10.95	44.97	55.98	37.38	105.48	47.73	35.88	8.62	0.00
6	0.00	0.00	9.07	41.91	56.97	38.65	133.54	60.29	61.28	13.90	0.00
7	0.00	0.00	7.34	37.51	55.06	38.17	157.89	70.42	92.22	20.17	0.00
8	0.00	0.00	5.85	32.66	51.30	36.36	177.40	78.02	127.36	27.19	0.00
9	0.00	0.00	4.62	27.88	46.53	33.65	191.58	83.21	165.32	34.70	0.00
10	0.00	0.00	3.63	23.47	41.37	30.45	200.47	86.19	204.84	42.52	0.00
11	0.00	0.00	2.83	19.54	36.22	27.06	204.46	87.24	244.71	50.44	0.00
12	0.00	0.00	2.21	16.14	31.33	23.71	204.12	86.61	283.80	58.28	0.00
13	0.00	0.00	1.72	13.24	26.83	20.54	200.20	84.62	321.32	65.94	0.00
14	0.00	0.00	1.33	10.80	22.80	17.62	193.43	81.53	356.56	73.29	0.00
15	0.00	0.00	1.03	8.78	19.24	15.00	184.51	77.61	388.93	80.26	0.00
16	0.00	0.00	0.80	7.10	16.15	12.68	174.08	73.10	418.09	86.78	0.00
17	0.00	0.00	0.62	5.73	13.49	10.66	162.64	68.19	443.66	92.77	0.00
18	0.00	0.00	0.48	4.61	11.21	8.92	150.66	63.06	465.44	98.19	0.00
19	0.00	0.00	0.37	3.70	9.29	7.43	138.50	57.86	483.35	102.98	0.00
20	0.00	0.00	0.29	2.96	7.66	6.16	126.45	52.71	497.30	107.11	0.00
21	0.00	0.00	0.22	2.36	6.30	5.09	114.73	47.70	507.49	110.58	0.00
22	0.00	0.00	0.17	1.88	5.16	4.19	103.53	42.92	514.10	113.41	0.00
23	0.00	0.00	0.13	1.49	4.22	3.44	92.93	38.40	517.12	115.53	0.00

Year	0	1	2	3	4	5	6	7	8	9	10
24	0.00	0.00	0.10	1.19	3.44	2.81	83.00	34.17	516.62	116.89	0.00
25	0.00	0.00	0.08	0.94	2.79	2.29	73.75	30.24	512.31	117.34	0.00
26	0.00	0.00	0.06	0.74	2.26	1.86	65.21	26.61	504.43	116.86	0.00
27	0.00	0.00	0.05	0.58	1.82	1.51	57.39	23.31	493.40	115.54	0.00
28	0.00	0.00	0.03	0.46	1.47	1.21	50.28	20.31	479.31	113.32	0.00
29	0.00	0.00	0.03	0.36	1.18	0.98	43.86	17.62	462.64	110.31	0.00
30	0.00	0.00	0.02	0.28	0.94	0.78	38.09	15.21	443.47	106.47	0.00
31	0.00	0.00	0.02	0.22	0.75	0.63	32.93	13.06	421.97	101.82	0.00
32	0.00	0.00	0.01	0.17	0.59	0.50	28.34	11.17	398.62	96.47	0.00
33	0.00	0.00	0.01	0.13	0.47	0.39	24.27	9.50	373.64	90.48	0.00
34	0.00	0.00	0.01	0.10	0.37	0.31	20.68	8.03	347.24	83.90	0.00
35	0.00	0.00	0.01	0.08	0.29	0.25	17.53	6.76	319.52	76.75	0.00
36	0.00	0.00	0.00	0.06	0.23	0.19	14.76	5.64	290.59	69.08	0.00
37	0.00	0.00	0.00	0.05	0.18	0.15	12.34	4.68	261.02	61.10	0.00
38	0.00	0.00	0.00	0.03	0.14	0.12	10.25	3.85	231.10	52.95	0.00
39	0.00	0.00	0.00	0.03	0.10	0.09	8.43	3.13	201.22	44.80	0.00
40	0.00	0.00	0.00	0.02	0.08	0.07	6.87	2.53	171.96	36.90	0.00
41	0.00	0.00	0.00	0.01	0.06	0.05	5.54	2.01	143.77	29.43	0.00
42	0.00	0.00	0.00	0.01	0.05	0.04	4.42	1.59	117.42	22.67	0.00
43	0.00	0.00	0.00	0.01	0.03	0.03	3.48	1.23	93.21	16.75	0.00
44	0.00	0.00	0.00	0.01	0.02	0.02	2.69	0.94	71.69	11.80	0.00
45	0.00	0.00	0.00	0.00	0.02	0.02	2.06	0.70	53.23	7.88	0.00
46	0.00	0.00	0.00	0.00	0.01	0.01	1.54	0.52	37.84	4.92	0.00
47	0.00	0.00	0.00	0.00	0.01	0.01	1.13	0.37	25.61	2.84	0.00
48	0.00	0.00	0.00	0.00	0.01	0.01	0.80	0.26	16.35	1.50	0.00
49	0.00	0.00	0.00	0.00	0.00	0.00	0.56	0.18	9.78	0.71	0.00
50	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.12	5.48	0.31	0.00

SPMS, secondary progressive multiple sclerosis.

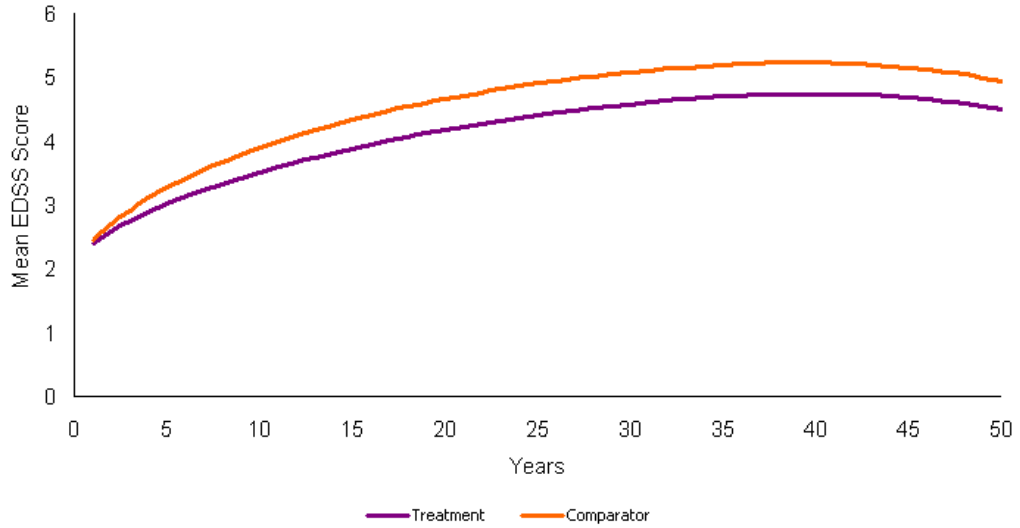
6.7.3 Please provide details of how the model assumes quality-adjusted life-years (QALYs) accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The treatment arm (fingolimod) acts in slowing the progression of patients through the EDSS states for the RRMS patients and, in doing so, delays an eventual conversion to SPMS, and eventually delays movement though EDSS states in SPMS. This results in QALY gain from increasing time spent in lower EDSS states, which are associated with higher HRQL.

The following graphs (**Figure 16** and **Figure 17**) link to the Markov trace data and demonstrate that fingolimod results in a lower mean EDSS score over the

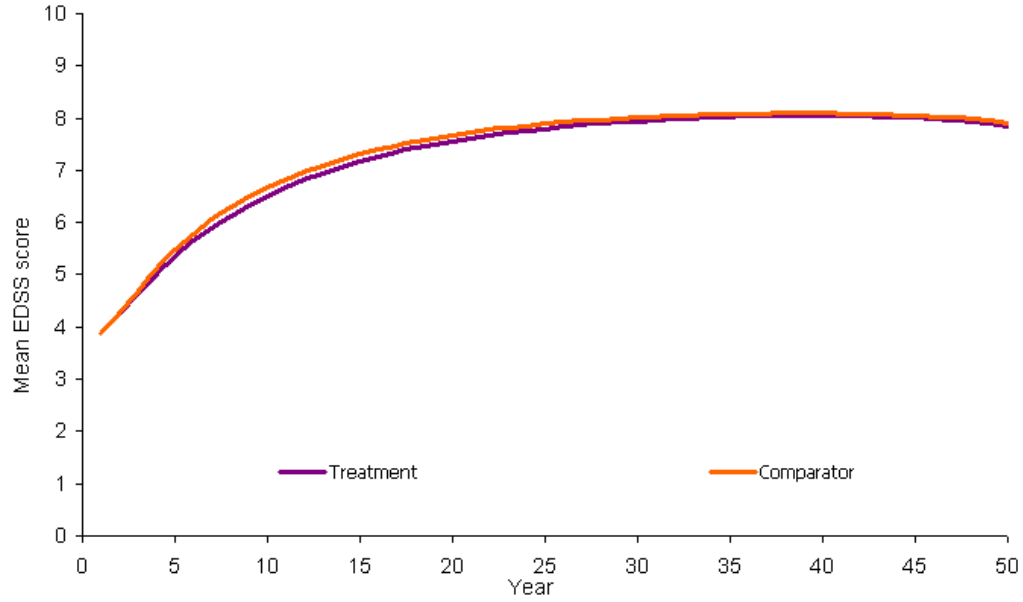
model time horizon for those patients who remain with RRMS disease type, when compared to Avonex. This translates into a utility gain as EDSS is strongly correlated with changes in quality of life.

Figure 16 Mean EDSS during time in RRMS states



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

Figure 17 Mean EDSS during time in SPMS states



EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

6.7.4 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.

The models structure is directly based on the primary clinical outcomes of progression and relapse. The model can therefore be used to demonstrate the QALY and cost results driven by these clinical outcomes (with the EDSS health states in the model). The QALY and cost data is presented for both treatments stratified by EDSS health state in Section 6.7.5 (Table 75 and Table 76).

6.7.5 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. Suggested formats are presented below.

Table 75 Summary of undiscounted QALY gains, by health state (per patient)*

	Health state (EDSS)	QALY: fingolimod	QALY: Avonex	Incre-ment	Absolute incre-ment	Percent-age of absolute incre-ment
RRMS	0	0.11	0.07	0.03	0.03	2%
	1	0.97	0.79	0.18	0.18	12%
	2	1.43	1.27	0.16	0.16	11%
	3	1.10	1.09	0.01	0.01	1%
	4	0.41	0.39	0.03	0.03	2%
	5	0.18	0.18	0.00	0.00	0%
	6	0.38	0.48	-0.10	0.10	6%
	7	0.01	0.01	0.00	0.00	0%
	8	0.00	0.00	0.00	0.00	0%
	9	0.00	0.00	0.00	0.00	0%
	10	0.00	0.00	0.00	0.00	0%
SPMS	0	0.00	0.00	0.00	0.00	0%
	1	0.00	0.00	0.00	0.00	0%
	2	0.02	0.02	0.00	0.00	0%
	3	0.04	0.04	0.00	0.00	0%
	4	0.05	0.05	0.00	0.00	0%
	5	0.02	0.02	0.00	0.00	0%

	Health state (EDSS)	QALY: fingolimod	QALY: Avonex	Incre-ment	Absolute incre-ment	Percent-age of absolute incre-ment
	6	0.01	0.01	0.00	0.00	0%
	7	0.02	0.02	0.00	0.00	0%
	8	0.00	0.00	0.00	0.00	0%
	9	0.00	0.00	0.00	0.00	0%
	10	0.00	0.00	0.00	0.00	0%
Drop-outs		1.45	0.54	0.91	0.91	59%
Relapse		-0.88	-0.98	0.10	0.10	6%
Total		5.33	3.99	1.33	1.55	100%

EDSS, Expanded Disability Status Scale; QALY, quality-adjusted life-year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

* Undiscounted QALY values.

Table 76 Summary of undiscounted costs, by health state (per patient)*

	Health state (EDSS)	Cost: Fingolimod	Cost: Avonex	Incre-ment	Absolute incre-ment	Percent-age of absolute incre-ment
RRMS	0	£2,442	£828	£1,614	£1,614	2%
	1	£24,483	£10,079	£14,403	£14,403	14%
	2	£40,641	£18,197	£22,474	£22,474	23%
	3	£43,332	£24,000	£19,332	£19,332	19%
	4	£14,381	£7,197	£7,184	£7,184	7%
	5	£8,044	£4,408	£3,636	£3,636	4%
	6	£20,095	£14,512	£5,583	£5,583	6%
	7	£1,325	£1,682	-£357	£357	0%
	8	£5,160	£6,608	-£1,448	£1,448	1%
	9	£40	£52	-£11	£11	0%
	10	£0	£0	£0	£0	0%
SPMS	0	£0	£0	£0	£0	0%
	1	£0	£0	£0	£0	0%
	2	£675	£322	£354	£354	0%
	3	£3,106	£2,054	£1,052	£1,052	1%
	4	£3,199	£2,181	£1,018	£1,018	1%
	5	£2,400	£1,815	£585	£585	1%
	6	£15,600	£14,131	£1,470	£1,470	1%
	7	£13,702	£13,704	-£3	£3	0%
	8	£260,974	£267,080	-£6,106	£6,106	6%

	Health state (EDSS)	Cost: Fingolimod	Cost: Avonex	Incre-ment	Absolute incre-ment	Percent-age of absolute incre-ment
	9	£46,745	£55,636	-£8,891	£8,891	9%
	10	£0	£0	£0	£0	0%

	Health state (EDSS)	Cost: Fingolimod	Cost: Avonex	Incre-ment	Absolute incre-ment	Percent-age of absolute incre-ment
Relapse		£37,748	£41,973	-£4,224	£4,224	4%
Total		£544,122	£486,460	£57,662	£57,662	100%

EDSS, Expanded Disability Status Scale; QALY, quality-adjusted life-year; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

* Undiscounted cost values.

Base-case analysis

6.7.6 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.

The following presents the undiscounted and discounted incremental results, comparing fingolimod to Avonex over a 50-year time horizon. The analysis considers non-responder patients with high disease activity despite prior treatment with a beta-interferon.

The incremental QALY and cost results can be found on the ICER – QALY sheet and the “Results” sheet in the model.

The cost per QALY was £43,197 (undiscounted) £55,634 (discounted) (Table 77 and Table 78).

Table 77 Base-case results (undiscounted)

Tech-nologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incre-mental (QALYs)
Avonex	486,460	31.34	3.99	—	—	—	—	—
Fingolimod	544,122	31.62	5.33	57,662	0.28	1.33	43,197	43,197

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-years.

Table 78 Base-case results (discounted)

Tech-nologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incre-mental (QALYs)
Avonex	271,647	N/A	3.98	—	—	—	—	—
Fingolimod	321,721	N/A	4.88	50,084	N/A	0.90	55,634	55,634

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; N/A, not available; QALY, quality-adjusted life-years.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The results of the deterministic sensitivity analysis are presented in Table 79 and **Figure 18**.

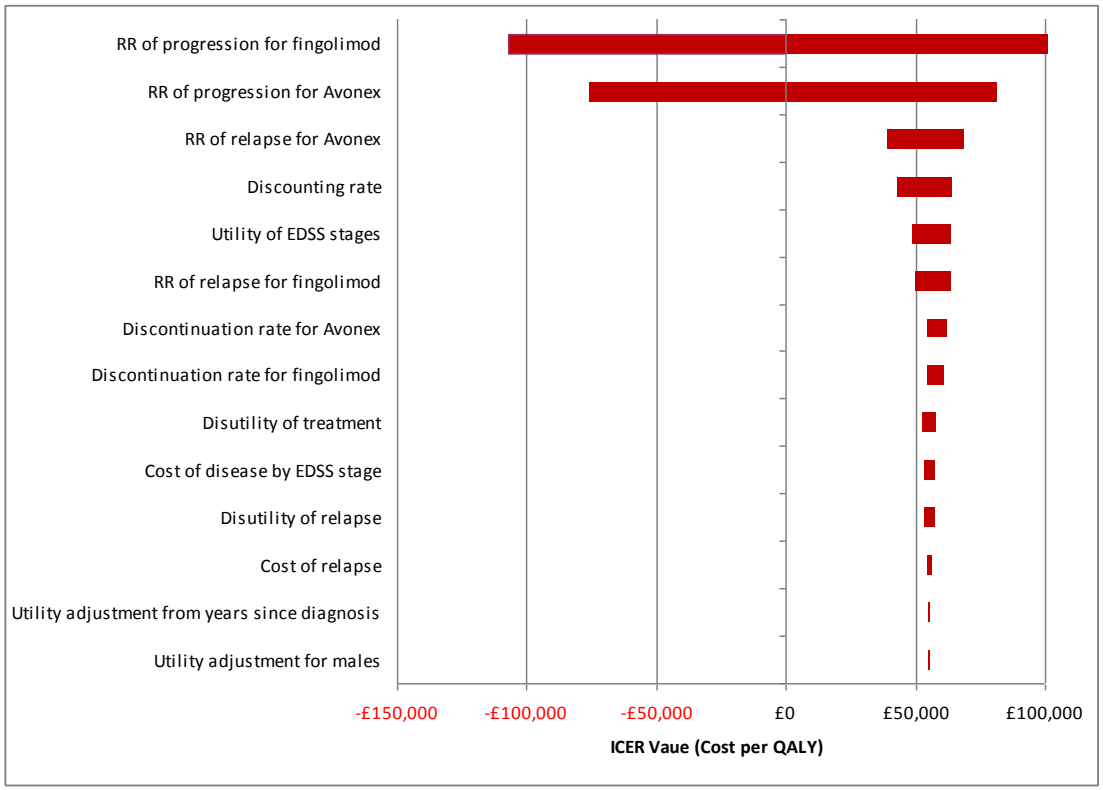
Table 79 Deterministic sensitivity analyses

Parameter		Level	Value	ICER
Efficacy	RR of progression for fingolimod	Lower 95% CI	0.332	£24,686
		Upper 95% CI	1.210	-£107,276
	RR of progression for Avonex	Lower 95% CI	0.308	-£75,683
		Upper 95% CI	2.404	£6,132
	RR of relapse for fingolimod	Lower 95% CI	0.388	£50,500
		Upper 95% CI	0.805	£64,107
	RR of relapse for Avonex	Lower 95% CI	0.567	£68,880
		Upper 95% CI	1.535	£39,558
	Discontinuation rate for fingolimod	Lower 95% CI	0.0045	£61,265
		Upper 95% CI	0.0342	£55,030
	Discontinuation rate for Avonex	Lower 95% CI	0.0138	£55,074
		Upper 95% CI	0.0545	£62,312
Cost	Cost of relapse	80% of base values	£2,431	£56,495
		120% of base values	£3,647	£54,773
	Cost of disease by EDSS stage	80% of base values	£597 to £16,241	£57,772
		120% of base values	£895 to £24,361	£53,495

Parameter		Level	Value	ICER
Utility	Utility of EDSS stages	80% of base values	RRMS: 0.696 to –0.125 SPMS: 0.660 to –0.161	£63,990
		120% of base values	RRMS: 1 to –0.188 SPMS: 0.990 to –0.241	£49,279
	Utility adjustment from years since diagnosis	Lower 95% CI	0.001	£55,851
		Upper 95% CI	0.003	£55,418
	Utility adjustment for males	Lower 95% CI	–0.007	£55,682
		Upper 95% CI	0.041	£55,586
	Disutility of relapse	Lower 95% CI	–0.096	£53,731
		Upper 95% CI	–0.046	£57,676
	Disutility of treatment	80% of base values	–0.0079 to –0.0383	£58,418
		120% of base values	–0.01188 to –0.05742	£53,103
	Discounting rate	Lowest value	0%	£43,197
		Highest value	6%	£64,340

CI, confidence interval; EDSS, Expanded Disability Status Scale; RR, relative risk.

Figure 18 Tornado plot

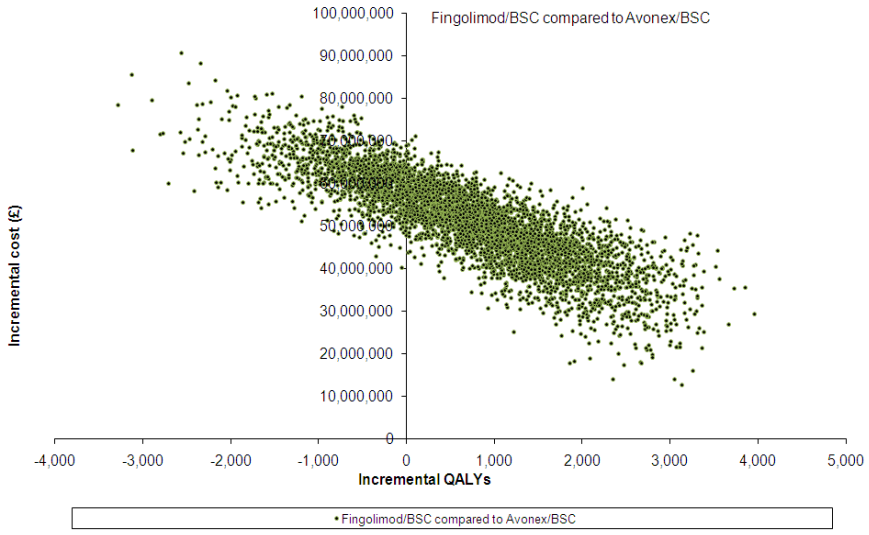


EDSS, Expanded Disability Status Scale; QALY, quality-adjusted life-year; RR, relative risk.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

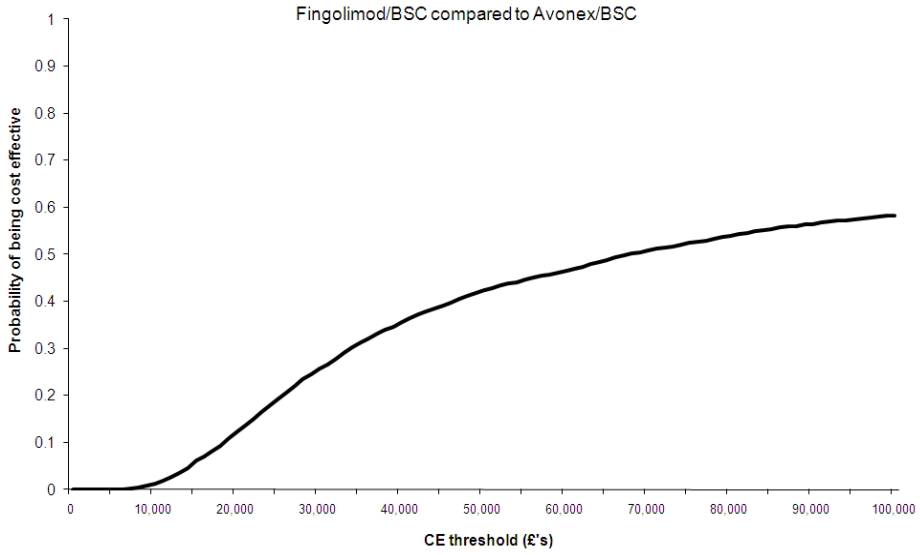
The following graphs show the scatter plot for results based on 5000 PSA iterations (Figure 19) and the resulting CEAC curve (Figure 20).

Figure 19 PSA scatter plot



BSC, best supportive care; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 20 Cost effectiveness acceptability curve



BSC, best supportive care; CE, cost-effectiveness.

In the great majority of PSA runs (75%), fingolimod had additional cost over Avonex but resulted in additional QALY benefits. The results of the PSA also showed that there was a 12% probability that the ICER for fingolimod versus Avonex is less than £20,000 per QALY. This probability increased to 26% when we considered a higher £30,000 per QALY threshold, with 50% of iterations falling under £68,000 per QALY.

These results suggest that the ICERs calculated in the deterministic analysis are robust to the overall uncertainty in the model parameter values when considered concurrently.

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 80 presents a set of economic results for a range of alternative scenarios covering the following:

- Waning of treatment effect after 2-years,
- Reduced time horizon (10-year and 20-year),

- Inclusion of a partial treatment effect on conversion from RRMS to SPMS,
- Discontinuation due to AEs limit to the first 10-year treatment period.

Table 80 Structural sensitivity analyses

Structural Parameter/Assumption		**ICER**
Waning of treatment effect	Continued treatment effect	£55,634
	Waning at 2 years: reduction to 50% efficacy levels	£73,191
	Waning at 2 years: reduction to 25% efficacy levels	£85,266
	Waning at 5 years: reduction to 50% efficacy levels	£63,890
	Waning at 5 years: reduction to 25% efficacy levels	£68,493
Time Horizon	10-year horizon	£97,159
	20-year horizon	£64,280
	30-year horizon	£56,368
	40-year horizon	£55,556
DMT Efficacy on SPMS conversion	25% effect on SPMS conversion rate	£53,576
	50% effect on SPMS conversion rate	£51,609
	75% effect on SPMS conversion rate	£49,720
	100% effect on SPMS conversion rate	£47,895
AE drop-out	Limit AE drop-out to the first 10-year treatment period only	£56,434

AE, adverse event; DMT, disease-modifying therapy, ICER, incremental cost-effectiveness ratio; SPMS, secondary progressive multiple sclerosis.

6.7.10 What were the main findings of each of the sensitivity analyses?

Deterministic

The deterministic sensitivity analysis clearly demonstrated that the key model parameter affecting the ICER for fingolimod is the assumed relative risk of disease progression for Avonex and also for fingolimod versus BSC.

In this case, we were able to use direct-comparison data for fingolimod via a subgroup analysis of non-responder patients with high disease activity within the FREEDOMS study. The corresponding data for Avonex were necessarily taken from an indirect link to BSC via the direct comparison to fingolimod in

the TRANSFORMS study. Additional data of non-responder patients with high disease activity for both treatments would help in reducing this large amount of uncertainty at the 95% confidence level.

Due to the 50-year horizon and long term treatment and QALY gains then assumptions on discounting rate also play a part in adding to the uncertainly in ICER values.

Uncertainly in all other parameter values lead to only marginal changes in the ICER value for fingolimod.

Structural

In our consideration of uncertainty related to structural assumptions (as opposed to parameter values) then we noted that a number of key sensitivities existed in calculating the UCE for fingolimod. The time horizon used is a key assumption as the ICER increases to £64,000-£97,000 when a shorter 10- to 20-year horizon is adopted. Also, if treatment efficacy is assumed to reduce after the first 2-years of treatment, then again the ICER rises. This is seen in particular over the first 5-years, after which treatment efficacy assumptions become much less impacting on the ICER.

Probabilistic

In the PSA analyses we varied all key model parameter values concurrently within their assigned statistical distributions. In this case we observed that the vast majority of cases (75%) resulted in fingolimod providing additional QALY benefits at an additional cost beyond that of Avonex. The PSA results therefore fell within the typical area of the cost-effectiveness plane where the ICER uncertainty can be considered and represented in a CEAC curve.

These data showed that there was a 50% likelihood of fingolimod being associated with an ICER under £68,000 per QALY.

6.7.11 What are the key drivers of the cost-effectiveness results?

See response to 6.7.10.

6.8 Validation

6.8.1 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 adapted from a global model developed for a more general application than in the UK. The global Markov cohort model therefore was designed as a flexible analytic framework intended to meet the needs of multiple jurisdictions. Data sources used in the UK model were substituted for those in the global model to reflect the most appropriate UK values for NICE appraisal purposes. Validation steps for the global and adapted versions are described below.

Independent review of the model by an external analyst not involved in the development of the global model

The global Markov cohort model was reviewed by an external analyst not involved in the initial model development. The purpose of this review was to critically assess the model to enable the development team to make appropriate subsequent improvements before adapting it to the UK setting. The model review included the technical validity of the model (i.e., correct implementation of model design and calculations), model assumptions, and face validity of the model. The independent analyst provided verbal and written comments to the modelling team. These included queries relating to potential errors. These comments were addressed by the modelling team during the model-adaptation stage.

Review of the adapted UK model by an independent analyst

The adapted version of the model was supplied to an independent analyst (one not involved with the model adaptation itself). The following validation procedures were performed:

- Execution of extreme tests to check the plausibility of model results,

- Check of all cell formulae,
- Comparison of the UK adapted model to previously published UK MS models—NICE TA32 (NICE, 2002), NICE TA127 (NICE, 2007), and Gani et al. (2008).

Verification of all model input data

In addition, quality-control procedures were performed according to a prespecified test plan designed to verify all model input data with the original sources.

Verification of model validity

A pre-set series of tests were conducted to validate the robustness of the model results. Table 81 resents the results of these tests.

Table 81 Tests conducted on model as part of the model verification

Index	Test	Expected effect	Observed effect	Action taken
1	Set initial number of cases to 0	Costs and QALY equal 0 across treatments	As expected	No action
2	Set initial cohort as only SPMS patients by setting the RRMS-SPMS conversion rate to 100%	No RRMS patients	As expected – set conversion rate to 100% in cycle 1 – in cycle 2 all SPMS	No action
3	Set all efficacies and withdrawal rates the same and SAE and treatment-specific disutilities disutility and mortality to 0	Same number of QALYS for fingolimod and Avonex	As expected – identical QALY	No action
4	As 3 with all efficacies = 1	All incremental QALYs = 0	As expected	No action
5	Set hazard ratios for progression to 0	No progression for RRMS patients	As expected – no treated patients progress in RRMS	No action
6	Set withdrawals the same and efficacies the same	Same number for fingolimod and Avonex on treatment	As expected	No action

Index	Test	Expected effect	Observed effect	Action taken
7	Set withdrawals to 100%	No patients on treatment after first year	As expected	No action
8	Set withdrawals to 0%	No patients off treatment	As expected – patients > EDSS 6.0 move to BSC	No action
9	Set mortality to 0%	No deaths	As expected	No action
10	Set deaths to 100% (includes setting the relative risk of death due to MS to 100%)	Whole cohort dead by end of first year	As expected	No action
11	Set the relative risk of death due to MS to 0	No deaths for any standard mortality rate	As expected	No action
12	Set natural history of relapse to 0	QALY is the same as if disutility of relapse is 0	As expected	No action
13	Let transition matrices for RRMS patients to have only 1's in diagonal and mortality set to 0	No change in patients per state in no treatment	As expected	No action
14	Let transition to SPMS = 1	No RRMS patients after 1st year	As expected	No action
15	Let transition to SPMS = 0	No SPMS patients	As expected	No action
16	Check sum of rows in each transition matrix	All rows should sum to 1	As expected	No action
23	Check the placebo group sums to cohort size plus deaths each year	Should sum to cohort size	As expected	No action
24	Check the fingolimod treatment group sums to cohort size plus deaths each year for both on treatment and withdrawals	Should sum to cohort size	As expected	No action
26	Set fingolimod cost and administrative costs to 0; relative risks and rates for efficacy to 1; withdrawals to 0; and SAE costs and utilities to 0	No difference between placebo and fingolimod	As expected for QALYs For costs, there is a very minor difference that can be explained by the rounding error of a magnitude of 0.0003% of the total cost	No action
27	Set costs discount rate to 0	Same costs as undiscounted rate	As expected	No action
28	Set benefits discount rate to 0	Same benefits as undiscounted rate	As expected	No action

Index	Test	Expected effect	Observed effect	Action taken
29	Set relapse cost to 0	Same cost as when the natural history relapse rates are set to 0	As expected	No action
30	Set DMT costs to 0 and fingolimod efficacy to 1; withdrawals to 0; and disutilities of treatments to 0	No difference between no treatment and DMT	As expected for QALYs For costs, there is a very minor difference that can be explained by the rounding error of a magnitude of 0.0003% of the total cost	No action
31	Set cost of SPMS to 0, transition to SPMS to 0 and hazard ratios to 1	Fingolimod and no treatment QALY the same	As expected	No action
32	Set utility of relapse to 0	Same utility as natural history relapse rate set to 0	As expected	No action
33	All utilities = 0	QALY = 0	As expected	No action
34	Set all utilities for states to 1 and other utility values to 0 and deaths to 0	No loss of utility for any patient	As expected	No action

AE, adverse event; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; QALY, quality-adjusted life-year; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SPMS, secondary progressive multiple sclerosis.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's *Guide to the methods of technology appraisal*, section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

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 5.3.7.

6.9.1 .Please clearly define the characteristics of patients in the subgroup.

No sub-group analyses were undertaken.

6.9.2 Please describe how the statistical analysis was undertaken.

No sub-group analyses were undertaken.

6.9.3 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 6.7.6 (base-case analysis).

No sub-group analyses were undertaken.

6.9.4 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 4.

No sub-group analyses were undertaken.

6.10 Interpretation of economic evidence

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

The level of ICER values that we see for fingolimod, in the £43,000 to £56,000 range, are similar to those reported for beta interferons and glatiramer acetate in the previous NICE technology appraisal; and base case ICER estimates ranged from £40,000 to £90,000 (NICE, 2002). The systematic review has proven that there is no published literature on cost-effectiveness of fingolimod specifically in MS.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 4?

The economic evaluation has been conducted and focused specifically on natural history and efficacy data for a patient group in line with the approved label for fingolimod: non-responder patients with high disease activity despite prior treatment with a beta-interferon. In this case we have available clinical data for fingolimod, Avonex and BSC.

The model structure is capable of being used to evaluate treatment in a wider group, those with any level of RRMS, and an appropriate set of MTC efficacy data and natural history transition data are included for this. However, this currently sits outside of the label text.

The model does not cover all aspects of the label for fingolimod and focuses specifically only on Part 1b:

- Part 1: Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy and have had at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion (Part 1a). A “non-responder” also could be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year (Part 1b).
- Part 2: Patients with rapidly evolving, severe, relapsing-remitting MS, defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.

This is largely due to the fact that Part 1 is the larger of the two subgroups in the label, and Part 1b has most efficacy when compared with Part 1a. Novartis believe that this also is the area of greatest clinical unmet need because there is no current therapy available for patients who have had an inadequate treatment response to DMTs and who do not quite qualify for natalizumab treatment.

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

The model is based on a well established and accepted set of natural history transition data, from the London Ontario dataset. Also the definitions of progression and relapse from the TRANSFORMS and FREEDOMS study are well established and transferable across studies.

There are a number of established utility data sets linked to EDSS which again are well known and established references for RRMS modelling.

The economic model structure has been used in previous submissions and has generally been accepted as appropriate.

The model uses head-to-head data for an active comparator. A specific population (i.e., non-responder patients with high disease activity despite treatment with a beta-interferon) of the licensed indication has been included in the analysis.

The weakness of the model at this stage would be accessing clinical efficacy data specific to the patient group consisting of non-responders with high disease activity for a wider set of potential treatment comparators (outside of the direct comparison in TRANSFORMS to Avonex).

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A detailed MTC based on available sub-group data for non-responder with high disease activity patient from existing published RCTs would improve the scope of the possible economic analyses including other comparators (Rebif, Betaferon, and Copaxone), and also the level of confidence in the relative risks of progression and relapse. This would require access to clinical data for a number of comparators and would best be performed through an independent HTA research group.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 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.

The estimate of the number of patients eligible for fingolimod has been derived from estimates of the following:

- The population of England and Wales,
- The prevalence and incidence of diagnosed MS,
- The proportion of MS patients with the relapsing form of MS,
- The proportion of RRMS patients within the license indication of fingolimod and other DMTs.

Table 82 shows the estimated population of England and Wales for 2010-2015, as derived from the Office of National Statistics (ONS, 2010).

Table 82 England and Wales population estimates

Year	2010	2011	2012	2013	2014
Male	27,250,111	27,482,489	27,712,264	27,937,639	28,162,578
Female	28,069,138	28,261,539	28,453,858	28,644,526	28,836,809
Total	55,319,249	55,744,028	56,166,122	56,582,165	56,999,387

An estimate of the prevalence and incidence of MS in England and Wales has been derived from the literature. The annual prevalence rate of MS for England and Wales has been estimated as 0.11% (Koutsouraki et al., 2010), with annual incidence rates of 3.4 per 100,000 population and 7.4 per 100,000 population for males and females, respectively (Alonso et al., 2007).

The model assumes that the prevalence remains static through the 5 years of analysis. Thus, the number of new MS patients derived from the incidence assumption is offset by the number of other MS patients no longer receiving treatment. The proportion of MS patients who have the relapsing form has been estimated as 35% (Kobelt et al., 2006). Of the total number of relapsing MS patients, it has been estimated that 31% would previously be treated with a DMT (Zajicek et al., 2010). Based on Synovate prescribing data for fourth quarter 2010 (Synovate, 2010), 53% of current RRMS patients previously treated with a DMT are eligible for fingolimod (i.e. 1 or more relapses in the last 12 months and the relapse frequency unchanged or increased).
Figure 21 details the calculation to estimate the number of patients receiving immunomodulator therapy, and Table 83 shows the estimated number of patients eligible for immunomodulator therapy for the 5 years of interest.

Figure 21 Calculation of patients receiving immunomodulator therapy

Default assumptions:

England and Wales population 2012 = 56,166,122 (1)

Prevalence of MS = 0.11% (2)

Proportion of patients with relapsing form of MS = 35.5% (3)

Proportion of RRMS patients receiving DMT = 31% (4)

Proportion of those receiving DMT who had 1 or more relapse in the last 12 months and the relapse frequency unchanged or increased = 53% (5)

Number of patients with RRMS receiving immunomodulator therapy in 2012:

= (1) × (2) × (3) × (4) × (5)

= 3,604

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

Table 83 Estimated number of patients with the relapsing form of MS eligible for immunomodulator therapy

Year	2010	2011	2012	2013	2014
Eligible patients	3,549	3,576	3,604	3,630	3,657

MS, multiple sclerosis.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Novartis believe that patients with RRMS are initiated with one DMT; if they fail to respond, they are cycled to an alternative DMT. This means that patients with high disease activity despite treatment with a beta-interferon are treated with the existing DMTs. Thus, the treatment comparators to fingolimod

consisted of all other DMT therapies currently indicated for treatment of RRMS, including the following:

- Interferon-beta-1a (Rebif) 22 mg,
- Interferon-beta-1a (Rebif) 44 mg,
- Interferon-beta-1a (Avonex),
- Interferon-beta-1b (Betaferon),
- Glatiramer acetate.

The use of natalizumab has been considered only in RES RRMS because this is the only population for which NICE recommend the use of natalizumab, NICE TA 127.

Obtaining the exact individual market share of each MS therapy in the UK was difficult because all such therapies are home delivered and because national sales data is not consistently reported. Therefore, estimates derived from the reporting of prescribing from a sample of clinicians have been used. The estimate of the current market share of immunomodulator therapies for RRMS in England and Wales (Table 84) has been derived from an analysis undertaken by Synovate in the second quarter of 2010 (Synovate data on file, 2010). There are not enough prescribing data available to check whether the market share data for all RRMS patients are the same as the market share data for RRMS patients not responding on their initial DMT. So Novartis assumes that the proportions of the use of these therapies will be the same for the population of RRMS patients not responding on their initial DMT.

Table 84 Estimated current market share in England and Wales for all RRMS patients

Treatment	Market-share percentage
Interferon-beta-1a (Rebif) 22 mg	6%
Interferon-beta-1a (Rebif) 44 mg	36%
Interferon-beta-1a (Avonex)	18%
Interferon-beta-1b (Betaferon)	14%*
Glatiramer acetate	26%

Treatment	Market-share percentage
Total	100%

RRMS, relapsing-remitting multiple sclerosis.

* Includes Extavia with a patient share of 1%

7.3 What assumption(s) were made about market share (when relevant)?

The model assumes that once fingolimod is accepted into the formulary, fingolimod is expected to secure 15% of the total market within 5 years. The model assumes that this market share will be derived in equal proportions from the other comparator treatments, as shown in Table 85.

Table 85 Estimated RRMS market share in England and Wales with fingolimod*

	Year				
Treatment	**2010**	**2011**	**2012**	**2013**	**2014**
Fingolimod	2%	5%	7%	12%	15%
Interferon-beta-1a (Rebif) 22 mg	6%	6%	6%	5%	5%
Interferon-beta-1a (Rebif) 44 mg	35%	34%	33%	32%	31%
Interferon-beta-1a (Avonex)	18%	17%	17%	16%	15%
Interferon-beta-1b (Betaferon)	14%	13%	13%	12%	12%
Glatiramer acetate	25%	25%	24%	23%	22%
Natalizumab†					
Total	100%	100%	100%	100%	100%

RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis.

* Note: totals may not sum to 100% due to rounding.

† The use of natalizumab is considered for RES RRMS only.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to

commissioners (for example, procedure codes and programme budget planning).

The costs considered in the budget impact include the drug costs, administration and monitoring costs, and costs saved from reduction in the annual number of relapses MS patients experience. Fingolimod has been shown to reduce the number of relapses in RRMS, as well as to delay the progression of the disease.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

7.5.1 Drug costs

The drug costs for the comparator treatments have been derived from the British National Formulary and the UK MS Risk Sharing Scheme (RSS) HSC 2002 and are shown in Table 86. The UK cost of fingolimod is £52.50 per 0.5-mg capsule.

Table 86 Drug costs used in the budget impact calculations

Treatment	Pack size	List price per pack	Days per pack	Packs per year	Cost per year (BNF)	Cost per year (PAS)
Fingolimod	1 × 0.5 mg	£1,470	28	13.04	£19,175	-
Interferon-beta-1a (Rebif) 22 mg	1 × 22 mg	£52.06	2.33	156.76	£8,161	£7,513
Interferon-beta-1a (Rebif) 44 mg	1 × 44 mg	£67.77	2.33	156.76	£10,623	£8,942
Interferon-beta-1a (Avonex)	1 × 30 mg	£163.50	7	52.18	£8,531	£8,502
Interferon-beta-1b (Betaferon)	1 × 300 mg	£39.78	2	182.62	£7,265	£7,259

Treatment	Pack size	List price per pack	Days per pack	Packs per year	Cost per year (BNF)	Cost per year (PAS)
Glatiramer acetate	1 × 20 mg	£18.73	1	365.24	£6,841	£5,823

BNF, British National Formulary; PAS, patient access scheme.

7.5.2 Administration and monitoring costs

The estimated cost for administration and monitoring each product has been derived from the Summary of Product Characteristics and is presented in Table 87.

Table 87 Administration and monitoring costs

Drug/costs related to administration	Unit cost (£)	Requiring	Annual resource use (units)	
			First year	Sub-sequent year
Fingolimod				
Oral administration	0.00	100%	0	0
NHS costs relating to administering PAS				
Physician visit				
Neurology visit	206.53	100%	2	1
Neurology visit (follow-up)		0%	0	0
Ophthalmology visit (treatment initiation)	105.47	100%	1	0
Ophthalmology visit (follow-up)	73.84	0.9%	1	0
Tests/imaging				
MRI		0%	0	0
Full blood count	3.06	100%	4	2
Liver function	1.29	100%	4	2
Pregnancy Test	1.29	69%	1	0
Blood-pressure test	0.00	100%	0	0
Basic metabolism	1.29	100%	2	2
Test for prior exposure to chicken pox	7.25	10%	1	0
Other				
Patient observation following first administration	501.43	100%	1	0

Drug/costs related to administration	Unit cost (£)	Requiring	Annual resource use (units)	
			First year	Sub-sequent year
Protocol-mandated hospitalisation	2,078.68	2%	1	0
AV block requiring atropine	0.68	0.2%	1	0
Evaluation of the fundus	105.47	3.5%	1	0
Interferon-beta-1a (Rebif) 22 mg				
Costs relating to administration				
Injection administration visits				
Assisted administration		0%		
Self-administration (training)	78.00	100%	1	0
Physician visits				
Neurology visit	206.53	100%	4	1
Ophthalmology visit (treatment initiation)	105.47	100%	1	0
Ophthalmology visit (follow-up)	73.84	0.9%	1	0
Tests/imaging				
MRI		0%	0	0
Full blood count	3.06	100%	4	2
Liver function	1.29	100%	4	2
Pregnancy test		0%	0	0
Blood-pressure test		0%	0	0
Basic metabolism		100%	0	0
Interferon-beta-1a (Rebif) 44 mg				
Costs related to administration				
Injection administration visits				
Assisted administration		0%		
Self-administration (training)	78.00	100%	1	0
Physician visits				
Neurology visit	206.53	100%	4	1
Ophthalmology visit (treatment initiation)		0%	0	0
Ophthalmology visit (follow-up)		0%	0	0
Tests/imaging				
MRI		0%	0	0
Full blood count	3.06	100%	4	2
Liver function	1.29	100%	4	2
Pregnancy test		0%	0	0
Blood-pressure test		0%	0	0
Basic metabolism		0%	0	0

Drug/costs related to administration	Unit cost (£)	Requiring	Annual resource use (units)	
			First year	Sub-sequent year
Interferon-beta-1a (Avonex)				
Costs related to administration				
Injection administration visits				
Assisted administration		0%		
Self-administration (training)	78.00	100%	1	0
Physician visits				
Neurology visit	206.53	100%	4	1
Ophthalmology visit (treatment initiation)		0%	0	0
Ophthalmology visit (follow-up)		0%	0	0
Tests/imaging				
MRI		0%		
Full blood count	3.06	100%	4	2
Liver function	1.29	100%	4	2
Pregnancy test		0%	0	0
Blood-pressure test		0%	0	0
Basic metabolism		0%	0	0
Interferon-beta-1b (Betaferon)				
Costs related to administration				
Injection administration visits				
Assisted administration		0%		
Self-administration (training)	78.00	100%	1	0
Physician visits				
Neurology visit	206.53	100%	4	1
Ophthalmology visit (treatment initiation)		0%	0	0
Ophthalmology visit (follow-up)		0%	0	0
Tests/imaging				
MRI		0%	0	0
Full blood count	3.06	100%	4	2
Liver function	1.29	100%	4	2
Pregnancy test		0%	0	0
Blood-pressure test		0%	0	0
Basic metabolism		0%	0	0
Glatiramer acetate				
Costs related to administration				
Injection administration visits				
Assisted administration		0%		

Drug/costs related to administration	Unit cost (£)	Requiring	Annual resource use (units)	
			First year	Sub-sequent year
Self-administration (training)	78.0	100%	1	0
Physician visits				
Neurology visit	206.53	100%	4	1
Ophthalmology visit (treatment initiation)		0%	0	0
Ophthalmology visit (treatment initiation)		0%	0	0
Tests/imaging				
MRI		0%	0	0
Full blood count		0%	0	0
Liver function		0%	0	0
Pregnancy test		0%	0	0
Blood-pressure test		0%	0	0
Basic metabolism		0%	0	0
Natalizumab				
Costs related to administration				
Infusion administration visits				
Day-case setting	1,293.00	100%	13.04	13.04
Outpatient setting				
Physician visits				
Neurology visit	206.53	100%	1	1
Ophthalmology visit (treatment initiation)		0%	0	0
Ophthalmology visit (follow-up)		0%	0	0
Tests/imaging				
MRI	173.57	100%	1	1
Full blood count		0%	0	0
Liver function		0%	0	0
Pregnancy test		0%	0	0
Blood-pressure test		0%	0	0
Basic metabolism		0%	0	0

AV, atrioventricular, ECG, electrocardiogram, MRI, magnetic resonance imaging; PAS, patient access scheme.

7.5.3 Relapses

In the budget impact calculations it was assumed that the average number of relapses per year prior to treatment was equal to 2. The relative annual reductions in relapse rate for each intervention were obtained from the MTC results (Table 35, Section 5.7.6).

7.6 Were there any estimates of resource savings? If so, what were they?

None.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 88 and Table 89 show the annual budget impact to the NHS of including fingolimod to the formulary for 2010-2014. Table 89 shows the total budget cost without fingolimod in the formulary.

Table 88 Total cost of RRMS in England and Wales without fingolimod

	Total cost of other treatments without fingolimod				
Year	**2010**	**2011**	**2012**	**2013**	**2014**
Drug	£30,684,208	£30,919,822	£31,153,947	£31,384,716	£31,614,427
Admini-stration	£855,220	£861,749	£868,239	£874,637	£881,015
Monitor-ing	£8,726	£8,793	£8,859	£8,924	£8,989
Other	£0	£0	£0	£0	£0
Costs of relapses	£17,540,973	£17,675,664	£17,809,505	£17,941,426	£18,072,743
Total	£49,089,127	£49,466,028	£49,840,549	£50,209,703	£50,577,174

RRMS, relapsing-remitting multiple sclerosis.

Table 89 shows the total cost of RRMS patients in England and Wales with the addition of fingolimod to the formulary.

Table 89 Total cost of RRMS in England and Wales with fingolimod

	2010	**2011**	**2012**	**2013**	**2014**
Total cost of fingolimod therapy					

	2010	2011	2012	2013	2014
Drug	£1,361,139	£3,428,977	£4,836,918	£8,353,280	£10,518,024
Admini-stration	£15,756	£39,657	£55,893	£96,447	£121,343
Monitor-ing	£839	£2,113	£2,981	£5,148	£6,482
Other	£1,916	£4,824	£6,803	£11,746	£14,787
Costs of relapses	£162,021	£408,162	£575,753	£994,317	£1,251,993
Total fingolimod	£1,541,670	£3,883,734	£5,478,348	£9,460,938	£11,912,629
Cost of other treatments					
Drug	£30,070,524	£28,732,642	£28,340,907	£27,016,005	£26,286,112
Admini-stration	£838,115	£818,661	£807,462	£769,681	£748,863
Monitor-ing	£7,474	£8,353	£8,238	£7,853	£7,640
Other	£0	£0	£0	£0	£0
Costs of relapses	£16,892,375	£16,791,881	£16,562,839	£15,788,455	£15,361,832
Total other treat-ments	£47,808,488	£46,351,537	£45,722,447	£43,581,994	£42,404,447
Total overall cost	£49,350,157	£50,235,271	£21,197,796	£53,042,932	£54,317,076
Budget impact	£261,030	£769,243	£1,357,247	£2,833,229	£3,739,902

RRMS, relapsing-remitting multiple sclerosis.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No. The costs associated with drug costs, administration costs and monitoring costs have been incorporated, and these represent the major cost aspects of treatment.

7.9 What assumption(s) were made about current treatment options and uptake of technologies?

We assume a restricted population of non-responder patients with high disease activity, and we have generated a profile of market uptake based on clinical opinion of most likely scenario.

7.10 What assumption(s) were made about market share (when relevant)?

Market share data came from a sample of the UK MS patients and is representative of the UK patient population (Table 84).

7.11 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Not applicable.

7.12 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Standard BNF and HRG costs were used (Table 66 and Table 68).

7.13 Were there any estimates of resource savings? If so, what were they?

Not applicable.

7.14 What is the estimated annual budget impact for the NHS in England and Wales?

See Table 89.

7.15 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

See Section 7.15.

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